

John Hopkins Heart Failure Bridge Clinic (HFBC)

CLINICAL RESEARCH PROTOCOL

**Prospective, Randomized, Parallel-Group Pilot Study Comparing
IV Furosemide to Subcutaneous Furosemide in Decompensated
Heart Failure Patients**

Protocol Number: 2015 - 1
Protocol Date: 05 August 2015

SYNOPSIS	
PROTOCOL TITLE	Prospective, Randomized, Parallel-Group Pilot Study Comparing IV Furosemide to Subcutaneous Furosemide in Decompensated Heart Failure Patients
PROTOCOL NUMBER	
SPONSOR	Johns Hopkins Heart Failure Bridge Clinic (HFBC)
INVESTIGATIONAL PRODUCT	Furosemide Injection Solution, (SCP-101) 8 mg/mL manufactured by Cook Pharmica for scPharmaceuticals, Inc. (test treatment) and Furosemide Injection, USP 10 mg/mL (reference treatment)
STUDY OBJECTIVES	<p>The objectives of this study are:</p> <p><u>Primary objective:</u> To determine the clinical efficacy of subcutaneously administered Furosemide Injection Solution (SCP -101) versus intravenous administration of Furosemide Injection, USP in adult patients at the HFBC presenting with decompensated heart failure.</p> <p><u>Secondary objective:</u> To determine the adverse effects and patient satisfaction with subcutaneously administered Furosemide Injection solution (SCP-101) versus intravenous administration of furosemide in adult patients at the HFBC presenting with decompensated heart failure.</p>
STUDY DESIGN & DURATION	<p>This clinical trial is a prospective, randomized, parallel-group pilot study comparing the intravenous administration of Furosemide Injection, USP, to subcutaneous administration of a buffered furosemide formulation - Furosemide Injection Solution (SCP-101), in patients presenting to the Johns Hopkins Hospital Heart Failure Bridge Clinic (HFBC) with decompensated heart failure. Patients presenting to the HFBC will be assessed to determine whether they need IV diuretics. If they do, they will be screened for eligibility. If they are eligible, written informed consent will be obtained. Patients will then be randomized to receive Furosemide Injection, USP intravenously or Furosemide Injection Solution (SCP-101) delivered subcutaneously. The IV patients will get the usual care of the HFBC, which includes having an IV placed and delivery of a one-time dose of IV furosemide with the dose determined by the providers (maximum dose 160mg IV). The subcutaneous patients will receive 80mg of Furosemide Injection Solution (SCP-101) administered subcutaneously over 5 hours (30mg in first hour and 12.5mg/hour for 4 hours). Administration will take place with the B Braun Perfusor® Space Infusion Pump System and a standard commercial infusion set. Both groups of patients will be observed for 6 hours to assess diuresis. The goal will be to enroll a total of 40 patients, 20 in the IV furosemide group, and another 20 in the subcutaneous furosemide group. Vital signs and urine output will be monitored closely for 6 hours. Patients will be asked to fill out a survey about their symptom improvement (Kansas City Cardiomyopathy questionnaire) and overall satisfaction related to the treatment experience. They will also be monitored for side effects including ototoxicity and discomfort at the access site (burning, itching, and pain). Electrolytes and renal function will be checked once after the patients receive diuretic therapy. Study participants will be on fluid</p>

	<p>restriction during the study, with no more than 100ml of fluid consumed during the 6 hours.</p> <p>Study Drug:</p> <ul style="list-style-type: none"> • Furosemide Injection, USP: Furosemide Injection, Solution, single dose determined by Investigator (maximum dose 160mg) administered intravenously by IV bolus over approximately 2 minutes (reference treatment) • Furosemide Injection Solution (SCP-101), 8 mg/mL: 80 mg dose administered subcutaneously as 30 mg over the first hour and then as 12.5 mg per hour over the subsequent 4 hours (test treatment) <p>Since the HFBC gives IV diuretics about 15 times per month, HFBC plans to enroll 40 patients within three to four months. The study requires only one clinical visit – a visit that would have already been scheduled for the patient.</p>
NUMBER OF SUBJECTS	The number of subjects in this prospective study is 40. 20 in the IV furosemide group and another 20 in the subcutaneous furosemide group.
NUMBER OF SITES	1
PARTICIPATING COUNTRIES	US
SUBJECT POPULATION	<p>Female and male subjects may be enrolled in the study only if all of the inclusion criteria and none of the exclusion criteria are met.</p> <p>Inclusion Criteria (low risk, intermediate risk):</p> <ul style="list-style-type: none"> • An Institutional Review Board (IRB) approved informed consent is signed and dated prior to any study-related activities. • Male and female subjects \geq 18 years of age • History of at least 3 months treated heart failure (NYHA class II/III/IV), or recent hospitalization for heart failure; presenting to HFBC with decompensated heart failure symptoms including elevated jugular venous pressure, dyspnea and peripheral edema where the decision is made to give IV diuretics • Able to participate in the study in the opinion of the investigator • Has the ability to understand the requirements of the study and is willing to comply with all study procedures <p>Exclusion Criteria (high risk):</p> <p>A subject is <u>not</u> eligible for inclusion if <u>any</u> of the following criteria apply:</p> <ul style="list-style-type: none"> • Presenting with symptoms where it is anticipated that there is a high chance of hospitalization such as ischemia, uncontrolled arrhythmia, infection, hemodynamic instability (elevated or low blood pressure), respiratory compromise, or electrolyte

	<p>abnormalities (>25% increase in creatinine from baseline, potassium, hyponatremia).</p> <ul style="list-style-type: none"> • On experimental medication or currently participating in a cardiovascular research study. • Presence or need for urinary catheterization, urinary tract abnormality or disorder interfering with urination • Any surgical or medical condition which in the opinion of the investigator may interfere with participation in the study or which may affect the outcome of the study • Inability to comply with study requirements
ENDPOINTS	<p>Primary Endpoints:</p> <ol style="list-style-type: none"> 1) Total volume of voids over a 6-hour period 2) Total natriuresis over a 6-hour period <p>Secondary endpoints:</p> <ol style="list-style-type: none"> 1) Volume of voids between 0-2 hours, 2-4 hours and 4-6 hours post initiation of treatment. 2) Heart Failure Symptom Scoring/Symptom Improvement- (Kansas City Cardiomyopathy questionnaire) 3) Overall Satisfaction with Treatment- (Treatment Satisfaction Survey) <p>Safety endpoints:</p> <ol style="list-style-type: none"> 1) Patient reported Pain 2) Increases in serum creatinine of 0.5 mg/dL or greater 3) Local skin reactions including hematoma, induration, infection, thrombosis, necrosis etc. 4) Occurrence of treatment-emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)
STATISTICAL ANALYSIS	<p><u>Determination of Sample Size:</u> For this pilot study, the determination of sample size was primarily based on clinical consideration; with the aim to yield meaningful preliminary data.</p> <p><u>Statistical Analysis Plan:</u> A full statistical analysis plan will be developed. All data will be analyzed as intention-to-treat. Continuous variables will be presented as mean \pm standard deviation and will be compared using the Students <i>t</i>-test (2-tailed), unpaired. Differences between treatment groups for the categorical variables will be analyzed using the chi-square test. For the purposes of this study, <i>P</i> values \leq .05 will be considered significant.</p> <p><u>Early Stopping Rules:</u> The study will be stopped early if there is a significant difference in number of patients with intolerable side effects: Ototoxicity, severe discomfort, burning and stinging at the access site, itching, and/or pain.</p>

Table 1. Time and Events Schedule

Time and Events Table	Screening Phase		Pre-Dose	Start of Dosing	Dosing	6 hours post Start of Dosing
Informed Consent	X					
Confirmation of Eligibility	X					
Co-morbidity	X					
Cardio-Pulmonary Examination	X					
Serum Creatinine	X					X
Weight and Height	X					
Vital Signs	X		X	X	X	X
12-lead EKG	X					
Collection and Measurement of Urine Voids				X	X	X
Urine Sodium			X			X
Clinical Chemistry	X					X
BNP/NT ProBNP			X			X
Study Drug Administration				X		X
Injection Site Pain Assessment						X
Injection Site Inspection			X			X
Randomization to Treatment Sequence	X					
Kansas City Cardiomyopathy questionnaire			X			X
Treatment Satisfaction Survey						X
Treatment Emergent Serious Adverse Events				X	X	X

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ABBREVIATIONS

AE	adverse event
BNP/NTProBNP	B-type natriuretic peptide/N-terminal prohormone of brain natriuretic peptide
bpm	beats per minute
BUN	blood urea nitrogen
C _{max}	peak plasma concentration, observed
CRF/eCRF	case report form / electronic case report form
ECG	electrocardiogram
EEG	electroencephalogram
EP	European Pharmacopoeia
GCP	good clinical practice
HFBC	Johns Hopkins Heart Failure Bridge Clinic
ICH	International Conference on Harmonization
IND	Investigational New Drug
IV	Intravenous
IRB/EC	Institutional Review Board/Ethics Committee
mmHg	millimeters of mercury
p.o.	by mouth, orally
SAE	serious adverse event
SC	subcutaneous
USP	United States Pharmacopoeia

1. INTRODUCTION

The prevalence of chronic heart failure is increasing, and it is the most common diagnosis in hospital patients age 65 years and older. Despite advances in the treatment of chronic heart failure, in-hospital mortality and readmission are high. Heart failure costs the US about 32 billion per year, and a large percentage of the costs are due to hospitalizations. The Heart Failure Society of America guidelines for the management of decompensated heart failure offer recommendations for clinical circumstances that should prompt hospital admission. Most clinicians would agree that patients with decompensated heart failure presenting with hypotension, worsening renal function and altered mental status should be hospitalized. However, there is a subset of patients presenting with dyspnea and edema due to volume overload that necessitate rapid symptom improvement but are hemodynamically stable. Oral diuretics would likely be ineffective but admission for IV diuretics seems excessive.

The Johns Hopkins Heart Failure Bridge Clinic (HFBC) was designed as a clinic to reduce heart failure hospital admissions. Patients with chronic heart failure are primarily seen either in the early post discharge period or if they are referred for an infusion of IV diuretic. The HFBC sees about 160 patients each month and administers on average 15 infusions of Intravenous (IV) diuretics. The average visit duration is 220 minutes, with mean IV furosemide dose 100mg resulting in average urine output 1460 ± 730 ml, and weight loss of 2.3 ± 1.8 kg.

The HFBC has been successful at preventing hospital admissions by treating patients with IV diuretics. However, it requires patients to come to the clinic for treatment and close monitoring. Subcutaneous diuretics present a potential alternative to IV diuretics and offer patients an opportunity to receive treatment outside of the hospital setting. Very few studies have evaluated the efficacy and safety of subcutaneous furosemide in chronic heart failure patients presenting with symptoms of volume overload.

1.1. Rationale for the Current Study

The research hypothesis is that subcutaneously administered furosemide will be an effective alternative to IV furosemide for hemodynamically stable chronic heart failure patients presenting with volume overload in the ambulatory setting. The significance of this research is finding a potential intervention that could help decrease heart failure hospitalizations and improve the quality of life for patients with chronic heart failure. In addition, we can decrease the costs associated with heart failure.

There is very little experience with subcutaneous administration of furosemide EP/USP (current form of commercially available furosemide injection solution). There are a few studies that show the delivery of subcutaneous furosemide by electric infusion pump in terminally ill patients is effective for weight loss and symptom improvement (1,2). A group in Spain was successfully able to resolve 41 episodes of decompensated heart failure in 24 elderly patients using continuous subcutaneous furosemide administered by elastomeric infusion pumps (2). They found that the elastomeric infusion pumps provided safe outpatient treatment without the need for daily monitoring. In addition, it helped prevent hospital admissions and decreased costs due to the low price of the devices. It was also a good alternative for patients with venipuncture failure and the inability to transition from intravenous to oral diuretics.

Furosemide USP has a pH of 8.3 -9.0 and may cause irritation and discomfort upon administration. A novel buffered formulation with a physiologic pH (7.4) is currently under development in support of a NDA submission later in 2015. The product is to be marketed with a wearable patch pump for a slow 5-hour administration to optimize 8-hour diuresis.

scPharmaceuticals, Inc. (Lexington, MA), the developer of the novel furosemide formulation and its drug delivery device, provided the following information. The pivotal clinical study with the buffered furosemide solution (Furosemide Injection Solution (SCP-101)) started in Q2 of 2015 in support of the NDA. This study is conducted in the United States in stable HF patients under IND 118,919.

The company has previously conducted a Phase I pilot study (NCT02350725) to investigate the pharmacodynamics and pharmacokinetic parameters of Furosemide Injection Solution (SCP-101) administered subcutaneously as compared to oral furosemide. The study was a randomized open-label cross-over study in patients with stable HF. Patients were mildly symptomatic with NT-proBNP of >300 pg/mL. Treatments were separated by a 14 +/- 3 day interval. Subcutaneous administration of Furosemide Injection Solution (SCP-101) (8mg/mL; 80 mg total), was delivered using a B Braun Perfusor® Space Infusion Pump System as 30 mg over the first hour followed by 12.5 mg per hour over the subsequent 4 hours. Reference treatment consisted of 80mg p.o. furosemide.

Ten subjects were enrolled (80% males) with a mean age of 69.9 years and mean plasma NTproBNP of 1638 ng/mL. All patients were on standard medication including ACE inhibitors and beta blockers. Main daily dose of oral furosemide was 40 mg/day.

Subcutaneous administration of the novel formulation was well-tolerated. All participants achieved therapeutic plasma furosemide levels of over 1000ng/mL within one hour of start of subcutaneous infusion. Therapeutic plasma levels were maintained for a minimum of 5 hours (Figure 1).

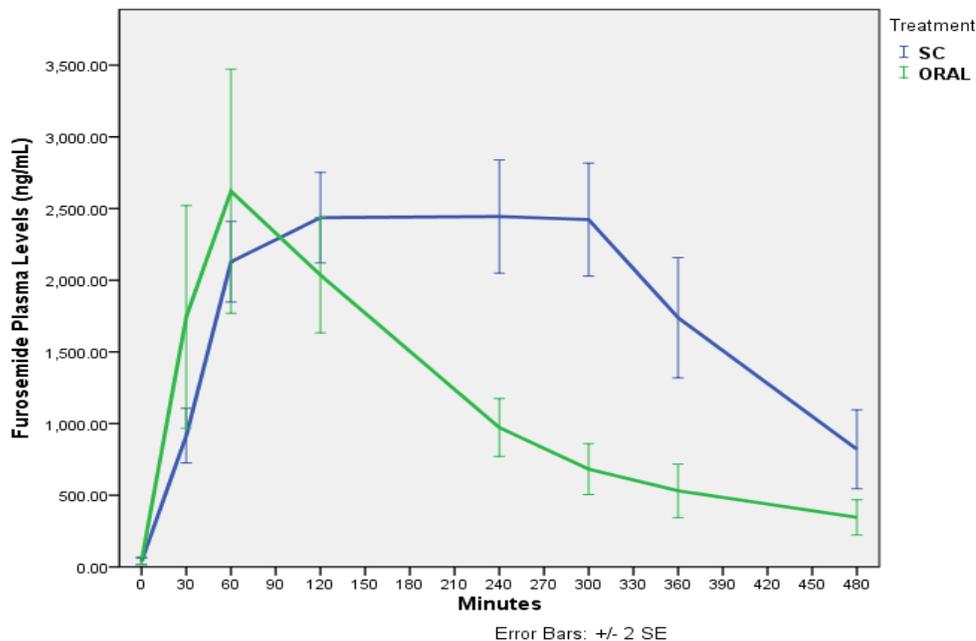


Figure 1: Mean Plasma Furosemide Levels after SC or Oral Administration

Figure 1. Plasma furosemide levels were measured just prior to dosing (Time 0) and at 30, 60, 120, 240, 300, 360 and 480 minutes post dosing. Mean plasma levels + 2 SE across the 10 subjects are shown for each treatment period.

Plasma furosemide levels in the plateau phase (60-300 minutes post start of infusion) were maintained in a narrow range (67%-93%) from the C_{max} when compared to oral (11% - 40%). P.o. furosemide administration resulted in highly variable plasma levels: 90% of the participants achieved levels of 1000ng/mL at some point following administration; but only one participant (10%) maintained plasma levels over 1000 ng/mL for 5 hours. The mean total furosemide exposure (expressed by area under the curve, AUC) was 66% higher after subcutaneous administration when compared to oral ($p < 0.0001$).

2. STUDY OBJECTIVES

The objectives of this study are:

(1) Primary objective: To determine the clinical efficacy of subcutaneously administered Furosemide Injection Solution (SCP-101) versus intravenous administration of Furosemide Injection, USP in adult patients at the HFBC presenting with decompensated heart failure.

(2) Secondary objective: To determine the adverse effects and patient satisfaction with subcutaneously administered SCP-101 versus intravenous furosemide in adult patients at the HFBC presenting with decompensated heart failure.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This clinical trial is a prospective, randomized, parallel-group pilot study comparing the intravenous administration of Furosemide Injection, USP, to subcutaneous administration of a buffered furosemide formulation – Furosemide Injection Solution (SCP-101), in patients presenting to the Johns Hopkins Hospital Heart Failure Bridge Clinic with decompensated heart failure. Patients presenting to the HFBC will be assessed to determine whether they need IV diuretics. If they need it, they will be screened for eligibility. If they are eligible, written informed consent will be provided. Patients will then be randomized to receive Furosemide Injection, USP intravenously, or SCP-101 delivered subcutaneously. The IV patients will get the usual care of the Heart Failure Bridge Clinic, which includes having an IV placed and delivery of a one-time dose of IV furosemide with the dose determined by the providers (maximum dose 160mg IV). The subcutaneous patients will receive 80mg of Furosemide Injection Solution, 8 mg/mL, administered subcutaneously over 5 hours (30mg in first hour and 12.5mg/hour for 4 hours).

Administration will take place with the BBraun Perfusor® Space Infusion Pump System and a standard commercial infusion set. Both groups of patients will be observed for 6 hours to assess diuresis. The goal will be to enroll a total of 40 patients, 20 in the IV furosemide group, and another 20 in the subcutaneous furosemide group. Vital signs and urine output

will be monitored closely for 6 hours. Patients will be asked to fill out a survey about their symptom improvement (Kansas City Cardiomyopathy questionnaire) and overall satisfaction related to the treatment experience. They will also be monitored for side effects including ototoxicity and discomfort at the access site (burning, itching, and pain). Electrolytes and renal function will be checked once after the patients receive diuretic therapy. Study participants will be on fluid restriction during the study, with no more than 100 ml of fluid consumed during the 6 hours.

Study Drug:

- **Furosemide Injection, USP:** Furosemide Injection, Solution, single dose determined by Investigator (maximum dose 160mg) administered intravenously by IV bolus over approximately 2 minutes (reference treatment).
- **Furosemide Injection Solution, 8 mg/mL (SCP-101):** 80 mg dose administered subcutaneously as 30 mg over the first hour and then as 12.5 mg per hour over the subsequent 4 hours (test treatment)

3.1.1. Endpoints

Primary Endpoints:

- 1) Total volume of voids over a 6-hour period
- 2) Total natriuresis over a 6-hour period

Secondary endpoints:

- 1) Volume of voids between 0-2 hours, 2-4 hours and 4-6 hours post initiation of treatment.
- 2) Heart Failure Symptom Scoring/Symptom Improvement- (Kansas City Cardiomyopathy questionnaire)
- 3) Overall Satisfaction with Treatment- (Treatment Satisfaction Survey)

3.1.2. Safety Endpoints

- 1) Patient reported Pain
- 2) Increases in serum creatinine of 0.5 mg/dL or greater
- 3) Local skin reactions including hematoma, induration, infection, thrombosis, necrosis etc.
- 4) Occurrence of treatment-emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

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

Inclusion Criteria (low risk, intermediate risk):

- An Institutional Review Board (IRB) approved informed consent is signed and dated prior to any study-related activities
- Male and female subjects \geq 18 years of age
- History of at least 3 months treated heart failure (NYHA class II/III/IV), or recent hospitalization for heart failure; presenting to HFBC with decompensated heart failure symptoms including elevated jugular venous pressure, dyspnea and peripheral edema where the decision is made to give IV diuretics
- Able to participate in the study in the opinion of the investigator
- Has the ability to understand the requirements of the study and is willing to comply with all study procedures

4.2. Exclusion Criteria

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

- Presenting with symptoms where it is anticipated that there is a high chance of hospitalization such as ischemia, uncontrolled arrhythmia, infection, hemodynamic instability (elevated or low blood pressure), respiratory compromise, or electrolyte abnormalities (>25% increase in creatinine from baseline, potassium, hyponatremia)
- On experimental medication or currently participating in a cardiovascular research study.
- Presence or need for urinary catheterization, urinary tract abnormality or disorder interfering with urination
- Any surgical or medical condition which in the opinion of the investigator may interfere with participation in the study or which may affect the outcome of the study
- Inability to comply with study requirements

4.3. Enrollment

It is anticipated that enrollment of 40 participants will take approximately 3 to 4 months based on HFBC current estimate of providing IV diuretics 15 times a month.

4.4. Removal of Subjects from Therapy/Premature Discontinuation

Participants may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The subject's participation may be terminated by the investigator for safety reasons or if, in the opinion of the investigator, continued participation may interfere with clinical management.

The study will be stopped early if there is a significant difference in number of patients with intolerable side effects: Ototoxicity, severe discomfort, burning and stinging at the access site, itching, and/or pain.

5. TREATMENTS

5.1. Treatments Administered

Study drug will be administered by qualified study staff only in accordance with the procedures described in this protocol.

5.2. Identity of Investigational Product(s)

Furosemide Injection Solution, 8mg/mL (SCP-101): 80 mg undiluted buffered furosemide solution, manufactured by Cook Pharmica, Bloomington, IN, USA for scPharmaceuticals, Inc. under GMP conditions (test treatment).

Contains Tris Hydrochloride, Sodium Chloride and may contain Sodium Hydroxide and Hydrochloric acid for pH adjustment: pH 7.4 (7.0 - 7.8). Furosemide Injection Solution (SCP-101) will be provided by scPharmaceuticals to the investigational site.

Furosemide Injection, USP: Furosemide Injection, Solution, single dose determined by Investigator (maximum dose 160mg) by intravenous bolus administration. (reference treatment)

5.2.1. Labeling

Study test drug (Furosemide Injection Solution (SCP-101)) will bear a label that meets applicable laws for an investigational drug, which may include, but is not limited to, the following information:

- Federal law statement
- Batch number
- Storage information

Furosemide Injection, USP for intravenous administration will be obtained from local pharmacy commercial stock with commercial labeling.

5.2.2. Storage and Handling

Store at 20° - 25°C, (68° - 77°F), excursions permitted between 15°C and 30°C, (between 59°F and 86°F). Protect from Light.

5.3. Method of Assigning Subjects to Treatment Groups

5.3.1. Treatment Assignment/Randomization

Randomization will be performed in blocks of 4. Treatment assignment will be performed by means of numbered envelopes, which will identify the treatment group.

5.4. Selection of Doses in the Study

The attending physician will decide the IV furosemide dose to be administered (max 160mg). IV furosemide is to be administered by single IV bolus over approximately 2 minutes.

The subcutaneous furosemide dose is predefined at 80mg total – 30mg of which is administered over the first hour followed by 12.5mg/hour for 4 hours.

5.5. Procedures for Blinding

Not Applicable - This is an open label study.

5.6. Prior and Concomitant Therapy

Heart failure patients are generally on multiple medications used in the management of heart failure. Additionally the majority of patients are on prescription or over-the-counter medications for one or more co-morbidities. The clinic staff will evaluate these medications on a case by case basis and decide what medications may be used on the day of administration. This determination will be made prior to randomization.

5.7. Contraindications

Subcutaneous administration of Furosemide Injection Solution is not intended for use in emergency situations such as acute decompensated heart failure or in patients with pulmonary edema.

5.8. Treatment Compliance

All study medication will be administered by study personnel and all information regarding study drug administration will be documented.

5.9. Study Drug Accountability

Study drug will be administered in accordance with the procedures of this protocol. Only authorized site personnel may supply or administer study drug and only subjects enrolled in the study may receive study drug, in accordance with applicable regulatory requirements.

6. STUDY PROCEDURES

6.1. Study Measurements and Assessments

6.1.1. Assessment of Efficacy

Diuresis:

Urine will be collected from start of treatment through 6 hours post initiation of treatment. Individual voids will be measured and then pooled over the 6 hour time period, and the volume of the pool will be recorded. Time of voids and volume of each void will be recorded.

Natriuresis:

Participants will not be given any fluid by mouth during the 6-hour observation period, except when required for taking oral medication, in which case fluid intake will be limited to 100mL over the 6 hour period.

A 5mL aliquot of the first void, and a 5 mL aliquot of the total 6 hour pool will be obtained by the study staff for determination of sodium.

Symptomatic Improvement

Symptom scoring using the Kansas City Cardiomyopathy questionnaire will be performed prior to drug administration and at the end of the 6 hour observation period. A treatment satisfaction survey will be conducted at 6 hours.

6.1.2. Assessment of Safety

Evidence in Kidney Injury

Serum creatinine will be obtained just before administration and at the end of the 6 hour observation period.

Adverse Events

Incidence of Treatment-Emergent adverse events (AEs) or serious adverse events (SAEs) will be assessed. Treatment associated pain and any local skin reaction including hematoma, induration, infection, thrombosis, necrosis etc. will be assessed.

6.1.3. Clinical Laboratory Tests

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

- **Blood Clinical Chemistry:** blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, chloride, magnesium and bicarbonate.
- **BNP/NTproBNP**
- **Urinalysis:** A 5 ml aliquot from the first void post start of treatment and a 5 ml aliquot from the pooled urine voids over the 6 hour observation period will be analyzed for sodium.

6.1.4. Physical Examinations

A cardiopulmonary examination will be conducted and consist of assessments of the following: heart sounds, murmur, chest sounds, pedal edema and peripheral pulses.

6.1.5. Heart Failure Symptom Scoring

The Kansas City Cardiomyopathy questionnaire will be used in this study to assess subjects and monitor overall response to treatment.

6.1.6. Vital Signs

Vital signs will include respiration rate (breaths per minute), oral temperature, and supine blood pressure (mmHg) and heart rate (beats per minute [bpm]). Blood pressure and heart rate will be obtained after the subject has been resting in supine position for 5 minutes.

6.1.7. 12-Lead ECG

12-lead ECGs will be performed after the subject has rested quietly for at least 5 minutes in a supine position.

6.1.8. Pain Assessment

Pain assessment will be conducted at the end of the 6 hour observation period. Subjects will be asked to verbally rate the intensity of any discomfort using numeric rating scale of 0 to 10 with zero equivalent to no pain and 10 being the worst possible pain. (Appendix 2)

6.1.9. Injection Site Inspection

Study staff will inspect the injection site for erythema and edema using the Draize Scale which includes a 5-point scale for erythema and a 5-point scale for edema. (Appendix 3)

In addition to the Draize scale scoring, the investigator will assess the injection site area for other local reactions, including hematomas, thrombosis, induration, infection, necrosis, etc. The Investigator will rate the reactions as mild, moderate or severe and make an assessment as to causality.

6.1.10. Meals and Dietary Restrictions

Participants will not be given any fluid by mouth during the 6-hour observation period, except when required for taking oral medication, in which case fluid intake will be limited to 100mL over the 6 hour observation period.

7. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. Only treatment-emergent AEs and SAEs (occurring after the first dose of study drug through the appropriate follow-up period) will be recorded in this study. Treatment Emergent AEs, will be assessed continuously after administration of study drug through discharge.

7.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE **does** include any:

- Exacerbation of a pre-existing illness.
- Increase in frequency or intensity of a pre-existing episodic event or condition.

- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

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

- Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions).
- Overdose of either study drug or concurrent medication without any signs or symptoms.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.

7.2. Definition of a Serious Adverse Event

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

- a. Death.
- b. A life-threatening AE.
 - *NOTE: Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.*
- c. Inpatient hospitalization or prolongation of existing hospitalization.
 - *NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.*
 - *NOTE: "Inpatient" hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.*
- d. A disability/incapacity.
 - *NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.*
- e. A congenital anomaly in the offspring of a subject who received drug.

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

7.3. Severity of AEs/SAEs

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

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

7.4. Assessment of Relatedness to Study Drug

The Investigator will assess each AE and SAE for causality based on their medical judgment and the observed symptoms associated with the event. Each AE and SAE will be assessed as related or unrelated to study drug based on the following criteria:

- Unrelated This category applies to those AEs that the Investigator determines are most likely due to extraneous causes (disease, environment, etc.)
- Related This category applies to those AEs that the Investigator determines are most likely due to test drug.

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

Patients will be evaluated for AEs and SAEs at the end of the 6 hour observation. After the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking a non-leading question such as “How are you feeling?”

7.6. Reporting SAEs

7.6.1. Timeframes for Reporting SAEs

The Investigator must report SAEs according to the following time frames:

- **Death or Life-Threatening Event:**
 - *Initial notification* must be provided to the sponsor or designee **within 24 hours** of the Investigational site learning of the death or life-threatening event (regardless of causality).
 - *Complete SAE information* (i.e., all SAE pages) must be sent to the manufacturer or designee **within 48 hours**
 - Follow-up information must be sent to the sponsor or designee within 48 hours of receipt of the information by the Investigational site.
- **All other SAEs**
 - Complete SAE information (i.e., all SAE pages) must be sent to the sponsor or designee within 24 hours
 - Follow-up information must be sent to the sponsor or designee within 48 hours of receipt of the information by the Investigational site.

7.6.2. SAE Information to Report

At a minimum, SAE reports must contain the subject ID, the serious adverse event term, onset date, relationship to study drug, and a brief narrative of the event.

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

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

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs, 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 drug administration or that are present before study drug administration but worsen after study drug administration should be assessed for AE criteria.

7.6.4. Documenting AEs and SAEs

All adverse events, including SAEs, which occur after the first dose of study drug must be documented in the subject's medical records and on the CRF.

A separate set of SAE pages should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE page.

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.

7.6.5. Regulatory/Ethics reporting requirement

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

The sponsor of the IND must report SAEs and AEs to the FDA in accordance with 21CFR312.32.

8. STATISTICS

8.1. Determination of Sample Size

For this pilot study, the determination of sample size was primarily based on clinical consideration; with the aim to yield meaningful preliminary data.

8.2. Statistical Analysis Plan

A full statistical analysis plan will be developed. All data will be analyzed as intention-to-treat. Continuous variables will be presented as mean \pm standard deviation and will be compared using the Students *t*-test (2-tailed), unpaired. Differences between treatment groups for the categorical variables will be analyzed using the chi-square test. For the purposes of this study, *P* values $\leq .05$ will be considered significant.

8.3. Safety Analyses

Extent of Exposure, Adverse Events, Clinical Laboratory Assessments and Vital Signs will be summarized with descriptive statistics.

Pain assessments and local injection site reactions will be tabulated and assessed using descriptive statistical analysis.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

This protocol and any accompanying material to be provided to the Subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted, by the Investigator, to an IRB. Approval from the IRB

must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

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

9.1.3. Informed Consent

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

9.1.4. Confidentiality

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

9.1.5. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories (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, IRB approval 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 (ECG), electroencephalogram (EEG), 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 (ICH) region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, until two years after the IND is discontinued and regulatory authorities have been notified. The Investigator must notify sPharmaceuticals 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.

9.1.6. Case Report Forms

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

9.1.7. Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) and Subject dispensing records and returned or destroyed 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 study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with study requirements. At the end of the study, following final drug reconciliation by the monitor, the study site will be instructed by the Sponsor to return or destroy all unused study drug supplies, including empty containers.

9.1.8. Inspections

9.1.9. Access to Information for Monitoring

scPharmaceuticals, Inc. (Lexington, MA) is the manufacturer of the test product. The manufacturer may monitor the study in accordance with industry practices.

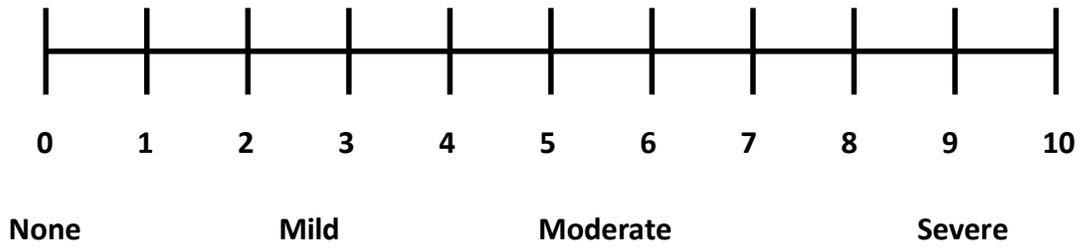
10. REFERENCES

1. Goenaga, MA, Millet M, Sanchez E, Garde, C, Carera JA, Arzelius E, Subcutaneous furosemide. *Ann Pharmacother.*, 2004. 38(10):1751
2. Garcia-Gonzalez, P, Cozar-Santiago, P, Fabregat-Andres, O., Sanchez-Jurado, R., Estornell-Erill, J., Ridocci-Soriano, F., Subcutaneous Infusion of Furosemide Administered by Elastomeric Pumps for Decompensated Heart Failure Treatment: Initial Experience. *Scientific letters/Rev Exp Cardiol.*, 2013 66(12):999

Appendix 1: Time and Events Schedule

Time and Events Table	Screening Phase		Pre-Dose	Start of Dosing	Dosing	6 hours post Start of Dosing
Informed Consent	X					
Confirmation of Eligibility	X					
Co-morbidity	X					
Cardio-Pulmonary Examination	X					
Serum Creatinine	X					X
Weight and Height	X					
Vital Signs	X		X	X	X	X
12-lead EKG	X					
Collection and Measurement of Urine Voids				X	X	X
Urine Sodium			X			X
Clinical Chemistry	X					X
BNP/NT ProBNP			X			X
Study Drug Administration				X		X
Injection Site Pain Assessment						X
Injection Site Inspection			X			X
Randomization to Treatment Sequence	X					
Kansas City Cardiomyopathy questionnaire			X			X
Treatment Satisfaction Survey						X
Treatment Emergent Serious Adverse Events				X	X	X

Appendix 2 Numeric Pain Scale



Verbally indicate the number on the Numeric Rating Scale that best represents the intensity of pain at or around the injection site NOW, with 0 being no pain and 10 being the worst possible pain.

Appendix 3 The Draize Scale for Erythema and Edema Scoring

Erythema formation		Edema formation	
Description	Score	Description	Score
No erythema	0	No edema	0
Very slight erythema (barely perceptible)	1	Very slight edema (barely perceptible)	1
Well defined erythema	2	Well defined edema	2
Moderate erythema	3	Moderate edema (raise approx. 1 mm)	3
Severe erythema (beet redness) to slight eschar formation	4	Severe Edema (raised more than 1 mm and beyond exposure area)	4
