Study Title:

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

NCT Number: NCT03458325

Amendment 6 Date: February 2, 2021

scPharmaceuticals

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

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

IND Number:	118919
Sponsor:	scPharmaceuticals, Inc.
Protocol Number:	scP-01-005
Investigational Product:	Furoscix On-Body Infusor
Original Protocol Date:	February 5, 2018
Amendment 1 Date:	February 26, 2018
Amendment 2 Date:	March 28, 2018
Amendment 3 Date:	May 22, 2018
Amendment 4 Date:	March 27, 2020
Amendment 5 Date:	November 05, 2020
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CONFIDENTIALITY STATEMENT

PRINCIPAL INVESTIGATORS

Dan Bensimhon, MD
Medical Director, Advanced Heart Failure Clinic
Moses Cone Hospital
1200 N Elm St
Greensboro, NC 27401
[redacted]

W. Frank Peacock, MD, FACEP, FACC
Associate Chair and Research Director
Baylor College of Medicine
1 Baylor Plaza
Houston, TX 77030
[redacted]

William S. Weintraub, MD, MACC, FAHA, FESC
Director of Outcomes Research
MedStar Heart & Vascular Institute, Suite 4B1
MedStar Washington Hospital Center
110 Irving Street NW
Washington, DC 20010
[redacted]

SPONSOR CONTACT INFORMATION

John Mohr, PharmD, FIDP
Sr. Vice President, Clinical Development and Medical Affairs
2400 District Avenue, Suite 310
Burlington, MA 01803
[redacted]

SUMMARY OF CHANGES

Amendment 1: The protocol has been amended to include current terminology for the study drug and device (Furoscix Infusor), clarify study patient description and expand the range of days for the first in-clinic visit. The Amendment added the exclusion of patients with local abdominal skin conditions on treatment day and modified instruction to not engage in strenuous activities. The determination of sample size of historical controls matched to Furoscix treated patients increased from 1:1 to 4:1. Figure 2 has been modified to show the study design for both the prospective treatment arm and propensity matched historical control arm.

Amendment 2: The protocol amendment includes replacing TARGET:HF script with a Telephone Script, minor corrections to the Schedule of Assessments, adding the definition of an Unexpected Adverse Event/Reaction and renaming Limited Physical to Cardiopulmonary Exam. The details of the changes are summarized in the table below.

Amendment 3: The protocol has been amended to clarify the study procedures if and when the Investigator prescribes additional doses of Furoscix during the 30-day study period (beyond the original dosing regimen prescribed upon ED discharge). The intent of the protocol is to allow the Investigator, in response to clinical triggers, to prescribe Furoscix at any time during the 30 day study period; and to use their clinical judgement with regard to patient follow up. As such, the protocol has been amended to replace the current text *" an additional course of treatment of Furoscix can be initiated" to "additional doses of Furoscix can be prescribed as needed" to clarify that there is not a specific "course" of treatment. In addition, Amendment 3 also replaces the current text "If subjects are prescribed a second course, the course of follow-up events will restart and proceed according to the original sequence"* to *"In addition to the scheduled phone and clinic visits, the investigator can utilize unscheduled clinic or phone visits for additional assessments at any time"*. Explanation of the updated language is summarized in the table below.

Amendment 4: The protocol has been amended to include the device changes that occurred after scPharmaceuticals received a Complete Response Letter (CRL). scPharmaceuticals received a CRL (Reference ID: 4275803) from the Division in reference to NDA 209988 for the Furoscix Infusor on 11 June 2018. scPharmaceuticals then committed to take all of the agency's input into account and decided to identify a new device that could meet the Agency's requirements. The new device constituent is equivalent in function to the original device design but includes certain design features that address issues noted in the CRL (e.g. prefilled cartridge which eliminates need to fill device, dose delivery notification including fault notification in the case of an under delivery due to an occlusion). Amendment 4 includes updated terminology for device description (including new Figure 1) and study drug information along with identifying a maximum of 7 doses permitted during the 30-day study period. It also provides more clarity on study endpoints.

Amendment 5: The protocol has been amended to include updated explanation for interim analysis intervals, to provide more clarity to study objectives and end points and for administrative changes. It also includes reference to the statistical plan for propensity scoring, updates the method and clarifies capturing of all AEs and removal of "treatment emergent" adverse events. The details of the changes are summarized in the table below.

Amendment 6: The protocol has been amended to remove that the device can be applied in the ED 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 on the day of enrollment or the next day.

Version	Date	Page	Change	Reason for Change
Original	05 Feb 2018	N/A	Original Version	New Document
Amendment 1	26 Feb 2018	Multiple Sections and Pages	"sc2Wear" removed. "SCP-101" removed	Updated to use current terminology

Version	Date	Page	Change	Reason for Change
			from Furosemide Injection Solution. scFurosemide changed to "Furoscix". sc2Wear Furosemide Combination Product changed to "Furoscix Infusor".	as of date of this amendment.
Amendment 1	26 Feb 2018	Protocol Title, p. 1, 6, 7, 9, Synopsis, Study Design, p. 9, Subject Population, p. 11, 1. Introduction and Rationale, p. 18, 3.1 Overall Study Design and Plan, p. 20, 4.1 Inclusion Criteria, p. 24	Description of ED patient population for this study changed from "with acute decompensated heart failure" to "with worsening" heart failure	Updated to indicate intended population for enrollment.
Amendment 1	26 Feb 2018	Synopsis, Study Assessments and Procedures, p. 12, Section 1.1.3., p. 19, Section 6.2., p. 30, Section 6.2.4., p. 32, 33, Section 6.2.5., p. 33	In-clinic visits conducted between Days 2-3 changed to between Days 2-4.	Expanded range of days for in-clinic visit to 2-4 to accommodate subjects enrolled later in the week and clinics not open on weekends.
Amendment 1	26 Feb 2018	Synopsis, Subject Population, Exclusion Criteria, p. 11 Section 4.2., p. 25	Added exclusion criteria "Any local abdominal skin condition on the day of treatment i.e. sunburn, rash, eczema, etc."	To exclude subjects with local abdominal skin conditions on treatment day.
Amendment 1	26 Feb 2018	Synopsis, Subject Population, p. 12, Section 3.2. Furoscix Infusor, p. 22, Section 4.2. Exclusion Criteria, p. 25, Section 5.9. Other Restrictions, p. 27	Changed instruction to "avoid" strenuous physical activity, etc. to "not engage in".	Modified to align with Instructions for Use.
Amendment 1	26 Feb 2018	Section 3.1. Overall Study Design and Plan, p. 20, Section 8.1. Determination of Sample Size, p. 42	Replaced statement regarding "1:1 propensity-matched design" with "...will explore ratios ranging from 1:1 to 4:1..."	To allow flexibility in propensity-matching ratios to ensure an optimized level of precision without biasing the variance.
Amendment 1	26 Feb 2018	Section 6.2., Figure 2: Study Phases and Procedures, p. 31	Updated Figure 2 to include propensity matched claims data base controls.	To provide study phases and procedures for both prospective cohort

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				and propensity matched historical controls.
Amendment 2	28Mar2018	Schedule of Assessments Table, p. 15, Section 6.2.3., Day 1 and 7 (Telephone Call Follow-Up), p. 33, Section 6.2.5., Days 14-21 (Telephone Call Follow-Up), p. 34	Changed "Target: HF Script" to "Telephone Script".	Target: HF Script will be replaced with a Telephone Script for the study.
Amendment 2	28Mar2018	Schedule of Assessments Table, p. 15	Added missing "X" for Interim Medical History, Concomitant Medications and Subject Diary for Unscheduled (Clinic) and Unscheduled (Phone) visits.	To correct table to show all assessments for Unscheduled (Clinic) and Unscheduled (Phone) visits.
Amendment 2	28Mar2018	Synopsis, Subject Population, p. 13, Section 4.2., Exclusion Criteria, p. 26	Removed "Subjects are advised to not engage..."	Removed as it is not part of the Exclusion Criteria. Statement is located in Section 5.9., Other Restrictions, p. 28; Section 3.2., Furoscix Infusor, p. 23
Amendment 2	28Mar2018	Section 7.4. Definition of an Unexpected Adverse Event, p. 39	Added Definition of an Unexpected Adverse Event/Reaction	Included definition as a guideline for reporting AEs.
Amendment 2	28Mar2018	Schedule of Assessments Table, p. 15, Section 6.2.1. Screening Phase (Day 0), p. 32, Section 6.2.4. Day 2-4 (In-Clinic Visit), p. 34 Section 6.2.6. Day 30 ± 3 (In-Clinic Visit), p. 34 Section 6.2.7. Unscheduled Telephone Calls and Clinic Visits, p. 35 Section 6.2.8. Physical Examinations, p. 35	Renamed Limited Physical to Cardiopulmonary Exam and added edema.	To clarify conducting Cardiopulmonary Exam.
Amendment 3	22May2018	Study Design, p. 12, Schedule of Assessments Table, p. 16,	Changed "During the 30-day study period, an additional course of treatment.." to "During	To clarify the study procedures if and when the Investigator prescribes additional

Version	Date	Page	Change	Reason for Change
		Section 3.1: Overall Study Design and Plan, p. 22, Section 6.2: Study Phase and Procedures, p. 32	the 30-day study period, additional doses of Furoscix.." AND Changed "If subjects are prescribed a second course, the course of follow-up events will restart and proceed according to the original sequence" to "In addition to the scheduled phone and clinic visits, the investigator can utilize unscheduled clinic or phone visits for additional assessments at any time"	doses of Furoscix during the 30-day study period (beyond the original dosing regimen prescribed upon ED discharge). In response to clinical triggers, the Investigator, may prescribe Furoscix at any time during the 30 day study period; and should use their clinical judgement with regard to patient follow up. All subject will complete the scheduled phone and clinic visits. If additional doses of Furoscix are prescribed, the Investigator can use unscheduled phone or clinic visits for any additional follow up they think warranted.
Amendment 4	27Mar2020	Cover page and Synopsis, Investigational Product, p. 12	Changed Investigational product to "Furoscix On-body Infusor."	Updated to clarify new drug device combination product which will be referred to as "Furoscix Infusor."
Amendment 4	27Mar2020	Synopsis, Study Design, p. 12, Study Assessments and Procedures, p. 15 Schedule of Assessments, p. 18 Section 1.1.3, p. 23 Section 6.2, p. 32-34 Section 6.2.2, p. 35	Added that no more than 7 doses of Furoscix are permitted during the 30-day study period unless approved by Medical Monitor. Modified Figure 2.	Updated to add maximum of 7 doses and additional doses require approval from Medical Monitor.
Amendment 4	27Mar2020	Synopsis, Study Treatments, p. 12 Section 1, p. 22 Section 5.2, p. 29	Modified Study Drug description.	Revised Study Drug information with current terminology.

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Amendment 4	27Mar2020	Synopsis, Study Design, p. 12, Subject Population, p. 14, Study Assessments and Procedures, p. 15 Section 1, p. 22 Section 3.1, p. 23, 24	Revised study population, from patients with HF and fluid overload to patients with worsening HF due to congestion.	Updated to better define the study population.
Amendment 4	27Mar2020	Synopsis, Study Treatments, p. 12, Study Assessments and Procedures, p. 15 Section 3.2 Furoscix Infusor Figure 1, p. 24-26 Section 5.5, p. 30 Section 6.2, p. 32, 33 Section 6.2.2, p. 34	Removed all prior device description and functionality and updated with new device information.	Replaced prior device information with new device description, instructions and Figure 1.
Amendment 4	27Mar2020	Synopsis, Study Endpoints, p. 15, Statistical Analysis, p. 16 Section 3.2.1, p. 26 Section 3.2.2, p. 26 Section 6.1.1, p. 32 Section 6.1.2, p. 32 Section 8.3.1, p. 45 Section 8.3.2, p. 45, 46	Revised primary and secondary endpoints.	Updated to provide more clarity on study endpoints.
Amendment 4	27Mar2020	Storage and Handling Section 5.2.2, p. 29	Modified study drug Storage and Handling.	Updated Storage and Handling conditions.
Amendment 4	27Mar2020	Other Restrictions Section 5.9, p. 30	Removed restriction: "Subjects using insulin and other injectable medications will be instructed not to inject medication on the side of the abdomen where the Furoscix Infusor is placed."	Removed because it is not in current IFU.
Amendment 4	27Mar2020	Previous Sections removed: Synopsis, Device Performance Metrics, Section 6.1.3 Assessment of Device Performance, Section 7.9 Alleged Device Failure or Malfunction	Removed Assessment of Device Performance and Device Failure or Malfunction.	Removed Assessment of Device Performance and Device Failure or Malfunction because not applicable with the new device.
Amendment 4	27Mar2020	Day 2-4 (In-Clinic visit) Section 6.2.4, p. 35-36	Modified description of device items to be returned.	Updated study materials to be returned based on the new device.
Amendment 4	27Mar2020	Furoscix Infusor Section 3.2, p. 24-26	Updated Study Product Training.	Updated Study Product Training

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		Study Product Training Section 6.2.15, p. 39		based on the new device.
Amendment 5	05Nov2020	Synopsis, Study Objectives, p. 14 Section 2, p. 24.	Removed "and direct medical costs", removed "versus" and replaced with "compared to". Added "costs" in the objective.	Rephrased study objectives to provide more clarity.
Amendment 5	05Nov2020	Synopsis, Study Design, p. 14, Section 3.1 p. 24.	Replaced "fluid overload" with "worsening" HF, removed "patients admitted for diuresis only will be identified by using diagnostic codes for admittance from a claims database.", removed "codes suggesting those patients were in the hospital for other reasons or who required inotropic support or other advanced therapies for HF" and replaced it with "with renal failure or those that were in the hospital for other reasons"	Updated to clarify how control arm will be populated and what filters will be used to analyze diagnostic codes.
Amendment 5	05Nov2020	Synopsis, Number of Subjects, p. 15.	Rephrased the explanation for interim analysis intervals.	Modified to allow more flexibility for interim analysis intervals.
Amendment 5	05Nov2020	Synopsis, Number of Sites, p. 15.	Number of sites changed from 10 to "up to 20".	Number of sites was increased to assist with recruitment.
Amendment 5	05Nov2020	Synopsis, Study Assessments and Procedures, p. 16, Schedule of Assessments, p. 19, Section 1.1.3 p. 24 Section 6.2 p. 33 Section 6.2.3 p. 36 Section 6.2.5 p. 37 Section 6.2.7 p. 38 Section 6.2.15 p. 40 Section 7.6 p. 43 Section 7.10.1 p. 44	Added " or designee"	Added "or designee" to include additional site staff

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		Section 7.10.6 p. 45 Section 9.1.3 p. 48 Section 9.1.8 p. 49 Section 9.1.9 p. 49 Section 9.1.11 p. 50.		
Amendment 5	05Nov2020	Synopsis, Safety Analysis p, 18, Schedule of Assessments, p. 19, Section 6.2.7 p. 38, Section 7 p. 41, Section 8.4 p. 47	Removed "treatment emergent" from treatment emergent adverse events.	Removed to capture all adverse events.
Amendment 5	05Nov2020	Synopsis, Study Endpoints & Statistical Analysis, p. 18 Section 3.2.1. p. 27 Section 3.2.2 p. 27 Section 6.1.1. p. 33 Section 6.1.2. p. 34 Section 8.3.1 p. 46.	Added "and heart failure related healthcare" in addition to overall costs. Replaced the phrase "versus" with "compared to propensity score".	Edited to clarify study endpoints.
Amendment 5	05Nov2020	Section 3.1 p. 24, Section 8.1 p. 46.	Removed "Monte-Carlo simulations per the methods reported by Austin 2010 and Rasen et al 2012" and replaced with "Millar and Pasta 2010"	Updated the matching method
Amendment 5	05Nov2020	Section 5.10 Study Stopping Criteria, p. 32.	Added "This will include re-assessment of the sample size at N=34 in the Furoscix cohort by using a group sequential design and testing to allow for stopping. It is not expected that the sample size for the Furoscix Infusor arm would exceed N=75, but the maximum value cannot be definitively stated until the analysis at N=34 is completed."	Expanded on study stopping criteria by reiterating sample size.
Amendment 5	05Nov2020	Section 8.1 Determination of Sample Size, p. 46.	Updated explanation for sample size and adaptive trial design and removed previous explanation.	Updated to clarify adaptive trial design procedures for sample size re-estimation.
Amendment 5	05Nov2020	Section 8.3.1 Primary Endpoint, p. 46.	Added "Propensity scoring methods will be described in the	To reference statistical analysis plan for propensity scoring methods.

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			statistical analysis plan".	
Amendment 5	05Nov2020	Section 8.3.2 Secondary Endpoints, p. 47.	Removed "Wilcoxon tests using two-tailed statistical test with Type I Error, alpha, set to 5%" and replaced it with "appropriate statistical test dependent on the distribution of the outcome".	Clarified how secondary endpoints will be evaluated.
Amendment 6	02Feb2021	Synopsis, Study Assessments and Procedures, p. 17, Section 3.2 Furoscix Infusor, p. 27, Section 5.5 Selection and Timing of Dose for Each Subject, p. 31, Section 6.2 Study Phases and Procedures, p. 34, Section 6.2.2 Treatment Phase (Day 0 – Discretion of the investigator), p. 36.	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 ED but press the start button when they arrive home. The dose must be started within 1 hour of applying the Furoscix Infusor onto the skin of the abdomen." And "In that case, the dose would not be prepared in the ED." Specified that the initial dose of the study product may be administered on the day of enrollment or the next day.	To remove that the device can be applied in the ED and started at home and to specify initial dose may be on day enrolled or next day.

PROTOCOL APPROVAL PAGE

Protocol Title:	Economic Impact of Reducing Hospital Admissions for Patients Presenting to the Emergency Department with Worsening Heart Failure: An Adaptive Clinical Trial of Furoscix Infusor
Protocol Number:	scP-01-005
Original Protocol Date of Issue:	February 5, 2018
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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**
Prepared by:	[redacted] scPharmaceuticals, Inc.	Approvals obtained through MasterControl
Prepared by:	[redacted] scPharmaceuticals, Inc	Approvals obtained through MasterControl
Reviewed and Approved by:	[redacted] scPharmaceuticals, Inc.	Approvals obtained through MasterControl
Reviewed and Approved by:	[redacted] scPharmaceuticals, Inc.	Approvals obtained through MasterControl

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title:	Economic Impact of Reducing Hospital Admissions for Patients Presenting to the Emergency Department with Worsening Heart Failure: An Adaptive Clinical Trial of Furoscix Infusor
Protocol Number:	scP-01-005 Amendment 6

By my signature, I

a. agree to conduct the study(ies) 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.
b. agree to personally conduct or supervise the described investigation(s).
c. 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.
d. agree to report to the Sponsor adverse experiences that occur in the course of 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.
e. agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
f. 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.
g. 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 IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
h. 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

ABBREVIATIONS

AE	adverse event
CRF	case report form
ED	emergency department
HF	heart failure
IFU	instructions for use
IV	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
NYHA	New York Heart Association
SAE	serious adverse event
TAU	treatment as usual
USA	United States of America

SYNOPSIS

SHORT TITLE	FREEDOM-HF
PROTOCOL TITLE	Economic Impact of Reducing Hospital Admissions for Patients Presenting to the Emergency Department with Worsening Heart Failure: An Adaptive Clinical Trial of Furoscix Infusor
PROTOCOL NUMBER	scP-01-005
SPONSOR	scPharmaceuticals, Inc.
INVESTIGATIONAL PRODUCT	Furoscix On-body Infusor drug-device combination product (hereinafter referred to as Furoscix Infusor)
STUDY OBJECTIVES	1. To evaluate differences in healthcare resource utilization costs for subjects treated with the Furoscix Infusor outside the hospital ("Furoscix arm", "Furoscix cohort" or "Furoscix Infusor cohort") compared to patients receiving intravenous furosemide for ≤ 72 hours in the hospital setting for 30 days post-discharge from the emergency department. 2. To evaluate the safety of Furoscix administered outside the hospital. 3. To evaluate and describe quality of life and patient satisfaction for patients who receive the Furoscix Infusor outside the hospital setting.
STUDY DESIGN	This adaptive clinical trial will include a prospective treatment arm (i.e., Furoscix administered via the Furoscix Infusor) administered outside the hospital that will be compared to a propensity-matched historical control arm of patients admitted to the hospital for ≤ 72 hours (i.e., Treatment As Usual (TAU)) that will be derived from administrative claims data. Eligible patients for the Furoscix arm will be patients with worsening HF due to congestion who initially present to the emergency department (ED) and who are expected to require parenteral diuresis. The control arm will be populated with claims data for patients who presented to the emergency department with worsening HF and are admitted to the hospital for ≤ 72 hours for the treatment of HF. The filter will be further strengthened by analyzing diagnostic codes and resource utilization during their hospital stay to remove patients with renal failure or those that c were in the hospital for other reasons. The eligibility of patients in the control arm will be determined based on a propensity-matched design according to the characteristics of the patients in the prospective Furoscix arm. Patients presenting to the emergency department with worsening HF and meeting all study eligibility criteria may be consented and enrolled in the study to receive diuresis outside of the hospital setting with Furoscix. 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 by 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. Subjects should be transitioned back to their oral maintenance diuretic regimen when clinically indicated at the discretion of the investigator (approximately 4 doses). After Subjects have been transitioned to their oral maintenance diuretic regimen, additional doses of Furoscix can be prescribed during the 30-day study period as needed based on the presence of clinical triggers (dyspnea on exertion, edema, and/or excess weight gain) as determined by the investigator. No more than 7 doses of Furoscix is permitted during the 30-day study period. Additional doses beyond 7 requires approval by the medical monitor.

	If subjects receiving Furoscix are hospitalized for heart failure during the treatment period, Furoscix should be discontinued and the subject treated with IV diuretics as clinically indicated. In addition to the scheduled phone and clinic visits, the investigator can utilize unscheduled clinic or phone visits for additional assessments at any time.
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	Based on an average hospital cost of a patient hospitalized for ≤ 72 hours with a primary diagnosis of HF (Diagnosis Related Group Code 291, 292 and 293) of $8,600 (standard deviation: $3,045), 68 patients (34 in each group) are required to have an 80% chance of detecting a decrease in hospital costs to $6,500 at a significance level of 5%. The target sample size of the Furoscix cohort will initially be N=34 subjects. Given the anticipated overdispersion of the primary outcome (i.e., difference in total HF-attributable direct medical costs), we will employ adaptive trial design procedures for sample size re-estimation. This adaptive-total information criterion approach was taken due to the risk of incorrectly estimating the sample size due to misspecification of the cost outcome parameters. This will include re-assessment of the sample size at N=34 in the Furoscix cohort by using a group sequential design and testing to allow for stopping. It is not expected that the sample size for the Furoscix Infusor arm would exceed N=75, but the maximum value cannot be definitively stated until the analysis at N=34 is completed. The methodology by which the sample size will be re-estimated and stopping rules will be implemented will be detailed in the statistical analysis plan.
NUMBER OF SITES	Up to 20 sites
COUNTRY	United States of America (USA)
SUBJECT POPULATION	Male and female patients 18-80 years old with worsening HF presenting to the emergency department with evidence of congestion or fluid overload requiring parenteral diuresis in the judgment of the investigator, and who are receiving 40-160 mg of oral furosemide equivalents daily (20-80 mg Torsemide or 1-4 mg Bumetanide). Subjects may be enrolled in the study only if all of the inclusion criteria and none of the exclusion criteria are met.

	Inclusion Criteria 1. Age 18-80 years 2. NYHA Class II-III HF presenting to the ED for worsening HF at baseline 3. On background therapy including 40-160 mg of oral furosemide equivalents daily (20-80 mg Torsemide or 1-4 mg Bumetanide) 4. Signs of extracellular volume expansion, defined as one or more of the following: a. jugular venous distention b. pitting edema (≥ 1+) c. abdominal distension d. pulmonary congestion on chest x-ray e. pulmonary rales 5. After initial emergency department evaluation and treatment (i.e., at the time of the care transition decision*), candidates for parenteral diuresis outside of the hospital, defined as all the following: a. Oxygen saturation ≥ 90% on exertion b. Respiratory Rate < 24 breaths per minute c. Resting Heart Rate < 100 beats per minute d. Systolic Blood Pressure > 100 mmHg 6. Adequate environment for at-home administration of Furoscix *Decision point when the patient leaves the emergency department. **Exclusion Criteria** A Subject is not eligible for inclusion if any of the following criteria apply: 1. Presence of a complicating condition, other than HF that requires immediate hospitalization or anticipated hospitalization in the next 30 days 2. Evidence of acute renal failure as determined at the discretion of the investigator 3. Known allergy to the active and inactive ingredients of the study medication or device adhesive 4. Any local abdominal skin condition on the day of treatment i.e. sunburn, rash, eczema, etc. 5. Currently participating in another interventional research study 6. Women who are pregnant or who could become pregnant and are not willing to use an adequate form of contraception 7. Estimated Creatinine Clearance < 30 mL per minute by Cockcroft-Gault equation CrCl (mL/min) = $\frac{(140 - age) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72}$ (x 0.85 if female) 8. If baseline creatinine value is available: an increase of $\geq$ 0.5 mg/dL in creatinine from baseline 9. HF requiring immediate hospitalization
STUDY ASSESSMENTS AND PROCEDURES	Patients will be assessed in the emergency department by the investigator and/or study staff for signs and symptoms of worsening HF due to congestion or fluid overload. If it is determined by the investigator that the patient requires parenteral diuresis or continued diuresis outside of the ED care setting, and meets all study eligibility criteria, he/she may be consented and enrolled into the study.

	The treatment comprises a 5-hour subcutaneous infusion of Furoscix via the Furoscix Infusor. Subjects will be instructed on the use of the Furoscix 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 on the day of enrollment. Some subjects may not require their initial dose until the next day. 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. No more than 7 doses of Furoscix are permitted during the 30-day study period. If a subject uses the allotted 7 doses and additional doses are required to control signs and symptoms of congestion when oral diuretics are not effective, approval by the medical monitor is required. Subjects will receive scheduled at-home telephone calls from a HF nurse, or designee, on Days 1 and 7, and one call between Days 14-21. Unscheduled calls can be conducted as needed. Planned in-clinic visits will be conducted between Day 2-4 and then Day 30$\pm$3 days. Unscheduled at-home telephone calls by an HF nurse, or designee, and unscheduled in-clinic visits may be performed if felt clinically indicated by the study team or the clinical provider. The study period will be up to 30 days after enrollment. All outcomes will be assessed up to 30 days after the initial discharge from the emergency department.
STUDY ENDPOINTS	**Primary Endpoint** The difference in overall and heart failure related healthcare costs between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department compared to propensity score matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge. **Secondary Endpoints** To compare the measurements listed below between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department compared to propensity score matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge. 1. Number of hospital admissions and duration with-in 30 days post discharge from the emergency department 2. Number of HF-related hospital admissions and duration with-in 30 days post discharge from the emergency department 3. Number of HF-related emergency department visits with-in 30 days post discharge from the emergency department 4. Number of HF-related clinic visits with-in 30 days post discharge from the emergency department 5. Description of health-related quality of life using the twelve-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12, for Furoscix Infusor cohort only) 6. Change in BNP or NT-proBNP (for Furoscix Infusor cohort only) 7. Subject and/or caregiver satisfaction with Furoscix Infusor (for Furoscix Infusor cohort only) **Safety Assessments**

	The Furoscix Infusor cohort will be monitored for adverse events, and any adverse events will be recorded and reported according to Food and Drug Administration guidelines. Reactions at the infusion site and frequency of these reactions will be recorded as part of the safety assessments.
STATISTICAL ANALYSIS	**Primary Endpoint** Overall and heart failure related costs between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department for worsening heart failure due to fluid overload compared to propensity score matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge. Comparison of these data between the matched (paired) cohorts will be conducted via a t-test or a Wilcoxon signed-rank test depending on the distribution of the data. **Secondary Endpoints** Outcomes for the endpoints related to healthcare utilization (i.e., Secondary Endpoints 1-4) will be evaluated by appropriate statistical test dependent on the distribution of the outcome. Health-related quality of life outcomes will be evaluated for the Furoscix cohort only and will descriptively compare KCCQ-12 questionnaire responses at Day 0 versus Day 30. Change in BNP or NT-proBNP will be evaluated for the Furoscix cohort only and will descriptively compare values obtained at Day 0 versus Day 30. Subject and/or caregiver satisfaction with Furoscix Infusor will be descriptive. **Safety Analysis** There are no pre-planned analyses to compare Furoscix versus hospitalized cohort on the basis of safety. However, the safety of Furoscix will be monitored during the trial, and identified safety issues (including AEs, SAEs, and adverse reactions) will be summarized descriptively for the Furoscix cohort. The incidence (number and percentage of subjects) of adverse events will be presented overall and by MedDRA System Organ Class and Preferred Term for the Furoscix cohort. Reactions at the infusion site and frequency of these reactions will be reported. This analysis will be repeated for serious adverse events, for treatment-related adverse events, and for adverse events leading to premature study withdrawal.

SCHEDULE OF ASSESSMENTS

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

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

CONTENTS

1. INTRODUCTION AND RATIONALE

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

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

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

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

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

1.1. Risk: Benefit Evaluation

1.1.1. Potential Benefits of Participating in the Study

The potential benefit to the participants beyond their contribution to the development and testing of this product is the potential avoidance of a hospital admission and administration of parental diuretics outside of the hospital setting.

1.1.2. Potential Risks of Participating in the Study

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

1.1.3. 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 (approximately 4 doses). After Subjects have been transitioned to their oral maintenance diuretic regimen, additional doses of Furoscix can be prescribed during the 30-day study period as needed based on the presence of clinical triggers (dyspnea on exertion, edema, and/or excess weight gain) as determined by the investigator. No more than 7 doses of Furoscix is permitted during the 30-day study period. Additional doses beyond 7 requires approval by the medical monitor.

Subjects will receive scheduled at-home telephone calls from a HF nurse, or designee, on Days 1 and 7, and one call between Days 14-21. Unscheduled calls can be conducted as needed. The primary purpose of the calls will be to evaluate the safety and efficacy of diuresis and the need to adjust diuretic therapy. Two planned in-clinic visits will be conducted: the first occurring within Days 2-4 and the second occurring on Day 30 $\pm$ 3 days. These visits will include laboratory testing of creatine and electrolytes.

Unscheduled at-home telephone calls by an HF nurse, or designee, and unscheduled in-clinic visits may be performed if felt clinically indicated by the study team or the clinical provider.

2. STUDY OBJECTIVES

The objectives of this study are:

1. To evaluate differences in healthcare resource utilization costs for subjects treated with the Furoscix Infusor outside the hospital compared to patients receiving intravenous furosemide for ≤ 72 hours in the hospital setting for 30 days post-discharge from the emergency department.
2. To evaluate the safety of Furoscix administered outside the hospital.
3. To evaluate and describe quality of life and patient satisfaction for patients who receive the Furoscix Infusor outside the hospital setting.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This adaptive clinical trial will include a prospective treatment arm (i.e., Furoscix administered via the Furoscix Infusor) administered outside the hospital that will be compared to a propensity-matched historical control arm consisting of patients admitted to the hospital for ≤ 72 hours (i.e., TAU). This healthcare cost data from the control arm will be generated from administrative claims data. Eligible patients for the Furoscix arm will be patients with worsening HF due to congestion who initially present to the emergency department and who are expected to require parenteral diuresis. The decision as to whether a patient will be enrolled in the study to receive Furoscix will be made collaboratively by an emergency medicine physician and a heart failure specialist or cardiologist.

The control arm will be populated with claims data for patients who presented to the emergency department for worsening HF and are admitted to the hospital for ≤ 72 hours for the treatment of HF.. The filter will be further strengthened by analyzing diagnostic codes and resource utilization during their hospital stay to remove patients with renal failure or those that were in the hospital for other reasons. Furoscix-treated patients will be matched to

controls from an administrative claims database in ratios ranging from 1:1 to 4:1 using methods reported by Millar and Pasta 2010.[1] The simulations will be used to find the matching ratio at which the level of precision is optimized without biasing the variance of the outcome measure. Additional methodological details are described in the prespecified statistical analysis plan.

Patients presenting to the emergency department with worsening HF and meeting all study eligibility criteria may be consented and enrolled in the study to receive diuresis outside of the hospital setting with Furoscix.

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 total duration in days and total number of doses of the initial therapy will be determined by the investigator based on an estimated volume of diuresis desired to transition patient back to their oral diuretic maintenance therapy. The decision of when to discontinue Furoscix and switch to oral diuretics will be based on clinical judgement. If subjects receiving Furoscix are hospitalized for heart failure during the treatment period, Furoscix should be discontinued and the subject treated with IV diuretics as clinically indicated. During the 30-day study period, additional doses of Furoscix can be prescribed as needed due to clinical triggers (dyspnea on exertion, 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.

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.

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

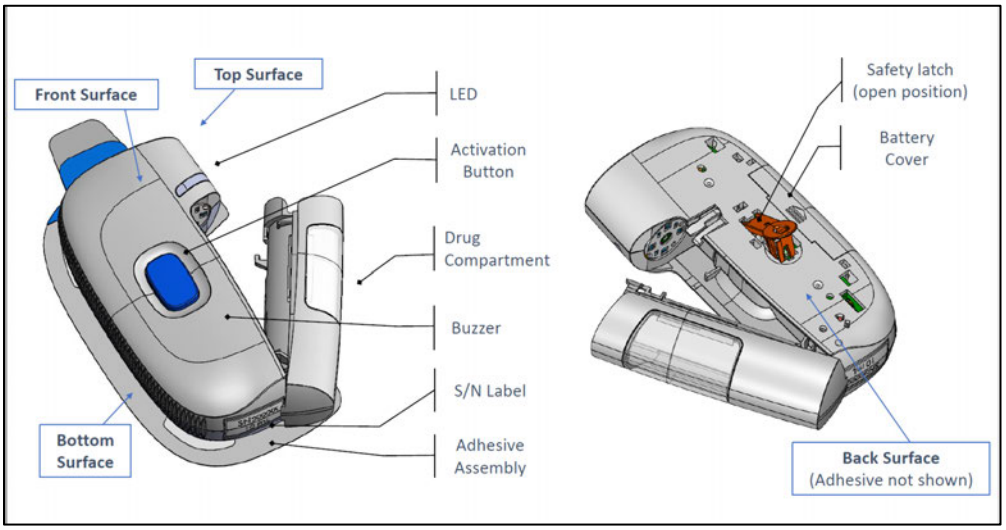


Figure 1: Main Components of the Furoscix Infusor

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). The steps include:

1. Wash hands, check expiration date on the carton and remove supplies from carton.
2. Check the Infusor and prefilled cartridge for any damage. Check the liquid medicine in the prefilled cartridge. The liquid should be clear to slightly yellow.
3. Clean the tip of the prefiled cartridge with an alcohol wipe.
4. Load prefilled cartridge into the Infusor.
5. Select a site on the stomach on either side of the belly button. Prepare application site.
6. Apply the Furoscix Infusor by peeling away the adhesive liner and firmly pressing the Furoscix Infusor onto the skin.
7. Start the infusion by firmly pressing and releasing the blue start button.
8. Allow all the medicine to deliver for 5 hours.
9. When the infusion is complete, remove the Furoscix Infusor from skin by holding the skin down and pulling on the blue tab.
10. Check the infusion site. If there is any bleeding us a cotton ball or apply a small adhesive bandage.

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 on the day of enrollment. Some subjects may not require their initial dose until the next day. 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 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 Endpoint

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

3.2.2. Secondary Endpoints

To compare the measurements listed below between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department compared to propensity score matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge.

1. Number of hospital admissions and duration with-in 30 days post discharge from the emergency department
2. Number of HF-related hospital admissions and duration with-in 30 days post discharge from the emergency

department
3. Number of HF-related emergency department visits within 30 days post discharge from the emergency department
4. Number of HF-related clinic visits with-in 30 days post discharge from the emergency department
5. Description of health-related quality of life using the KCCQ-12 (for the Furoscix Infusor arm only)
6. Change in BNP or NT-proBNP (for Furoscix Infusor arm only)
7. Subject and/or caregiver satisfaction with Furoscix Infusor (for Furoscix Infusor cohort only)

3.2.3. Safety Assessments

The Furoscix Infusor cohort will be monitored for adverse events, and any adverse events will be recorded and reported according to the Food and Drug Administration guidelines. Reactions at the infusion site and frequency of these reactions will be recorded as part of the safety assessments.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Male and female patients 18-80 years old with NYHA Class II-III HF presenting to the emergency department with evidence of fluid overload requiring parenteral diuresis in the judgment of the investigator, and who are receiving 40-160 mg of oral furosemide equivalents daily (20-80 mg Torsemide or 1-4 mg Bumetanide).

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

1. Age 18-80 years
2. NYHA Class II-III HF presenting to the ED with worsening HF at baseline
3. On background therapy includes those receiving 40-160 mg of oral furosemide equivalents daily (20-80 mg Torsemide or 1-4 mg Bumetanide).
4. Signs of extracellular volume expansion, defined as one or more of the following:
   a. jugular venous distention
   b. pitting edema (≥1+),
   c. abdominal distension
   d. pulmonary congestion on chest x-ray
   e. pulmonary rales
5. After initial emergency department evaluation and treatment (i.e., at the time of the care transition decision*), candidates for parenteral diuresis outside of the hospital, defined as all the following:
   a. Oxygen saturation ≥ 90% on exertion
   b. Respiratory Rate < 24 breaths per minute
   c. Resting Heart Rate < 100 beats per minute
   d. Systolic Blood Pressure > 100 mmHg
6. Adequate environment for at-home administration of Furoscix

*Decision point when the patient leaves the emergency department.

4.2. Exclusion Criteria

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

1. Presence of a complicating condition, other than HF that requires immediate hospitalization or anticipated hospitalization in the next 30 days

2. Evidence of acute renal failure as determined at the discretion of the investigator
3. Known allergy to the active and inactive ingredients of the study medication or device adhesive
4. Any local abdominal skin condition on the day of treatment i.e. sunburn, rash, eczema, etc.
5. Currently participating in another interventional research study
6. Women who are pregnant or who could become pregnant and are not willing to use an adequate form of contraception
7. Estimated Creatinine Clearance < 30 mL per minute by Cockcroft-Gault equation
   $$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ if female})$$
8. If baseline creatinine value is available: an increase of ≥ 0.5 mg/dL in creatinine from baseline
9. HF requiring immediate hospitalization

4.3. Removal of Subjects from Therapy and 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
- Subject non-compliance with study procedures specified in 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. As far as possible, subjects who withdraw from the study after treatment, and before completion should be seen by the Principal Investigator 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 in accordance with the procedures described in this protocol and in the Instructions for Use.

5.2. Identity of Investigational Product

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 (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) and study device (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 limited to Investigational Use
- Batch number
- Storage information

Subject 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 room temperature 15° to 30°C, (59° to 86°F). Protect from Light.

5.3. Method of Assigning Subjects to Treatment Groups

5.3.1. Treatment Assignment/Randomization

Not applicable.

5.4. Selection of Doses in the Study

The dose of 80 mg is the fixed dose of the study product. This was selected on the basis of clinical criteria and physician prescribing and is consistent with the approved labeling of furosemide injection, United States Pharmacopeia. Furoscix will be administered daily. 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 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 patient back to their oral diuretic maintenance therapy.

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). Device removal will occur within 3 hours of completion of drug delivery. 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 total duration in days and the total number of doses will be determined by the investigator based on an estimated volume of diuresis desired to transition patient back to their oral diuretic maintenance therapy.

Patients 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 on the day of enrollment. Some subjects may not require their initial dose until the next day. Doses will be provided to the patient 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

Not applicable. This is an unblinded study.

5.7. Prior and Concomitant Therapy

Prior and concomitant therapy will include all prescription medications and therapies 7 days prior to enrollment through Day 30. All information on prior and concomitant therapies will be recorded in the subject's source and on the subject's case report form (CRF). Requisite details will include the name of the therapy or drug and duration of the treatment (start and stop dates) including diuretics and electrolyte supplementation.

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 will be advised to not engage in 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 readily available access to toilet facilities.

5.10. Study Stopping Criteria

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

To avoid biasing the outcomes by artificially restricting the variance, the study will be stopped once the fixed confidence interval width for the difference in the primary endpoint between the prospective arm (Furoscix Infusor) and the historical control (treatment as usual) is reached. This will include re-assessment of the sample size at N=34 in the Furoscix cohort by using a group sequential design and testing to allow for stopping. It is not expected that the sample size for the Furoscix Infusor arm would exceed N=75, but the maximum value cannot be definitively stated until the analysis at N=34 is completed.

The methodology by which this stopping rule will be implemented is detailed in a separate statistical analysis plan.

5.11. 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 and disposition of the study products received from the sponsor. 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 Endpoint

The difference in the overall and heart failure related healthcare costs between subjects treated with the Furoscix Infusor through 30 days post discharge from the emergency department compared to propensity score matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge. Overall and heart failure related healthcare costs comprised of all direct medical costs attributable to healthcare resource utilization incurred overall and for treatment of HF.

6.1.2. Assessment of Secondary Endpoints

The difference in the measurements listed below between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department compared to propensity score matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge.

1. Number of hospital admissions and duration with-in 30 days post discharge from the emergency department
2. Number of HF-related hospital admissions and duration with-in 30 days post discharge from the emergency department
3. Number of HF-related emergency department visits with-in 30 days post discharge from the emergency department
4. Number of HF-related clinic visits with-in 30 days post discharge from the emergency department
5. Description of health-related quality of life using the KCCQ-12 (for the Furoscix Infusor arm only)
6. Change in BNP or NT-proBNP (for Furoscix Infusor cohort only)
7. Subject and/or caregiver satisfaction with Furoscix Infusor (for Furoscix Infusor cohort only)

6.1.3. Safety Assessments

The Furoscix treatment cohort will be monitored for adverse events, and any adverse events will be recorded and reported according to guidelines specified by the United States Food and Drug Administration. Reactions at the infusion site and frequency of these reactions will be recorded as part of the safety assessments.

6.2. Study Phases and Procedures

The Screening Phase will be conducted in the emergency department in a collaborative effort between the emergency physician and the cardiologist. 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. Study drug administration can start on the day of screening and enrollment, and administration may commence either in the emergency department or at home.

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 $\geq$ 2 hours after the completion of the first dose. Subjects should be transitioned back to their oral maintenance diuretic regimen when clinically indicated at the discretion of the investigator (approximately 4 doses). After Subjects have been transitioned to their oral maintenance diuretic regimen, additional doses of Furoscix can be prescribed during the 30-day study period as needed based on the presence of clinical triggers (dyspnea on exertion, edema, and/or excess weight gain) as determined by the investigator. No more than 7 doses of Furoscix is permitted during the

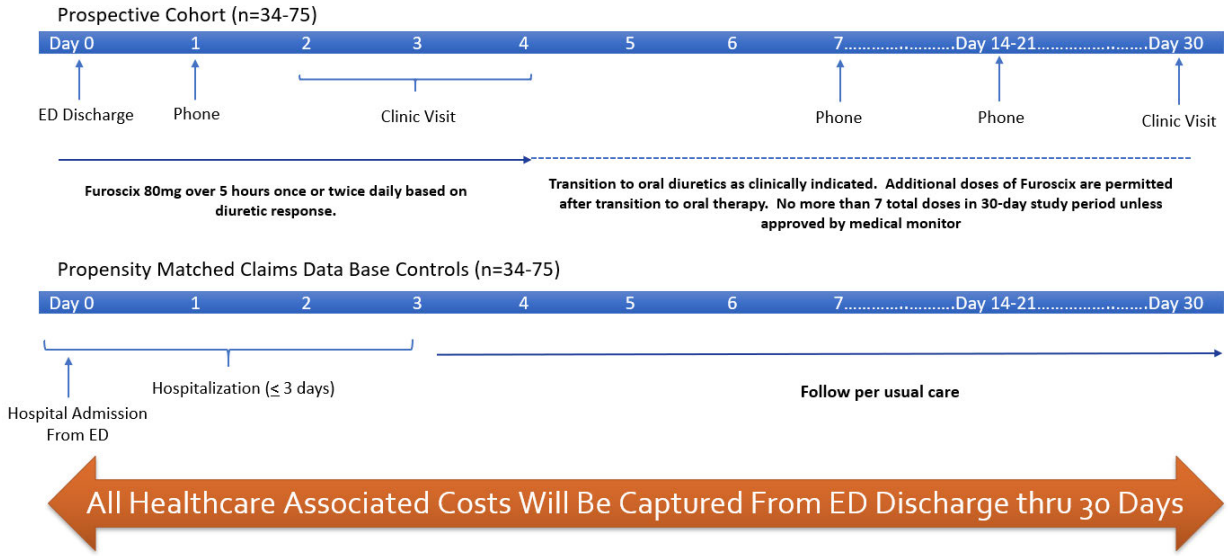
30-day study period. Additional doses beyond 7 requires approval by the medical monitor. If subjects receiving Furoscix are hospitalized for heart failure during the treatment period, Furoscix should be discontinued and the subject treated with IV diuretics as clinically indicated. In addition to the scheduled phone and clinic visits, the investigator can utilize unscheduled clinic or phone visits for additional assessments at any time.

Prior to leaving the emergency department 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 on the day of enrollment. Some subjects may not require their initial dose until the next day. Doses will be provided to the patient for self-administration or administration by a caregiver in the home setting as directed by the investigator or study staff. No more than 7 doses of Furoscix are permitted during the 30-day study period unless approved by the medical monitor. Planned in-person follow-ups include a clinic visit occurring between Days 2-4 and a clinic visit on Day 30±3 days. Scheduled remote follow-ups conducted by telephone by a HF nurse, or designee, will occur on Days 1 and 7, and one call between Days 14-21. Unscheduled at-home telephone calls and unscheduled in-clinic visits may be performed if felt clinically indicated by the study team or the clinical provider.

The Follow-Up Phase will occur on Day 30±3 days for a post treatment follow-up visit completing Subjects' study participation.

Refer to Figure 2 for an overview of study phases and procedures. Note that the depiction in Figure 2 of Furoscix administrations after Day 1 is for demonstration purposes. Again, the investigator can prescribe additional Furoscix dosing and administration at his/her discretion as long as this does not conflict with safe use practices as defined in this protocol and supplementary materials.

Figure 2: Study Phases and Procedures



6.2.1. Screening Phase (Day 0)

The initial Screening assessment will be conducted the same day as the start of the Treatment Phase and will occur in the emergency department.

The following procedures/assessments will be performed at Screening:

- Informed consent (must be completed prior to any of the following procedures)
- Eligibility review
- Medical history and Subject demographics
- Cardiopulmonary Exam including NYHA Classification
- Weight and height obtained for body mass index (BMI)
- Vital Signs
- Venous blood for clinical chemistries, hematology, BNP or NT-proBNP
- Urine pregnancy test on females of child bearing potential
- Administer the KCCQ-12 (short form)
- Perform site skin assessment where the study product will be placed
- Record concomitant medications (all medications taken within 7 days prior to dosing)
- Study product training with subject and/or caregiver
- Assessments and laboratory tests done as usual care within 12 hours of study enrollment may be collected and entered into the eCRF for the study.

6.2.2. Treatment Phase (Day 0 – Discretion of the investigator)

After the screening activities have been completed and eligibility confirmed, the subject may be enrolled into the Treatment Phase.

The treatment includes a daily, preprogrammed bi-phasic 5 hour drug administration via the Furoscix Infusor. Eighty (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 (approximately 4 doses). After Subjects have been transitioned to their oral maintenance diuretic regimen, additional doses of Furoscix can be prescribed during the 30-day study period as needed based on the presence of clinical triggers (dyspnea on exertion, edema, and/or excess weight gain) as determined by the investigator. No more than 7 doses of Furoscix is permitted during the 30-day study period. Additional doses beyond 7 requires approval by the medical monitor.

Prior to leaving the emergency department 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 on the day of enrollment. Some subjects may not require their initial dose until the next day. Doses will be provided to the patient for self-administration or administration by a caregiver in the home setting as directed by the investigator or study staff.

For all treatment days, these data will be recorded in the Subject Diary daily by the subject and reported to the study staff during phone contacts:

- Infusor start and stop times for each dose
- Diuretic use in addition to the study drug (name, route, dose)
- Assessment for adverse events
- Assessment for interval hospitalizations, emergency department visits, or unscheduled clinic visits

The subject will be reminded to complete the Subject Diary daily for each dose, recording the start and end time for each dose and any issues preparing the dose.

6.2.3. Day 1 and 7 (Telephone Call Follow-Up)

Telephone call follow-ups will be conducted by an HF nurse, or designee, on Days 1 and 7 post discharge from the ED. The primary purpose of the follow-up telephone calls will be to evaluate the safety and efficacy of diuresis and the need to adjust diuretic therapy. The telephone follow-up will be guided by a suggested Telephone Script. Assessments during each phone call will include:

- Suggested Telephone Script to review Subject Diary
- Infusor start and stop time for each dose
- Change in diuretic treatment since last point of contact (record on concomitant medication form)
- Assessment for adverse events
- Assessment for interval hospitalizations, emergency department visits, or unscheduled clinic visits
    - Been admitted to the hospital
    - Been admitted to the hospital for HF-related issues
    - Been seen at the emergency department for HF-related issues
    - Been seen in an outpatient clinic (including immediate care clinic) for HF-related issues
    - Sought any additional or new medical treatment for HF-related issues
- Problems with drug or device use

6.2.4. Day 2-4 (In-Clinic visit)

The following procedures/assessments will be performed at the Day 2-4 in-clinic visit:

- Interim medical history and medication review
- Cardiopulmonary Exam, focused on signs and symptoms of congestion
- NYHA Classification

- Weight obtained for BMI
- Vital Signs
- Venous blood for clinical chemistries, hematology, BNP or NT-proBNP
- Change in diuretic treatment since last point of contact (record on concomitant medication form)
- Assessment for selective electrolyte replacement (record on concomitant medication form)
- Comfort of Wear Questionnaire
- Abdominal skin assessment
- Assessment for adverse events
- Assess for interval hospitalizations, emergency department visits, or unscheduled clinic visits
  - Been admitted to the hospital
  - Been admitted to the hospital for HF-related issues
  - Been seen at the emergency department for HF-related issues
  - Been seen in an outpatient clinic (including immediate care clinic) for HF-related issues
  - Sought any additional or new medical treatment for HF-related issues
- Problem with drug or device use
- Review of Subject Diary for completeness
- Return of all used study devices

6.2.5. Days 14 – 21 (Telephone Call Follow-Up)

Telephone call follow-ups will be conducted by an HF nurse, or designee, as deemed necessary by the investigator between Days 14-21. The primary purpose of these calls will be to assess whether the subject has experienced or is experiencing a study related adverse event, to assess status of change back to oral medication, and to assess congestion.

The suggested script for conducting these telephone calls is the same that is described previously and will include:

- Suggested Telephone Script
- Additions or discontinuations of concomitant medications as per section 5.7 (record on concomitant medication form)
- Assessment for adverse events
- Assessment for interval hospitalizations, emergency department visits, or unscheduled clinic visits
  - Been admitted to the hospital
  - Been admitted to the hospital for HF-related issues
  - Been seen at the emergency department for HF-related issues
  - Been seen in an outpatient clinic (including immediate care clinic) for HF-related issues
  - Sought any additional or new medical treatment for HF-related issues
- Device start and stop time for each dose (if received study drug after Day 2-4 clinic visit)
- Problems with drug or device use (if received study drug after Day 2-4 clinic visit)

6.2.6. Day 30 ± 3 days (In-Clinic Visit)

The following procedures/assessments will be performed at the Day 30 in-clinic visit:

- Directed medical history and medication review
- Cardiopulmonary Exam focused on signs and symptoms of congestion
- NYHA Classification
- Weight for BMI
- Vital Signs

- Venous blood for clinical chemistries, hematology, BNP or NT-proBNP
- Administer the KCCQ-12
- Abdominal skin assessment
- Assessment of adverse events
- Assessment of interval hospitalization, emergency department visits, or unscheduled clinic visits
  - Been admitted to the hospital
  - Been admitted to the hospital for HF-related issues
  - Been seen at the emergency department for HF-related issues
  - Been seen in an outpatient clinic (including immediate care clinic) for HF-related issues
  - Sought any additional or new medical treatment for HF-related issues

Information regarding HF-related healthcare utilization collected before and at the 30-day in-clinic visit will be verified by the investigator through subjects' medical records.

6.2.7. Unscheduled Telephone Calls and Clinic Visits

There are two forms of unscheduled follow-ups specified in this protocol: telephone call and clinic visit. These may be assigned at any time at the discretion of the investigator and may arise from a request by the subject or caregiver, a request by the HF nurse, or designee, conducting telephone follow-ups, or by the judgement of the investigator. Note that the investigator can pre-specify at any time the number and timing of unscheduled follow-up visits.

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 will be performed:

- Cardiopulmonary Exam including NYHA Classification
- Vital Signs
- Weight
- Labs drawn at the discretion of the investigator (including BNP or NT-proBNP)
- Assess for adverse events

All subjects will have the option to receive unscheduled phone call by an HF nurse, or designee, at any time following the initial discharge from the emergency department. The primary purpose is to respond to issues affecting proper use and administration of the Furoscix Infusor. While these calls will follow according to the aforementioned script, the HF nurse, or designee, will address - per his or her best professional judgement - specific issues reported by the patient or caregiver.

Additionally, the HF nurse, or designee, will ask (and document the responses) whether the subject has since the previous follow-up:

- Been admitted to the hospital
- Been admitted to the hospital for HF-related issues
- Been seen at the emergency department for HF-related issues
- Been seen in an outpatient clinic (including immediate care clinic) for HF-related issues
- Sought any additional or new medical treatment for HF-related issues

6.2.8. Cardiopulmonary Examinations

A cardiopulmonary examination will be performed consisting of assessments of the following: jugular venous distension, lungs/chest, heart, abdomen and edema.

6.2.9. BNP or NT-proBNP Assessments

BNP or NT-proBNP will be tested at all clinic visits (scheduled and unscheduled), sent to a local laboratory, and values recorded in the CRF.

6.2.10. 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: Creatinine, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, magnesium
- Hematology: (CBC): Red blood cell count (RBC), Total white blood cell count (WBC), Differential WBC (neutrophils, lymphocytes, monocytes, eosinophils, basophils), Hemoglobin, Hematocrit (Hct), and Platelet count
- Urine Pregnancy test: beta hCG 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.

6.2.11. Heart Failure Symptom Scoring

NYHA Functional classes will be used in this study.

Class 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.

Class 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.

Class 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.

Class 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.

6.2.12. Vital Signs

Vital signs will include respiratory rate (respirations per minute), blood pressure (mmHg) and heart rate (beats per minute). Blood pressure and heart rate will be obtained after the Subject has been resting in sitting position for 5 minutes.

Weight and height will be collected for BMI. Height collected Day 0 only.

6.2.13. Kansas City Cardiomyopathy Questionnaire – Short Form (KCCQ-12)

The KCCQ-12 consists of 12 items pertaining to the impact of HF on quality of life. This self-administered instrument quantifies physical function, symptoms, social function, self-efficacy and knowledge, and quality of life.

6.2.14. Comfort of Wear Questionnaire

Subjects will complete a comfort of wear questionnaire at the clinic visit. The questionnaire includes questions regarding the comfort of the device while performing activities as well as subject/caregiver satisfaction with the device/study product.

6.2.15. 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 Furoscix Infusor IFU and a demonstration device. The trainer will have the subject/caregivers perform the steps following the IFU. Using the demo device, subjects and their caregivers will demonstrate their ability to properly prepare and place the device prior to leaving the ED. Additionally, subjects and caregivers will receive upon discharge the IFU and subject specific instructions and will have planned and on-demand phone calls with an HF nurse, or designee, to discuss any issues.

6.2.16. Skin Inspection

Study staff will inspect the skin on the subject's abdomen during screening and subsequent in-clinic visits. Any anomalies will be recorded. Subjects and their caregivers will also be instructed to monitor for any skin reactions after dosing.

7. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the definition of an adverse event (AE) or serious adverse event (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, and Definitely Related to the investigational product.

7.1. Definition of an Adverse Event

An AE is any untoward medical occurrence associated with the use of an investigational product in humans, whether or not considered related to the investigational product. 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, and does not imply any judgment about causality. An adverse event can arise with any use of the investigational product (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 administration of the investigational product 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 course of 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 electrocardiogram, pulse oximetry, or spirometry) that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to interruption or discontinuation of the investigational product, must be considered an AE.

All AEs judged to be clinically significant, including clinically-significant laboratory, electrocardiogram 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 investigational 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:

- 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 an Adverse Reaction

An adverse reaction means any AE caused by an investigational product. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the investigational product caused the event.

7.3. Definition of a Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the investigational product caused the adverse event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the investigational product and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

7.4. Definition of an Unexpected Adverse Event

An adverse event or Suspected Adverse Reaction is considered “unexpected” if it is not listed in the investigator brochure, product labeling or is not listed at the specificity or severity that has been observed.

7.5. Definition of a Serious Adverse Event

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 department.
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 department or at home, blood dyscrasias or convulsions that do not result in Subject hospitalization, or the development of drug dependency or drug abuse.
    - NOTE: Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

7.6. Severity of Adverse Events and Serious Adverse Events

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.

The severity (mild, moderate, or severe) of each AE or SAE must be assessed by the Investigator or designee.

7.7. Outcome of Adverse Events and Serious Adverse Events

Not Recovered / Not Resolved - One of the possible results of an AE outcome that indicates that the event has not improved or the patient recuperated.

Recovered / Resolved - One of the possible results of an AE outcome that indicates that the event has improved or patient recuperated.

Recovered / Resolved with Sequelae - One of the possible results of an AE 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 AE 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 AE.

7.8. 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 investigational product. 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 AE to dosing and drug pharmacology, there is no reasonable relationship between the investigational product and the AE.

Possibly Related - Relationship exists between the AE and IP, when the AE follows a reasonable sequence from the time of the investigational product administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.

Probably Related - Relationship exists between the AE and the investigational product when the AE follows a reasonable sequence from the time of investigational product administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the investigational product and the investigational product is the most likely of all causes.

Definitely Related - Relationship exists between the AE and the investigational product when the AE follows a reasonable sequence from the time of the investigational product administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the investigational product and no other reasonable cause exists.

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

AEs and SAEs will be assessed in the frequency and manner as described in Section 6.2 of this protocol.

7.10. Reporting Serious Adverse Events

7.10.1. Timeframes for Reporting Serious Adverse Events

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.

7.10.2. Serious Adverse Event 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 and causality is very important and must be included in the initial report as it may impact expedited regulatory reporting requirements for the event.

There may be instances when copies of medical records for certain cases are 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 and SAE pages. If medical records are submitted, all Subject personal identifiers must be completely redacted prior to submission.

7.10.3. Other Assessments as Adverse Events and Serious Adverse Events

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., electrocardiogram, 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.

7.10.4. Documenting Adverse Events and Serious Adverse Events

All AEs, 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.

7.10.5. Regulatory and Ethics reporting requirement

The Investigator will comply with the applicable local regulatory requirements related to the reporting of SAEs to the Institutional Review Board.

7.10.6. Follow-up of Adverse Events and Serious Adverse Events

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. 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.

8. STATISTICS

8.1. Determination of Sample Size

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

Given the anticipated overdispersion of the primary outcome (i.e., difference in total HF-attributable direct medical costs), we will employ adaptive trial design procedures for sample size re-estimation. This adaptive-total information criterion approach was taken due to the risk of incorrectly estimating the sample size due to misspecification of the cost outcome parameters. By using the adaptive sample size design, which includes no penalty for repeated interim analysis, the final sample size will be sufficient to provide adequate power to test the stated hypothesis.

This will include re-assessment of the sample size at N=34 in the Furoscix cohort by using a group sequential design and testing to allow for stopping. It is not expected that the sample size for the Furoscix Infusor arm would exceed N=75, but the maximum value cannot be definitively stated until the analysis at N=34 is completed.

We will explore ratios ranging from 1:1 to 4:1 for the number of historical controls to be matched to Furoscix-treated patients using methods reported by Millar and Pasta 2010. The simulations will be used to find the matching ratio at which the level of precision is optimized without biasing the variance of the outcome measure. Additional methodological details are described in the prespecified statistical analysis plan.

The methodology by which the sample size will be re-estimated and stopping rules will be implemented will be detailed in the statistical analysis plan.

8.2. Baseline Characteristics and Subject Disposition

Overall Baseline and demographic data will be summarized using descriptive statistics. Subject disposition (e.g., the number of Subjects enrolled, completed, and discontinued) will be summarized and medical history data will be listed.

8.3. Endpoint Analyses

Full descriptions of statistical assessments for primary and secondary endpoints are given in a separate statistical analysis plan. Included herein are brief descriptions.

8.3.1. Primary Endpoint

The primary endpoint analysis will compare the difference in the overall and heart failure related healthcare costs between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department for worsening heart failure due to fluid overload with propensity score matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge. Propensity scoring methods will be described in the statistical analysis plan. Comparison of these data between the matched (paired) cohorts will be conducted via a t-test or a Wilcoxon signed-rank test depending on distribution of data.

8.3.2. Secondary Endpoints

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

8.4. Safety Analyses

There are no pre-planned analyses to compare Furoscix versus hospitalized cohort on the basis of safety. However, the safety of Furoscix will be monitored during the trial, and identified safety issues (including AEs, SAEs, and adverse reactions) will be summarized descriptively for the Furoscix cohort.

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

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), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use 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 investigational new drug application, 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. This study is also subject to and will be conducted in compliance with 21 CFR, part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

9.1.2. Institutional Review Board and Independent Ethics Committee 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 institutional review board or independent ethics committee. Approval from these bodies 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 will be submitted to these bodies 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 a consent form approved by the institutional review board for documenting written informed consent. Each completed 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 institutional review board, the Subject, or the appropriate regulatory authority) must be kept in confidence by the Principal Investigator.

The Investigator will 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 institutional review board. 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 will 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, CRF and query forms, approval by the institutional review board with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, 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, appointment book, original laboratory reports, electrocardiogram, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, 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 region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in the region(s); or, until two years after the investigational new drug 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 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

If a situation requires a deviation from the Clinical Study Protocol, the Principal Investigator or other investigator in attendance will contact the Medical Monitor as soon as possible in order to discuss the situation and agree on an appropriate course of action. If possible, the Principal Investigator or designee will contact the Medical Monitor prior to making the deviation. Any departure from the Clinical Study Protocol together with the rationale for the deviation must be recorded on the CRF and source document.

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 Food and Drug Administration, by scPharmaceuticals and its designees, and the institutional review board 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 the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

9.1.10. Financial Disclosure

The United States Food and Drug Administration 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 Food and Drug Administration in support of an application for market approval.

9.1.11. Drug and Device Product Accountability

The Investigator or designee 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.

At the end of the study, following final product reconciliation by the monitor, the study site will be instructed by the Sponsor to return all unused study product supplies.

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 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. Approval from an institutional review board must be obtained before changes can be implemented.

Note that this provision does not apply to early stopping or sample size increases that are governed by the adaptive nature of the clinical trial design.

9.3. Joint Investigator and Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

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

The monitor is responsible for routine review of the CRF 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 CRF. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of 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 authorities and institutional review board(s). In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the Subjects' interests.

Note that this provision does not apply to early stopping or sample size increases that are governed by the adaptive nature of the clinical trial design.