St. Elizabeth's Medical Center
736 Cambridge St, Brighton, MA 02135

CLINICAL PROTOCOL

An Open Label, Descriptive Study to Evaluate the Clinical Utility of a Novel Formulation of Furosemide Delivered Subcutaneously in Patients Presenting with Early Signs of Fluid Overload

IND Number:	Pending
Protocol Number:	Version 4.0
Protocol Date:	August 30, 2017
NCT Number	NCT03359161

Sponsor

St. Elizabeth's Medical Center
736 Cambridge St, Brighton, MA 02135

Study Sponsor: St Elizabeth's Medical Center

Principal Investigator: Lana Tsao. MD
St. Elizabeth's Medical Center
736 Cambridge St, Brighton, MA 02135
Phone: 617-789-3041
Email: Lana.Tsao@Steward.org

Co- Investigator Maxwell Eyram Afari, MD
St. Elizabeth's Medical Center
736 Cambridge St, Brighton, MA 02135
Phone: 617-789-3041
Email: Maxwell.Afari@Steward.org

Study Coordinator: Margaret Michaelian
St. Elizabeth's Medical Center
Cardiovascular Medicine Research Office
736 Cambridge St, Brighton, MA 02135
617-789-3041
margaret.michaelian@steward.org

Coordinating Center: Margaret Michaelian
St. Elizabeth's Medical Center
Cardiovascular Medicine Research Office
736 Cambridge St, Brighton, MA 02135
617-789-3041
margaret.michaelian@steward.org

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title: An Open Label, Descriptive Study to Evaluate the Clinical Utility of a Novel Formulation of Furosemide Delivered Subcutaneously in Patients Presenting with Early Signs of Fluid Overload

Protocol Number: Version 4.0

By my signature, I _____

• agree to conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of Subjects.

• agree to personally conduct or supervise the described investigation(s).

• agree to inform any patients, or any persons used as controls, that the study product is being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

• agree to report to the Sponsor adverse experiences that occur 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.

• agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

• agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

• will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

• agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Investigator's Signature: Date

Print Name:_____

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACC	American College of Cardiology
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
AHA	American Heart Association
BMP	Basic Metabolic Panel
BUN	Blood Urea Nitrogen
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eGFR	Estimated Glomerular Filtration Rate
ER	Emergency Room
FDA	Food and Drug Administration
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
NT-proBNP	pro-B-type natriuretic peptide
SEMC	St Elizabeth's Medical Center
SAR	Suspected advanced reactions
NYHA	New York Heart Association
SQ	Subcutaneous

2 EXECUTIVE SUMMARY

SYNOPSIS	
PROTOCOL TITLE	An Open Label, Descriptive Study to Evaluate the Clinical Utility of a Novel Formulation of Furosemide Delivered Subcutaneously in Patients Presenting with Early Signs of Fluid Overload
PROTOCOL NUMBER	Version 4.02
INVESTIGATOR	Lana Tsao, MD Director Advanced Heart Failure Program Associate Professor of Medicine, Tufts University School of Medicine. St. Elizabeth's Medical Center (SEMC) 736 Cambridge St, Brighton, MA 02135
INVESTIGATIONAL PRODUCT	Furosemide Injection, 8 mg/mL, (total dose =80 mg) administered subcutaneously by the sc2Wear Furosemide Infusor using a biphasic profile with 30 mg over the first hour and then as 12.5 mg per hour over the subsequent 4 hours. Participants may be prescribed a total of 3 days initial treatment followed by an optional additional 4 days of sc2Wear furosemide treatment based on initial clinical response.
STUDY OBJECTIVES	The Objectives of this study are: 1.) Evaluate the clinical effect of sc2Wear furosemide Infusor in the in-home management of mild to moderate decompensated heart failure. 2.) Evaluate the safety and tolerability of sc2Wear furosemide Infusor in the in-home management of mild to moderate decompensated heart failure.
STUDY ENDPOINTS	Efficacy • The treatment effect will be described as:

	• % weight loss between enrollment/screening compared to Post Visit #1 and Post Visit #2 • Reduction in pro-BNP between enrollment/screening compared to Post Visit #1 and Post Visit #2 • Proportion of patients requiring additional 4 days of diuresis based on a set of pre-defined criteria. • % of patients alive 30 days post enrollment • % of patients without hospitalization for worsening HF within 30 days after enrollment • % of patients without a significant HF related medical events within 30 days after enrollment. Safety • The safety of the sc2 Wear furosemide Infusor drug-device combination will be assessed by the incidence of adverse events. • Discontinuation due to presence of skin reaction to drug or device/adhesive.
STUDY DESIGN & DURATION	<u>Study Design:</u> This is a prospective, open-label, descriptive two-phase study to evaluate the clinical effectiveness of a novel formulation of furosemide delivered by subcutaneous administration. In the first phase of the study (Pilot Phase) the practicality and safety of the novel in-home treatment alternative will be evaluated in 20 patients presenting with mild to moderate decompensated heart failure to the cardiology service at St Elizabeth's Medical Center (SEMC) at Brighton, Massachusetts. After completion of the first phase, the representatives of the sponsor and scPharmaceuticals will convene to review the

	experience and results and consider any adjustments to the study or workflow before commencing the Evaluation Phase of the study in which an additional 40 patients will be recruited. The Evaluation Phase may involve participation by other Steward Health Care System hospitals. Adjustments to the study procedures are subject to IRB review and approval. Participants will be treated daily for 3 consecutive days at home after an assessment in the cardiology clinic. Patients will be homebound during the episode of care for decompensated heart failure. Patients will be visited daily by Steward Home Care and Hospice for home health nursing services. In the evening, participants will have the opportunity to supplement diuresis with their usual oral diuretic dose. Patients will be evaluated by a cardiologist at SEMC within 24 hours after the 3rd dose of sc2Wear furosemide. If a patient was found to have satisfactorily responded but requires additional parenteral diuretics an additional 4 days may be prescribed for a total of 7 consecutive treatments. Additionally, up to three sc2Wear furosemide at home treatments may be used as authorized by the treating physician in case the patient experience worsening of heart failure from day 7 to up to 30-days after enrollment. Response will be based on the weight loss, decrease in pro-BNP, or improvement in the dyspnea scale. If additional units are prescribed, patients will be re-evaluated by a cardiologist within 24 hours after the last dose of sc2Wear furosemide. Participants will require a final follow up with a cardiologist at 30-33 days after the start of the study for a post treatment interview and assessment. The protocol is subject to IRB review and approval. The study will be conducted under an Investigator-Initiated Investigational New Drug (IND) Application.
STUDY PROCEDURES	Screening Phase: The cardiology service will screen patients with mild to moderate fluid overload. Patients who present with other serious or life threatening condition for which hospitalization would be indicated are excluded. Women of child bearing potential will be screened for pregnancy with a urine pregnancy

	test. Eligible participants will be educated on device preparation, placement, removal and care in accordance with the Instructions of Use Manual. The screening phase includes evaluation of the home situation to ascertain that sufficient support is or can be made available for at home treatment as an alternative to inpatient care. In appropriate settings, lay caregiver will also be trained. **Pilot Phase.** Patients will be visited daily by Steward Home Care and Hospice for home health nursing services in accordance with standard procedures. Nursing services will include checking vitals, obtaining blood samples and evaluation for clinical improvement or worsening. The first visit will be performed within 24 hours after enrollment. The first sc2Wear Infusor will be prepared and placed on the patient as part of the training. The patient will go home with the sc2Wear furosemide Infusor in place on the abdomen to be activated upon arrival at home. Participants will be treated with the sc2Wear furosemide Infusor daily for 3 consecutive days at home. Participants will be evaluated by the cardiology service of SEMC within 24 hours after the 3rd dose of sc2Wear furosemide. If a patient was found to have responded satisfactorily but requires additional parenteral diuretics an additional 4 days may be prescribed for a total of 7 consecutive treatments. If additional units are prescribed patients are to be evaluated the cardiology service of SEMC within 24 hours after the last dose of sc2Wear furosemide Infusor. If the subject requires further parenteral diuresis after the 7 days of at home treatment, they will be converted to usual care at that time, which may require inpatient care. Participants will be instructed to record daily morning weights during and after treatment until the second post treatment evaluation. Interim clinic visits and laboratory assessments may be required based on clinical considerations. The following parameters will be studied at Baseline and follow-up treatment visits.

	• Body Weight • Vital signs • HF Physical examination • Dyspnea scale • Routine laboratory panel (incl. electrolyte, pro-BNP) • Adverse events • Injection site assessment Participants will visit the clinic 30 ± 3 days after the start of the study for a post treatment evaluation. **Evaluation Phase** The Evaluation Phase mirrors the Pilot Phase except that attempts will be made to test pre-defined clinical care paths based on the lessons of the Pilot Phase. Up to two additional Steward Health Care sites may participate in the Evaluation Phase.
SC2WEAR TREATMENT	Novel Furosemide Injection formulation at neutral pH, 8 mg/mL, (total dose =80 mg) administered subcutaneously by means of the sc2Wear Infusor as 30 mg over the first hour and then as 12.5 mg per hour over the subsequent 4 hours. Participants will be treated for 3 sequential days with one dose of sc2Wear Furosemide Infusor (80mg) daily. It is generally recommended that the sc2Wear infusor be applied in the morning. Oral diuretics should be continued concomitantly If a patient was found to have satisfactorily responded but requires additional parenteral diuretics an additional 4 days may be prescribed for a total of 7 consecutive treatments. Additionally, up to three sc2Wear furosemide at home treatments may be used as authorized by the treating physician in case the patient experience worsening of heart failure from day 7 to up to 30-days after enrollment. (Rescue Treatment).

NUMBER OF SUBJECTS	60 (20 in Pilot Phase, 40 in Evaluation Phase)
NUMBER OF SITES	Pilot Phase: St Elizabeth's Medical Center Evaluation Phase: Up to three hospitals in the Steward Health Care System
PARTICIPATING COUNTRIES	U.S.
SUBJECT POPULATION	Male and female patients over the age of 18 with mild to moderately decompensated heart failure not requiring hospital admission for care. Subjects may be enrolled in the study only if all inclusion criteria and none of the exclusion criteria are met.
INCLUSION AND EXCLUSION CRITERIA	Inclusion Criteria: 1. Age≥ 18 years 2. Symptomatic and chronic heart failure (NYHA Class II and III). 3. Patients on guideline directed medical therapy 90 days prior to enrollment. 4. Adequate home environment for at-home treatment. 5. Presenting or referred to the ER or clinic because of evidence of worsening heart failure with fluid overload (decompensation) 6. A modification in oral diuretics is not clinically appropriate as deemed by the investigator. 7. Estimated excess fluid weight of 4 lbs. or more from euvolemic state. 8. Participant able to give informed consent for participation in trial. Agreeing to sign informed consent and HIPAA authorization. 9. Understanding and willing to comply with the protocols of the trial. 10. Ability of the participant or caregiver to independently apply the investigational device and medication. Exclusion Criteria: 1. ACC/AHA Stage D heart failure or patients requiring IV inotrope therapy

	2. Massive volume overload (e.g., >20 lbs. of estimated fluid weight) or anasarca. 3. Suspected high risk clinical instability with outpatient treatment. 4. Pregnant females or women of child-bearing age who are not willing to use an adequate form of contraception. 5. Chronic Obstructive Pulmonary Disease (COPD) moderate or worse: FEV1/FCV ratio <0.7 and FEV1 <60 percent predicted. 6. Rapid atrial fibrillation (AF) (HR >100b/min). 7. Hypoxia (resting O2 saturation <90%). 8. Hypotension (systolic blood pressure (SBP) BP < 90 mmHg). 9. Uncontrolled diabetes mellitus (DM) (admission glucose levels > 300 mg/dL). 10. Advanced renal disease (eGFR < 30mL/min/1.73m2). 11. Acute coronary syndrome. 12. Serum potassium (K+) <3.2 mmol/L or > 5.5mmol/L. 13. On experimental medication or currently participating in an interventional cardiovascular research study, other than an observational or registry study. 14. Having received intravenous furosemide within 24 hours prior to enrollment. 15. Urinary tract abnormality or disorder interfering with urination 16. Allergy to the active and inactive ingredients of the study medication. 17. Inability to comply with study requirements. 18. Dementia. 19. Ongoing substance abuse. 20. Concern that the current episode of decompensation was precipitated by a serious medical condition which

	may require additional evaluation or treatment.
STATISTICAL ANALYSIS	Primary Outcome Description of treatment effect and as described in the study endpoints. Description of the seriousness, severity, relatedness of all adverse events observed during the study period.

1)

3 INTRODUCTION

3.1 BACKGROUND

Over 650,000 new heart failure cases are diagnosed annually, and it is estimated that one million people get hospitalized per year.[1] Readmission rates at 30 days and 6 months are estimated to be 25% and 50% respectively. Approximately 5 million people in the United States have symptoms or signs of heart failure with a $30 billion annual cost to the US healthcare system. Hospitals across the country have come up with practical and pragmatic strategies to manage acute decompensated heart failure (ADHF) in the ambulatory setting due to fiscal incentives.[2,3]
The oral bioavailability of furosemide varies from 20% to 90% and in ADHF the absorption of furosemide has been found to be unpredictable.[4] It is hypothesized that in ADHF, there is "gut edema", which makes it difficult for the absorption of oral furosemide. Thus, intravenous diuretic therapy has become the cornerstone of the treatment of patients with ADHF. However, intravenous (IV) therapy requires the placement of central or peripheral lines, usually placed and managed by health care practitioners. This is associated with increased maintenance expense, associated patient discomfort, and possible line complications. Also the disposition of patients to home as compared to nursing home rehabilitation facilities can be influenced by the type of IV line placed.

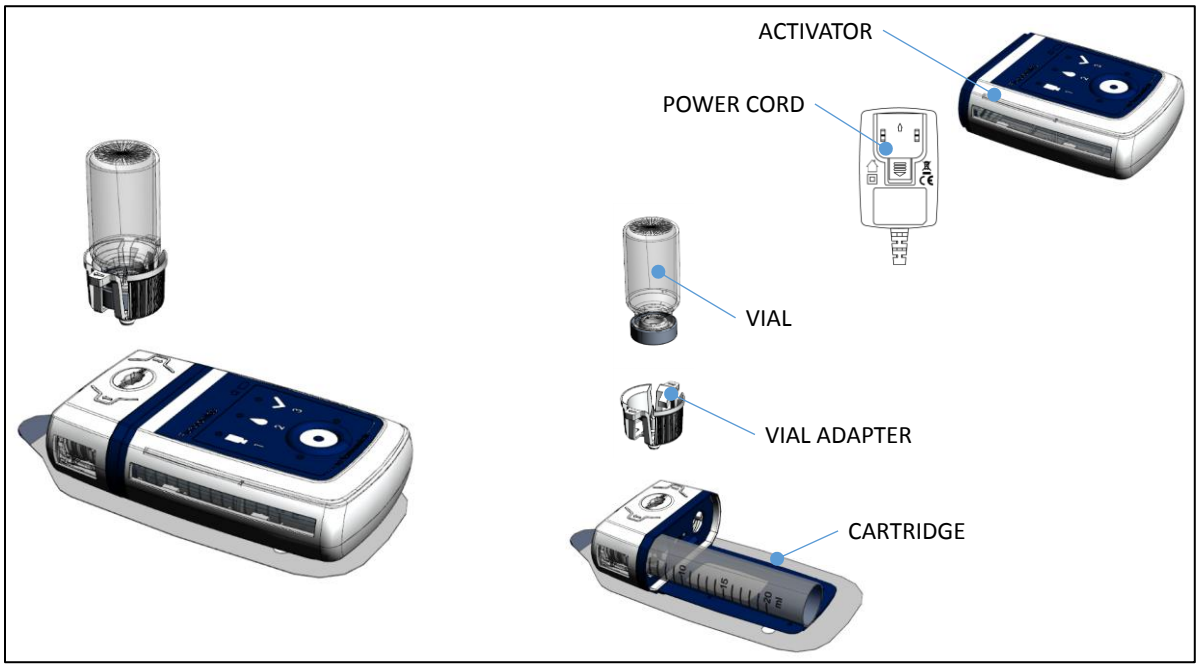
Subcutaneous furosemide has been proposed as an alternative to the delivery of parenteral loop diuretics. scPharmaceuticals, Inc (Burlington, MA, USA) has developed a subcutaneous formulation of furosemide injection, Furosemide Injection Solution (SCP-101) with a proprietary infusion pump for this purpose. Commercially produced furosemide USP is alkaline, with a pH of 8.0 to 9.3, and hence could cause irritation of the subcutaneous tissue. The proprietary SC formulation is the first buffered furosemide injection solution, which is isotonic, and has a neutral pH of 7.4. The sc2Wear™ Furosemide Infusor (scPharmaceutical Inc, Burlington, MA) is a two-component design, which combines a reusable component and a cost-effective single-use cartridge (**Figure 1**).

3.2 PRELIMINARY DATA

The sc2Wear™ Furosemide Infusor is designed to deliver a total of 80mg of parenteral furosemide over a period of 5 hours via SC infusion (30mg in hour 1, then 12.5 mg/hour over the next 4 hours). Pivotal pharmacokinetic and pharmacodynamics study evaluating a novel formulation of furosemide have shown 99.6% bioavailability with subcutaneous administration versus intravenous administration of the current parenteral formulation of furosemide. The subcutaneous furosemide formulation was also well tolerated with minimal skin reactions.[5] Subcutaneous infusion of furosemide has similar bioavailability as intravenous therapy with

therapeutic levels of furosemide achieved within 30 minutes.[6-8] Compared to people who got injected with normal saline (control), subcutaneous administration of furosemide was found to increase diuresis in normal volunteers.[9]

Figure 1. The sc2Wear™ Furosemide Infusor.



4 OBJECTIVES

1) Evaluate the clinical effectiveness of sc2Wear furosemide Infusor in the in-home management of mild to moderate decompensated heart failure.

2.) Evaluate the safety and tolerability of sc2Wear furosemide Infusor in the in-home management of mild to moderate decompensated heart failure.

5 OVERALL STUDY DESIGN

This is a prospective, open-label, two-phase study to evaluate the clinical utility of subcutaneous administration of a novel furosemide formulation. In the first phase of the study (Pilot Phase), the practicality and safety of the novel in-home treatment alternative will be evaluated in 20

patients presenting with mild to moderate ADHF to the cardiology service at St Elizabeth's Medical Center, Brighton, Massachusetts (SEMC).
After completion of the first phase, representatives of the sponsor and scPharmaceuticals will convene to review the experience and results and consider any adjustments to the study or workflow before commencing the Evaluation Phase of the study in which an additional 40 patients will be recruited. Adjustments to the study procedures are subject to IRB review and approval. The Evaluation Phase may involve participation by up to three Steward Health Care System hospitals.

Participants will be treated for 3 consecutive days at home. The sc2Wear™ Furosemide Infusor therapy is intended to be performed by the patient or a lay caregiver. Patients will be homebound during the episode of care for decompensated heart failure. Steward Home Care and Hospice will visit patients daily for home health nursing services. Participants will be visited at home by a visiting nurse who will give them further teaching on the sc2Wear™ Furosemide Infusor. The visiting nurse will also be responsible for obtaining history (symptoms), physical examination (including inspecting the skin for adverse reactions related to the pump), and laboratory draws, supplementation of electrolytes as needed and administration of the dyspnea scale.

Patients will be evaluated by the cardiology service of SEMC within 24 hours of the last dose of the sc2Wear™ Furosemide Infusor. If a patient is found to have satisfactorily responded but requires additional parenteral diuretics an additional 4 days may be prescribed for total of seven consecutive treatments. If additional units are prescribed, patients will be evaluated by the cardiology service of SEMC within 24 hours of the last dose of the sc2Wear™ Furosemide infusion.

Additionally, up to three-sc2Wear furosemide at home treatments may be used as authorized by the treating physician in case the patient experience worsening of heart failure within 30-days of enrollment (Rescue Treatment). Participants will be seen in clinic for follow up at 30±3 days after the start of the study for a post treatment follow up. A Time and Events Schedule is attached as **Appendix A**.

6 STUDY POPULATION AND ELIGIBILITY CRITERIA

The cardiology service at St Elizabeth's Medical Center will screen patients based on the eligibility criteria listed below. Patients who are deemed to qualify for this therapy will be seen at the St Elizabeth's Medical Center cardiology clinic.

6.1 INCLUSION CRITERIA

- Age≥ 18 years
- Symptomatic and chronic heart failure (NYHA Class II and III).
- Patients on guideline directed medical therapy 90 days prior to enrollment.
- Adequate home environment for at-home treatment.
- Presenting or referred to the clinic because of evidence of worsening heart failure with fluid overload (decompensation).
- A modification in oral diuretics is not clinically appropriate as deemed by the investigator.
- Estimated excess fluid weight of 4 lbs. or more from euvolemic state.
- Participant able to give informed consent for participation in trial. Agreeing to sign informed consent and HIPAA authorization.
- Understanding and willing to comply with the protocols of the trial.

Ability of the participant or caregiver to independently apply the investigational device and medication.

6.2 .EXCLUSION CRITERIA

- ACC/AHA Stage D heart failure or patients requiring IV inotrope therapy.
- Massive volume overload (e.g., >20 lbs. of estimated fluid weight) or anasarca.
- Suspected high risk clinical instability with outpatient treatment.
- Pregnant females or women of child-bearing age who are not willing to use an adequate form of contraception.
- Chronic Obstructive Pulmonary Disease (COPD) moderate or worse: FEV1/FCV ratio <0.7 and FEV1 <60 percent predicted.
- Rapid atrial fibrillation (AF) (HR >100b/min).
- Hypoxia (resting O2 saturation <90%).
- Hypotension (systolic blood pressure (SBP) BP < 90 mmHg).
- Uncontrolled diabetes mellitus (DM) (admission glucose levels > 300 mg/dL).
- Advanced renal disease (eGFR < 30mL/min/1.73m2).
- Acute coronary syndrome.
- Serum potassium (K+) <3.2 mmol/L or > 5.5mmol/L.
- On experimental medication or currently participating in an interventional cardiovascular research study, other than an observational or registry study.
- Having received intravenous furosemide within 24 hours prior to enrollment.
- Urinary tract abnormality or disorder interfering with urination.
- Allergy to the active and inactive ingredients of the study medication.
- Inability to comply with study requirements.
- Ongoing substance abuse.

- Concern that the current episode of decompensation was precipitated by a serious medical condition which may require additional evaluation or treatment.
- Dementia

6.3 REMOVAL OF SUBJECTS FROM THE STUDY

All patients who are withdrawn from the study will still need to be monitored closely for 30 days for their safety. The following will be reasons to withdraw a participant from the study.

1. Participant request to be withdrawn from the study.
2. Safety concerns (adverse events or reactions etc.).
3. Investigator discretion (will usually be related to patient safety).
4. Treatment failure (the need for a longer parenteral therapy or hospital admission).

7 STUDY WORK FLOW

This is a prospective, open-label, two-phase study to evaluate the clinical utility of SQ administration of a novel furosemide formulation. Patients seen in the cardiology clinic who are determined to be eligible will be enrolled in this study.

For participants in the trial, during the clinic visit the study investigator, co-investigator who are physicians in the cardiology division of SEMC, or a cardiology nurse practitioner will teach the participants everything they need to know about the sc2Wear™ Furosemide Infusor. scPharmaceuticals will conduct a training session for study staff on the device operation and placement and study site will have access to training materials developed by scPharmaceuticals.

The Pump will be filled and placed on the skin of the upper abdomen in accordance with the Instructions for Use Manual (Appendix C). The patient will be instructed on how to press the activator button to start the administration of the furosemide. When this button is pressed, a small needle is deployed automatically to the skin and the furosemide delivery starts. When the medicine has been delivered, the needle pulls back into the Cartridge and then the patient can then dispose of the cartridge. Participants will also be given Quick Reference Guide (QRG)(Appendix D) and will be given contact numbers from the cardiology department to call if any device troubleshooting questions come up. Participants will also be provided the technical support contact number related to the device.

8 Investigational Product

sc2Wear™ Furosemide Infusor delivery system comprises of reusable and disposable components. The components are described below.

(1) The reusable components which are needed for the drug delivery:

(a) The Activator consists of the electromotor and pump drive, control electronics, and user interface elements (buttons, visual indicators and audible tones),

(b) A Power Cord for recharging the Activator when not in use,

(2) The Disposable components:

(a) The drug product: Furosemide Injection Solution (8 mg/mL – total 80 mg in 10 mL), provided in a 10mL standard pharmaceutical glass vial,

(b) An Adapter for accessing the contents of the drug vial,

(c) A Cartridge that houses the needle and needle insertion mechanism, a micropiston pump, drug reservoir and adhesive (for attachment to the body),

(d) Cavilon No Sting Barrier Film - small wand applicator, 1.0 ml, One applicator wand, for protecting the skin.

(e) Alcohol Prep Pads for cleaning the top of the medicine Vial and the skin prior to applying the Pump.

(f) The device is adhered to the body using medical grade adhesive 1776 acrylate adhesive manufactured by 3M. The 1776 adhesive is identical to the commercially available 3M Medipore Tape [Class I, Exempt], except that a liner is added for converting/handling.

8.1 Buffered Furosemide Injection

Buffered furosemide injection (SCP-101, Furosemide Injection), 10mL of undiluted buffered furosemide solution (8 mg/mL), manufactured by Cook Pharmica, Bloomington, IN, USA under GMP conditions. Contains Tris Hydrochloride, Sodium Chloride and may contain Sodium Hydroxide and Hydrochloric acid for pH adjustment: pH 7.4 (7.0 - 7.8). The sc2Wear furosemide Infusor will be provided by scPharmaceuticals to the investigational site as a starter kit (containing the Activator, cartridge and drug) as well as refill kits containing the drug and cartridge.

8.2 Labeling

Study drug (Furosemide Injection Solution (SCP-101)) and study device (sc2Wear™ Furosemide 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
- Study/Investigator information
- Batch number

- Storage information

8.3 Storage and Handling

Store study drug at 20° - 25°C, (68° - 77°F), excursions permitted between 15°C and 30°C, (between 59°F and 86°F). Protect from Light. The sc2WearTM Furosemide Combination Product must be placed and activated within 7 hours of filling. Drug delivery must be started within 7 hours after filling the device.

9 STUDY EVALUATION

9.1 Baseline Evaluation

The following information will be obtained from patients who give informed consent.

- Age, sex, past medical history
- Physical examination
- Weight, height, Blood pressure, Heart Rate, Respiratory Rate, Temperature
- NYHA classification
- Laboratory draws (Sodium, potassium, chloride, Bun, Cr, Mg, pro-BNP, hemoglobin and hematocrit)
- Dyspnea Scale (Appendix B)
- Current medications

9.2 Study Days (3 ± 4 days)

During the study days, patients will be required to continue with their usual evening diuretic dose. The following information will be collected by the visiting nurse:

- Weight, Blood pressure, Heart Rate, Respiratory Rate, Temperature
- Physical exam
- Injection site inspection
- Blood draw (Sodium, potassium, chloride, bicarbonate, Bun, Creatine, and Mg)
- Current Medications
- Dyspnea scale (Appendix B)

- Electrolyte replacement
- Assessment for adverse events

9.3 Follow Up After Last Treatment

Subjects will be assessed in the office within 24 hours of termination of at home treatment. Assessments will include:

- Weight, Blood pressure, Heart Rate, Respiratory Rate, Temperature
- Physical examination
- NYHA classification
- Injection site assessment
- Blood test (Sodium, chloride, potassium, bicarbonate, Bun, Creatine, magnesium, pro BNP)
- Dyspnea scale (appendix B)
- Assessment for adverse events
- Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits

At this visit, the physician can decide if the treatment should be extended for four extra days (after the initial three days of therapy). If there is no interval improvement, the physician can withdraw the subjects from the trial for safety reasons. The initial follow up assessment will be included in the final analysis. Patients who show improvement with initial treatment (3 days or 3 day plus up to 4 days at home) may be offered 3 extra days of "rescue treatment" as needed within 30 days of enrollment in the trial. During the "rescue treatment" they will be evaluated daily by the visiting nurse and at follow up if they need further assessment as done during the treatment phase.

9.4 Day 30 ± 3 Clinic Visit

At Day 30, study follow-up (+/- 3 days). Subjects will undergo the following assessment.

- Medical history
- Physical examination
- Weight, Blood pressure, Heart Rate, Respiratory Rate, Temperature
- NYHA classification

- Injection site inspection
- Blood draw (sodium, potassium, chloride, bicarbonate, Bun, Creatine, magnesium, pro-BNP
- Current Medications
- Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits
- Assessment for adverse events
- Dyspnea Scale (Appendix B)

Visiting Nursing Timeline

A week prior to the initiating of the study, the visiting nurses will be given an orientation and will be taught how to use the sc2Wear Furosemide Infusor. They will also be trained on how to use the dyspnea scale to ensure consistency of the results.

The visiting nurse will visit the participant at home within 24 hours of starting the treatment. These visits will occur on the three treatment days and an additional 4 days if it is determined that the participant needs extra days. Also participants who need an extra three days of rescue treatment during 30 days will be seen on consecutive days by the visiting nurse.

9.5 Electrolyte Correction

At the clinic, prior to the start of therapy –a basic metabolic panel, pro-BNP, hemoglobin and hematocrit, and magnesium level will be drawn STAT to ensure that the results are back within 2 hours. Electrolytes will be replenished in accordance with established protocols (Tables 1 and 2) [10]. The same protocol will be utilized for electrolyte imbalances correction during the follow up visits by the visiting home nurse.

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Serum Creatinine (mg/dL)	Serum Potassium Level (mEq/L)				
	< 3.1	3.1-3.3	3.4-3.6	3.7-4.0	> 4.0
< 2.0	40 mEq then 40 mEq	40 mEq then 20 mEq	40 mEq	20 mEq	-
2.0-2.8	40 mEq then	20 mEq then	20 mEq	-	-

	20 mEq	10 mEq			
> 2.8	30 mEq	20 mEq	10 mEq	-	-

* If the serum potassium is < 3 mEq/L or > 5.5 mEq/L, additional monitoring should occur within 24 hours.

Serum Creatinine (mg/dL)	Magnesium Level (mEq/L)			
	< 1.0	1.0-1.5	1.6-1.9	> 1.9
< 2.0	3 gm	2 gm	1 gm	-
≥ 2.0	2 gm	1 gm	-	-

10 OUTCOMES DETERMINATION

10.1 Efficacy Endpoints

- % weight loss between enrollment/screening compared to Post Visit #1 and Post Visit #2
- Reduction in pro-BNP between enrollment/screening compared to Post Visit #1 and Post Visit #2
- Proportion of patients requiring additional 4 days of diuresis..
- Percentage of patients alive 30 days post enrollment
- Percentage of patients without hospitalization for worsening HF within 30 days after enrollment.
- Percentage of patients without a significant HF related medical event within 30 days after enrollment.

10.2 Safety Endpoints

- The safety of the sc2 Wear furosemide drug-device combination will be assessed by the incidence of adverse events.
- Discontinuation due to presence of skin reaction to drug or device/adhesive.

11 RISK MANAGEMENT

Furosemide has been available for over five decades and is considered a safe drug. The potential risks related to this study are not different from the risks of any form of diuresis whether inpatient or outpatient. During diuresis, sometimes there are rapid fluid shifts which could lead to electrolyte imbalance or postural hypotension. Subjects will be closely monitored and electrolytes will be supplemented as needed. Patients will be encouraged to avoid rapid postural changes during diuresis and will need to be homebound to ensure their safety.
Patients will be informed of the expected increased urine output. Rarely gout may also be precipitated when fluid is taken out of the body. Dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting will be monitored. There are rare risks of local allergic reaction from the adhesive of the infusor, activation of systemic lupus erythematosus or worsening kidney function in which case the SQ furosemide infusion will be stopped. Patients allergic to sulfa may be allergic to furosemide. Patients with diabetes mellitus should be told that furosemide may increase blood glucose levels and thereby affect urine glucose tests. The skin of some patients may be more sensitive to the effects of sunlight while taking furosemide. Patients may not participate in this study if they are pregnant or plan to be pregnant during the study since the effects of the study device system on an unborn baby are unknown.

12 SUMMARY OF BENEFITS

It is anticipated that patients will experience clinical improvement of the symptoms and signs of HF. Participants will also avoid the cost related to being admitted to the hospital for intravenous furosemide infusion.

13 PARTICIPANT SAFETY AND ADVERSE EVENTS
Adverse Events

An adverse event (AE) is any unfavorable or unintended medical occurrence associated with the use of an investigational product (IP). This does not necessarily imply causality.
Pre-existing conditions would be reported as AEs if the frequency, intensity, or character of the pre-existing condition worsens during the course of the study. Conditions detected after use of the IP are AE, though they might have prior existence. Laboratory or functional test abnormalities that meet the criteria for AEs are those that are associated with clinical signs or those whose clinical symptoms require medical intervention, and or which require the IP to be discontinued. When the patient withdraws from the study

13.1 Suspected Adverse Reactions

A suspected adverse reaction (SAR) refers to events which could have been possibly caused by the drug. Adverse reactions, a subset of SAE, indicates a higher certainty (that event was caused by IP).

13.2 Serious Adverse Events

Serious Adverse Event (SAE) refers to any event that result in the following

- Death
- Life-threatening AE
- A disability or incapacity
- Inpatient hospitalization due to the therapy. This may not include patients who choose to withdraw from the study and opt to be admitted or patients who are withdrawn from the study for better diuresis in the hospital.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect of an offspring

13.3 Anticipated Adverse Events and Procedure Effects

These refer to AEs related to acute heart failure.

- Acute coronary syndrome (unstable angina, non ST elevation myocardial infarction, ST elevation myocardial infarct)
- Arrhythmias and sudden cardiac death
- Venous thrombosis

- Cerebrovascular events (stroke or transient ischemic attacks)
- Worsening heart failure or heart failure refractory to therapy requiring inotropes or mechanical support
- Presyncope and syncope
- Acute kidney injury defined as a rise in creatinine > 0.3 mg/dL over 48 hours, or progressive loss of renal function over time.

13.4 Device Adverse Events

If the pump falls off during drug infusion or if the needle appears before pump placement there is a risk of needle stick. In this scenario, the pump will need to be handled carefully. Device adverse reactions could include local reaction/skin irritation or redness, allergic reaction to the adhesive agent, and rarely scarring.

13.5 Pre Specified Adverse Events

Hyperkalemia defined as K > 5.5 meq/L
Hypokalemia, defined as K<3.0 meq/ml
Hypomagnesemia, defined as Mg < 1.5 mg/dl
Worsening kidney function (50% increase in baseline creatinine level)

13.6 Relatedness of AE or SAE to IP

Using his/her best medical judgment and the available information on the Investigational Product (IP), the Investigator will determine if the AE and or SAE caused the observed symptoms associated with the event.

- **Not related**: Unestablished reasonable causal relationship between the IP and the AE.
- Unlikely related: No temporal association or cause of the event has been identified.
- **Possibly related**: There is reasonable evidence to suggest a causal relationship between the drug and adverse event, however there could be other confounders to the AE
- .**Related:** There **i**s a causal relationship

13.7 Severity of AEs

The severity of AEs should be documented using the following criteria.

- Mild: symptom does not influence performance. Subject barely notices it
- Moderate: Subject's daily performance is affected. Treatment may be needed.
- Severe: Subject experiences severe discomfort. Treatment necessary

13.8 Outcome of AEs

One of the following outcomes should be documented

- Not resolved: symptom No improvement
- Resolved: Symptoms have improved.
- Resolved with sequelae: Improvement of AE but has retained a pathological condition related to the event.
- Unknown: Subject refused further contact, not known Fatal: Death as a result of AE

13.9 Recording and Reporting of Adverse Events

At follow up visits or when visited by the Visiting nurse, participants should be asked non-leading questions such as "Have you had any issues lately", "How do you feel", "Have you made any changes to your medications recently" and "have you had any medical problems that I should know of". The principal investigator will be notified promptly of any AE or SAEs within 24 hours of the event.
All AE and SAE's should be promptly documented with Subject ID, the serious adverse event term, onset date, relationship to study product, and a brief narrative of the event. The investigator must promptly determine the relationship to study product or causality. Events should be recorded on the Case Report Forms attached as Appendix F. The Investigator should make the SAEs available to the IRB. Any AE or SAE occurring within 30 days of completion of the study should be reported.

14 STATISTICAL CONSIDERATIONS

An open label, descriptive study to evaluate the clinical utility of a novel formulation of furosemide delivered subcutaneously in patients early signs of fluid overload. Binary variables will be presented as percentages; Gaussian continuous variables will be presented as mean ± standard deviation (SD), while non-Gaussian continuous variables could be presented as median with interquartile range (IQR). There will be no head-to-head comparison of the participants of the study however the study is expected to provide valuable information on the efficacy of this therapy as measured by the primary endpoints which include percentage weight loss, reduction in pro-BNP, re-admission, percentage with extended treatment, percentage of patients with heart

failure related adverse events and survival at 30 days. As already outlined, safety will be reported based on the incidence of the adverse events and percentage of subjects with skin reaction requiring discontinuation. Data will be analyzed for the initial 20 patients in the pilot phase. At the end of the trial, all the 60 subjects (combined pilot and maintenance phase would be analyzed together). A study with 59 evaluable subjects has the power to detect with 95% confidence the presence of events with an incidence of 5% or greater. Failure of such material event to occur in a study with 59 evaluable patients indicates that the incidence of such event is less than 5%.

15 DATA MANAGEMENT PROCEDURES

Clinical study data will be saved on a password protected dedicated drive used for research purposes at the St Elizabeth Medical Center. Home visits by the visiting nurse and clinic visits will be documented on the provided CRF (attached as Appendix G). Participant file will have the following documents related to the patient such as the following (but not limited to): clinician and nurse's notes, laboratory and imaging reports, screening and enrollment log etc. The Investigator's study file will contain the informed consent, protocol/ amendments, CRF, and other appropriate documents and correspondence such as with the IRB and the FDA.
The investigator will endeavor to retain clinical study records for at least two years after the last approval of a marketing application in an ICH region; or, until two years after the IND is discontinued and regulatory authorities have been notified. scPharmaceuticals will be notified prior to destroying any clinical study records.

16 STUDY ADMINISTRATION

The Principal Investigator agrees by 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. The sc2Wear™ Furosemide Infusor will be returned to scPharmaceuticals at the completion of the study.
Data generated by this study must be available for inspection by the US FDA and other regulatory authorities, by scPharmaceuticals and its designees, and the IRB as appropriate. At a Subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information

obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethics and Good Clinical Practice

By signing this protocol, the investigator will ensure adherence to the protocol and to Good Clinical Practice as stated in the following documents.

1. The principles of the "Declaration of Helsinki"
2. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 312 (IND regulations), 54 (financial disclosure), 50 (informed consent) and 56 (IRB regulations).

17.2 Informed Consent

A written informed consent will be obtained from all participants prior to enrolling in the study. This consent , which is attached as appendix F, will be obtained by the Principal Investigator or designee A copy of the signed consent form will be provided to the Subject

17.3 Confidentiality and HIPAA requirements

Confidentially will be maintained for all the information collected on study participants per the Health Insurance Portability and Accountability Act of 1996 (HIPAA; Pub.L. 104–191, 110 Stat. 1936). Only authorized personnel will have access to subject information collected as part of this study.

17.4 Institutional Review Board/Independent Ethics Committee

This study will only be started when the Institutional Review Board (IRB) approves the protocol. All amendments to the protocol are subject to IRB review and approval

17.5 Monitoring

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The study will be monitored by the Principal Investigator to ensure compliance to the study protocol, verify the signing of informed consent by the subjects, and assist the study personnel with

any questions related to the study. Also an institution designated person will have direct access to the study data, informed consent and CRF to ensure consistency and accuracy in data gathering. This designee will have direct access to the Investigator's source documentation in accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP).

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19 APPENDICES

Appendix A. Schedule of Assessments

	Screening	Baseline	Treatment*	First Post Treatment	Second Post Treatment (if applicable)	Post-Treatment Visit
Day	0	0	Daily (3 ± 4 days)	Within 24hrs of last treatment	Within 24hrs of last treatment	30±3days after first dose
Informed Consent	X					
Pregnancy Test*	X					
Training		X				
Medical History		X				
Initial sc2Wear Treatment		X				
Weight		X	X	X	X	X
Height		X				
HF Physical Exam		X	X	X	X	X
NYHA		X		X	X	X
Baseline Labs[a]		X				
Monitoring labs[b]			X	X	X	X
Vitals Signs[c]		X	X	X	X	X
Dyspnea Scale		X	X	X	X	X
Electrolyte correction		X	X			
Injection Site Inspection			X	X	X	X
Current Medication	X	X	X	X	X	X
Adverse Events [d]		X	X	X	X	X

* To be performed by Steward Home Care and Hospice in accordance with standard practices for homebound heart failure patients

a. Baseline laboratory panel (Sodium, potassium, Bun, Cr, Mg, pro-BNP, Hemoglobin and Hematocrit)
b. Monitoring laboratory panel: (sodium, chloride, bicarbonate, potassium, Bun, Cr, Mg)
c. Vital signs: Blood pressure, heart rate, temperature, respiratory rate
d. Adverse Events: Major Event: death, hospitalization, MACE (major adverse cardiac event); Minor: ER visit for acute decompensated heart failure (excluding study related visits), admission to SNF or similar inpatient facility

Appendix B: Modified Medical Research Council Dyspnea Scale

Score	Modified Medical Research Council Scale
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing

Appendix C: Instructions for Use Manual

Appendix D. Quick Reference Guide (QRG)

Appendix E: Informed Consent Form

Appendix F: Case Report Form (Adverse Events)

Appendix G: Case Report Form (Home Visits)