Protocol for the Heart Failure Clinical Research Network

Subcutaneous Furosemide in Acute Decompensated Heart Failure
The SUBQ-HF Pilot Study

Compiled by:
The Heart Failure Network Research Group
3.0

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1.0 List of Abbreviations

Abbreviation	Definition
AHF	Acute Heart Failure
AE	Adverse Event
BID	Twice daily
BMP	Basic Metabolic Panel
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CC	Coordinating Center
CPET	Cardiopulmonary Exercise Test
CFR	Code of Federal Regulations
CRF	Case Report Form
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
EE	Expedited Event
EF	Ejection fraction
eGFR	Estimated Glomerular Filtration Rate
ER	Emergency Room
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HF	Heart Failure
HFCRN	Heart Failure Clinical Research Network
HFN	Heart Failure Network
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention To Treat
IV	Intravenous
JVP	Jugular Venous Pressure
NHLBI	National Heart, Lung and Blood Institute
NRS	Numerical Rating Score
NT-proBNP	N terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PO	By mouth
QD	Once daily
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SQ	Subcutaneous

2.0 EXECUTIVE SUMMARY

Title	**SUBQ-HF Pilot: Subcutaneous Furosemide in Acute Decompensated Heart Failure**
Indication	Patients hospitalized with acute decompensated heart failure.
Location	Approximately 3-5 clinical centers in the United States
Brief Rationale	Most Acute Heart Failure (AHF) hospitalizations are related to congestion, and the primary inpatient treatment modality is parenteral loop diuretics. The average length of stay for an AHF hospitalization in the US is 5.5 days. After initial stabilization, many patients remain in the hospital for several days with a primary goal of additional decongestion with IV loop diuretics. A novel subcutaneous furosemide pump has been developed that allows patients to self-administer the equivalent of 80 mg of IV furosemide over a 5-hour period outside of the hospital setting. Existing data suggest that this approach provides bioavailability similar to that of IV furosemide injection. The clinical utility of this approach in a real world AHF population has not been evaluated.
Primary Objective	The Pilot study is designed to evaluate the overall safety and feasibility of a strategy based on subcutaneous delivery of furosemide. It will be used to inform the subsequent evaluation phase of the study (separate protocol).
Patient Population	Patients hospitalized for AHF who have had at least 24 hours of inpatient therapy and are hemodynamically stable, but still have objective signs and symptoms of congestion necessitating ongoing parenteral diuretic therapy.
Study Design	Multi-center, open-label, pilot study conducted in 2 phases. Each phase will enroll 20 subjects that will be used to inform the study design of the SUBQ-HF Study (approximately 300 evaluable patients randomized to either usual inpatient care or early discharge with home subcutaneous furosemide for 2-7 days). *Inpatient Pilot Phase:* Eligible in-patients will be approached for participation. Subjects who consent for participation will be treated with subcutaneous furosemide for 48 hours, during which they will remain in the hospital. This will be primarily a safety and feasibility assessment. There will be no formal hypothesis tested, and statistical analysis will be descriptive in nature. *Outpatient Pilot Phase:* Eligible in-patients will be approached for participation. Subjects who

	consent for participation will be instructed on use of device, discharged to home and treated at home with subcutaneous furosemide for 1-7 days. This will be primarily a safety and feasibility assessment. There will be no formal hypothesis tested, and statistical analysis will be descriptive in nature.
Intervention	Inpatient pilot: A strategy of subcutaneous furosemide for 48 hours inpatient. Outpatient pilot: A strategy of subcutaneous furosemide for 1-7 days post discharge

3.0 INTRODUCTION

3.1 Background and Significance

Hospitalization for acute heart failure (AHF) is a major clinical event in the natural history of heart failure, associated with a high morbidity and mortality over the subsequent months, high health care utilization, and costs[1]. AHF is the most common cause of hospital admission in patients over age 65, accounting for 1,000,000 admissions, over 6 million hospital days, and $12 billion in costs annually[2]. The prognosis of patients admitted with AHF is dismal, with a 20-30% readmission rate and a 20-30% mortality rate within six months after admission. Approximately 75% of heath care spending on heart failure is driven by the costs of inpatient care, and costs of heart failure care are projected to more than double by 2030[3]. Given these facts, AHF has become a major focus of health care reform and public policy. Most AHF hospitalizations are for signs and symptoms of congestion, and successful decongestion is a central therapeutic goal of a heart failure hospitalization. The vast majority (> 90%) of AHF patients are still treated with loop diuretics as the primary therapy, and the need for ongoing parenteral diuretics is a primary determinant of length of stay[4].

Despite the utility of loop diuretics in relieving congestion in most AHF patients, data suggest that many AHF patients have persistent congestion at the time of hospital discharge, whether overt (symptoms and signs) or hemodynamic (elevated filling pressures). Persistent congestion has been shown in multiple studies to contribute to high readmission rates[5, 6]. However, the average length of stay for an AHF hospitalization in the United States is approximately 6 days, and even longer hospitalizations are observed in Europe and Asia[7]. Data from the ASCEND-HF study suggest that higher length of stays are associated with lower risks of readmission, even after adjustment for differing periods of time at risk for rehospitalization[8]. While prolonged use of parenteral diuretics may improve decongestion and decrease risk of rehospitalization, but this strategy is limited by patient factors as well as cost to the health care system (typical cost heart failure hospitalization is ~ $2500/day in the United States). An alternative system of parenteral loop diuretic delivery via a subcutaneous furosemide pump may allow parenteral loop diuretic use outside the hospital system in selected patients. Patients undergoing parenteral diuresis at home rather than in hospital may experience greater overall activity, improved sleep, and better overall well- being compared to being hospitalized. Outpatient parenteral diuresis may allow for more complete decongestion which could decrease readmission rates. Overall, the treatment strategy could potentially result in fewer hospital days, lower costs, lower rates of readmission, greater patient satisfaction and substantial public health impact.

3.2 Preliminary Data

Furosemide is traditionally administered orally or via intravenous injection. Variability in oral bioavailability of furosemide, particularly in volume overload states, is a known limitation of oral administration and contributes to the well-described clinical phenomenon of decreasing

effectiveness of oral furosemide in the days leading up to AHF hospitalization. Intravenous furosemide is effective at initiating diuresis in most patients but is limited to use in hospital or in specialized clinics. From a pharmacokinetic standpoint, furosemide infusion has theoretical advantages over IV bolus infusion, although the DOSE trial did not suggest a clinically important difference between these two strategies as initial therapy in AHF patients[9]. The device to be tested in this trial, the SC2Wear pump (subcutaneous pump) utilizes a reformulated neutral pH formulation of furosemide for subcutaneous delivery. The subcutaneoupump is designed to deliver a total of 80mg of parenteral furosemide over a period of 5 hours via subcutaneous injection (30 mg in hour 1, then 12.5 mg/hour over the next 4 hours) utilizing a reusable, subcutaneous delivery system (**Figure 1**).

Figure 1. SC2Wear furosemide pump.

Small preliminary studies examined the pharmacokinetics and pharmacodynamics of the furosemide delivery via a subcutaneous pump compared to oral furosemide or IV furosemide. In a preliminary study of 10 stable (NYHA class II heart failure patients), 80mg subcutaneous furosemide dose achieved similar peak furosemide level (C_{max}), longer half-life ($t_{1/2}$), and greater total exposure (AUC) compared to a single 80mg oral dose (**Figure 2**).

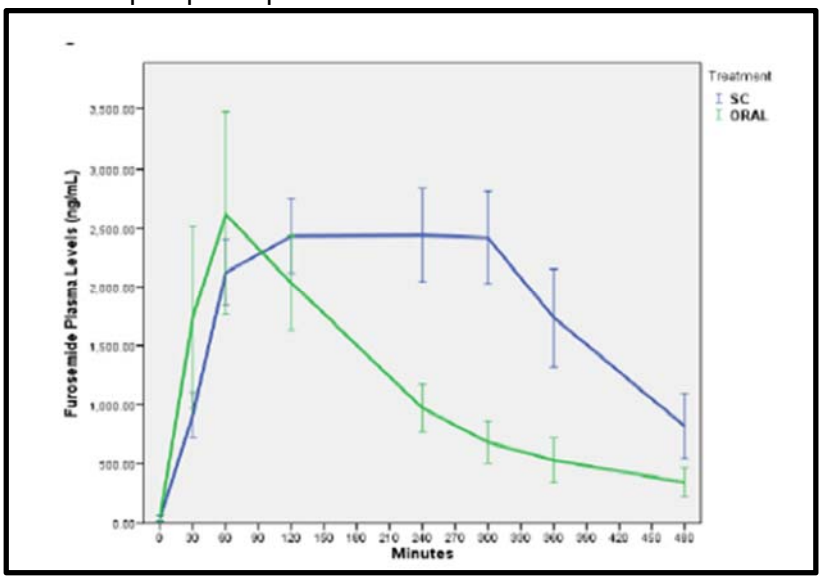
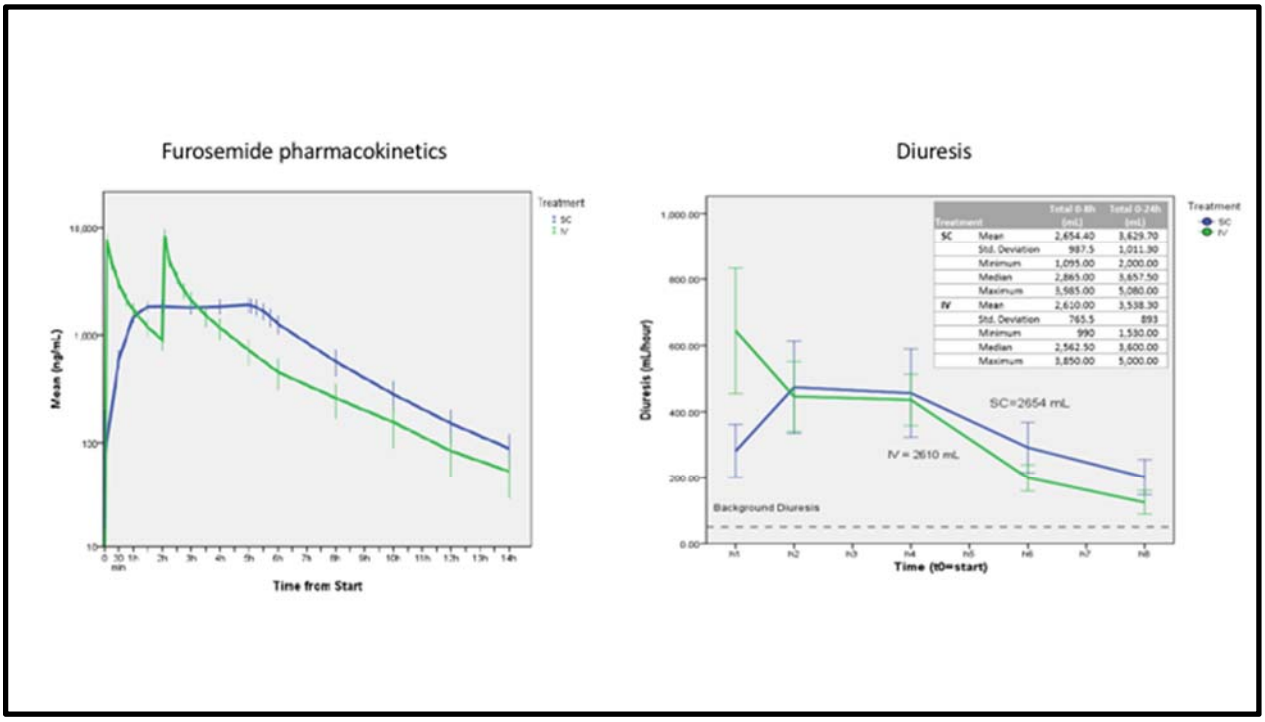


Figure 2. Plasma furosemide levels for oral furosemide and subcutaneous furosemide.

In a pharmacodynamic study of 80mg IV furosemide given as two 40mg IV pushes 2 hours apart (the FDA label dosing for IV furosemide) vs. 80mg subcutaneous furosemide produced similar diuretic effect over 8 hours (**Figure 3**). These data support the concept that subcutaneous delivery of furosemide can achieve results comparable to intravenous administration. The clinical utility of this approach has not been tested in AHF population. The goal of the SUBQ-AHF study is to test the ability of a treatment strategy utilizing the subcutaneous pump in selected AHF patients to improve the total days alive and out of the hospital within the 30 days after randomization, as well as lower overall costs of care.

Figure 3. Pharmacokinetics and diuresis from 80 mg furosemide via subcutaneous pump vs 80mg IV furosemide given as two 40mg boluses separated by 2 hours



4.0 OBJECTIVES

4.1 Primary Objectives

To determine if a strategy of a novel subcutaneous delivery of furosemide is safe and feasible in patients with AHF.

OUTCOME DETERMINATIONS
The analysis of data from the Pilot Phase will be primarily descriptive in nature and there will be

no formal hypothesis testing.

5.0 BASIC STUDY DESIGN

SUBQ-HF Pilot is a multicenter clinical trial of selected AHF patients with persistent congestion after initial stabilization. Broadly speaking, the pilot phase is designed to evaluate the overall safety and feasibility of a strategy based on subcutaneous delivery of furosemide. The pilot phase will consist of an inpatient and outpatient pilot occurring as described below and will be followed by review of data by the HF Network Steering Committee and Data Safety Monitoring Board. The same inclusion and exclusion criteria will be used for both phases of the pilot.

5.1 Inpatient Pilot

For the ***inpatient pilot***, 20 patients will be enrolled. The inpatient pilot will be a non-randomized feasibility assessment of subcutaneous furosemide in the target study population. After stabilized in the hospital for at least 24 hours of IV diuretic therapy. Subjects in the inpatient pilot will receive subcutaneous furosemide for 48 hours, during which they will remain in hospital. This will be primarily a safety and feasibility assessment. There will be no formal hypothesis tested, and statistical analysis will be descriptive in nature. The specific goals of the inpatient pilot will be to:

- Test patient tolerability of subcutaneous delivery of furosemide in AHF population
- Develop and refine screening and recruitment strategies to identify the target study population.

5.2 Outpatient Pilot

For the ***outpatient pilot***, an additional 20 patients will be enrolled. The outpatient phase will be a non-randomized feasibility assessment that will mirror the planned outpatient subcutaneous strategy planned for the larger trial. Eligible patients will be discharged home on either 80mg subcutaneous daily or BID (based on their anticipated diuretic requirements at the time of enrollment). Subcutaneous device therapy will continue for 1-7 days and dose (QD vs. BID) will be directed by the treating physician. Subjects in the outpatient pilot phase will have contact with the study site by telephone on D1, D3 and 5 days post enrollment. They will have a lab visit on D2 (+2d) post enrollment. They will have a clinic visit on D7 (+2d) post enrollment to assess the ability to utilize the subcutaneous device at home, the adequacy of diuresis, and resolution of signs and symptoms related to congestion. Subjects will have a D14 phone call to assess for adverse events. More frequent clinic contacts or laboratory monitoring may be performed as clinically indicated. A set of guidelines based on weight, symptoms, and subject-reported qualitative diuresis (see details in Appendix C) will be utilized in deciding when to transition from subcutaneous device therapy to oral diuretic therapy by the treating physician. Outpatients may not continue subcutaneous therapy beyond day 7.

The specific goals of the outpatient pilot will be to:

- Assess the feasibility of subcutaneous furosemide delivery in the target population in the outpatient setting, as measured by qualitative assessment of subject compliance and successful use of the device and related aspects of self-care (daily weights, blood pressure, etc.).
- Assess subject tolerability and safety of subcutaneous furosemide
- Assess and refine the planned guidelines for monitoring clinical response and adjustment of subcutaneous diuretics and transitioning to oral diuretics shown in Appendix C
- Assess and refine the frequency and nature of site interactions (phone calls, clinic visits, lab visits) that will be utilized in the Evaluation phase

At the completion of the pilot phase, the results will be reviewed by the HF Network Steering Committee and the Data and Safety Monitoring Board. The main SUBQ-HF study protocol will be amended, if needed, based on the analysis of the results from the pilot phase experience. If there are no substantive concerns about safety or feasibility, the SUBQ-HF study will proceed as designed.

6.0 STUDY FLOW DIAGRAM

Figure 6A. Inpatient Pilot Flow Diagram

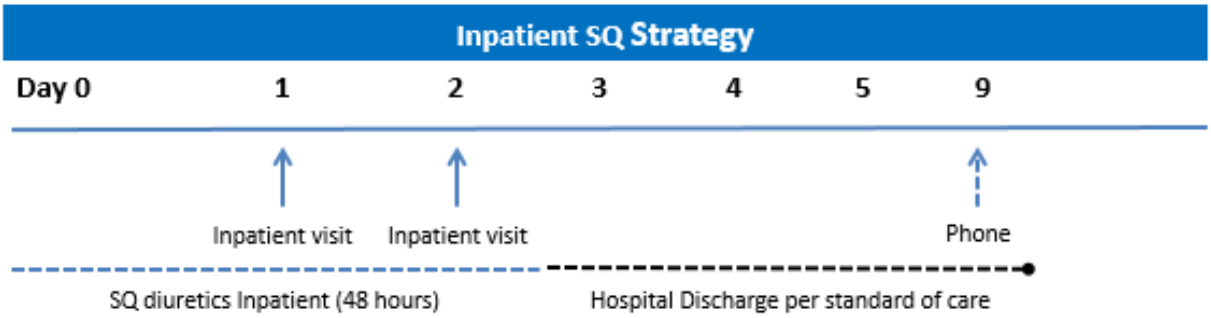
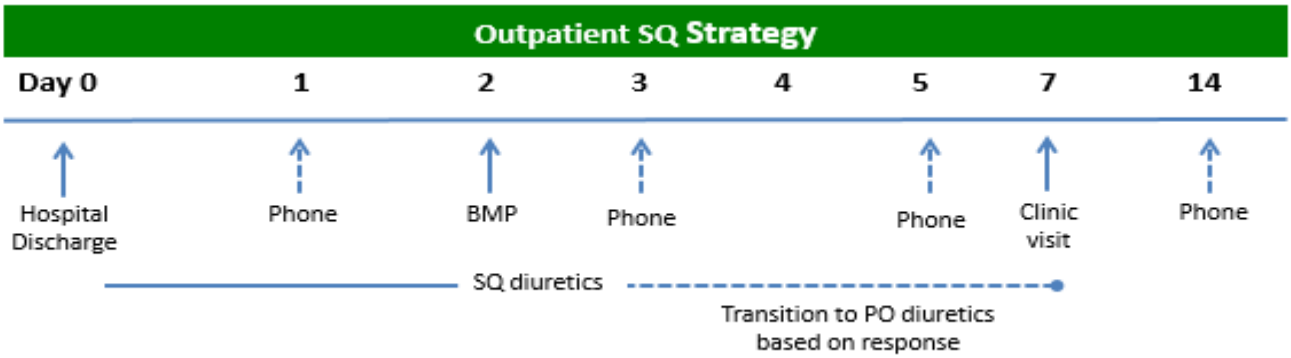


Figure 6B. Outpatient Pilot Phase Flow Diagram



7.0 STUDY POPULATION AND ELIGIBILITY CRITERIA

The study population for both the Inpatient and Outpatient Pilots will be identical. Patients hospitalized with acute heart failure (AHF) will be screened for participation in the study using the inclusion and exclusion criteria listed below.

7.1 Inclusion Criteria

1. Age ≥18 years
2. Willingness and ability to provide informed consent
3. Hospitalization for AHF with at least 1 symptom (dyspnea, orthopnea, or edema) AND 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography, BNP > 250 ng/mL or NTproBNP > 1000 ng/mL) of congestion
4. Persistent congestion despite at least 18 hours of IV therapy, defined by the presence of at least 2 or more of the following *at the time of consent:*
    a. Peripheral edema
    b. Rales
    c. Elevated JVP
    d. Ascites
    e. BNP > 250 ng/mL or NTproBNP > 1000 ng/mL
5. Total anticipated daily IV furosemide dose (at time of screening) ≥80-200 mg (or equivalent)/day
6. Anticipated need for at least 24 more hours of parenteral diuretic therapy

7.2 Exclusion Criteria

1. Severe renal dysfunction (eGFR< 30 ml/min/1.73m^2)
2. Requirement for inotropes (other than digoxin) or mechanical support during hospitalization
3. Clinically significant electrical instability during hospitalization
4. Ongoing need for other intravenous therapies beyond diuretics (vasodilators, antibiotics, etc.)
5. Anticipated need for ongoing parenteral electrolyte repletion
6. Planned discharge to location other than home (e.g, hospice, skilled nursing facility, etc.)
7. Anticipated cardiac transplantation or left ventricular assist device within the next 30 days
8. Primary hypertrophic cardiomyopathy, infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis or tamponade
9. Known or anticipated pregnancy in the next 30 days
10. Prior use of subcutaneous furosemide pump or current use of any subcutaneous pump, on-body infusion devices or patients who give regimented injections at the intended site of the furosemide infusion device
11. Other psychosocial or physical barriers to following the protocol and using a subcutaneous pump device outside the hospital setting
12. Unable to accurately measure urine output
13. Known allergy to furosemide
14. Known sensitivity or allergy to medical adhesive tape

8.0 TREATMENT INTERVENTIONS

8.1 Inpatient Pilot

Eligible patients who are in the hospital for AHF will receive subcutaneous furosemide, with planned treatment for 48 hours. Subject's last dose must start prior to 48-hour time period and will have a maximum of 4 doses. They will be treated with 5-hour 80 mg subcutaneous furosemide injection either once or twice daily, based on clinical assessment of diuretic requirements. Assessment of renal function and electrolytes will be performed as clinically indicated consistent with standard of care for inpatient treatment of AHF. The subjects will be instructed on the pump and have it applied for the first dose. The subjects will be encouraged to apply the pump while supervised at their next dosing. Subjects will be phoned at day 9 to collect safety data.

8.2 Outpatient Pilot

Eligible patients who are in the hospital for AHF will receive subcutaneous furosemide at hospital discharge, with planned treatment for 1-7 days in the outpatient setting. They will be treated with 80 mg subcutaneous furosemide injection over 5 hours either once or twice daily, based on clinical assessment of diuretic requirements. Prior to discharge the subjects will be instructed on the pump and the subject will apply it, while supervised. It is anticipated that the subject will then be discharged and they will self-administer pump at home for remainder of usage. In subjects whose hospitalization extends beyond the anticipated period, the protocol driven assessments should occur during the inpatient stay when possible.

8.2.1 Subcutaneous furosemide outpatient strategy:

Subjects will receive device training and study materials (subcutaneous pump device and 7-day supply of subcutaneous furosemide vials) on the day of planned hospital discharge (study day 0). It is assumed the subject will be discharged within 24 hours. If they are not discharged within 24 hours the subject will remain on the pump as ordered by the treating physician. Training will include instruction on daily weights and dyspnea numerical rating for symptoms. Scales will be provided to all subjects. Subjects will be discharged with a planned treatment with 80 mg 5-hour subcutaneous furosemide injection either QD or BID depending on anticipated diuretic requirements. If there are unanticipated delays in discharge after enrollment, subjects will continue with their assigned therapy and assessments in the hospital. Discharged subjects will receive a phone contact from study team on D1, D3, and D5 in order to assess adequacy of diuresis, persistence of congestion, and planned duration and dose of ongoing subcutaneous therapy (see Appendix C for guidelines on adjusting therapy). Additional clinical contact (additional phone contacts or clinical visits) may be performed if felt clinically indicated by the study team or clinical provider. All subjects will have a clinic visit at Day 7 (+2) and a safety follow up phone call at Day 14. Subjects will have assessment of electrolytes and renal function by protocol at 48 hours from discharge. Day 2 (+2) labs can be done at the study site or via home laboratory testing that is set up by study site prior to discharge if assurances are made that results will be sent to the study team in a timely manner (<24 hours). More frequent electrolyte monitoring can be performed at the discretion of the study team or clinical provider as clinically indicated. Subjects receiving the subcutaneous pump for outpatient use should be

prescribed a supplementation regimen based on electrolyte supplementation needs in the hospital with IV therapy. The duration of subcutaneous therapy will be planned from 1-7 days depending on clinical response. Dose and frequency of oral diuretics once subcutaneous therapy is completed will be per the discretion of the treating physician.

8.3 Diuretic Dose Adjustments

Diuretic therapy will be adjusted as needed based on clinical assessment of signs and symptoms of congestion, vital signs, laboratory values, and diuretic response by their attending provider. All study participants will be on 80mg subcutaneous by subcutaneous pump either once or twice daily. Outpatient pilot subjects will be prescribed either 80mg subcutaneous by subcutaneous pump either once or twice daily at hospital discharge depending on the provider assessment of their degree of congestion and diuretic responsiveness. For inadequate diuretic response, providers may either increase to 80mg subcutaneous BID (if initially treated with 80mg subcutaneous QD) or add additional open label oral diuretics, or other adjunctive treatments (such as metolazone, based on clinical judgment). The timing and dosage of the decision to discontinue subcutaneous therapy and switch to oral diuretics will be based on clinical judgment. Outpatients may not continue subcutaneous therapy beyond day 7. If subjects are readmitted for heart failure during the treatment period, subcutaneous therapy should be discontinued and the patient treated with IV diuretics as clinically indicated.

8.4 Electrolyte Repletion

Repletion of electrolytes will be based on clinical assessment of potassium and/or magnesium balance and subject's prior need for supplementation. The extent of ongoing electrolyte monitoring will be based on clinical judgment.

8.5 Concomitant Medications

Other than SUBQ pump diuretic therapy, all subjects will be treated with standard of care heart failure therapy as directed by treating providers. Information on cardiovascular medications, diuretics and electrolytes will be collected.

9.0 RECRUITMENT PROCEDURES

All patients admitted to the participating Heart Failure Clinical Research Network centers with a diagnosis of AHF will be screened for possible participation in the study. Given that the protocol requires patients to be stabilized for at least 18 hours of IV therapy prior to enrollment, this will allow for identifying and following potential patients for eligibility. Patients meeting eligibility criteria will be approached regarding participation in this study. Patients who agree to participate will be enrolled. There is no screening period in this study.

10.0 STUDY SCHEDULE

A complete schedule of assessments throughout the pilot study is provided in **Appendix A**.

10.1 Baseline Evaluation: Inpatient Pilot

At the time of enrollment, all study subjects will undergo:

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including weight)
- NYHA Classification prior to decompensation
- Input and Output measurement starts at enrollment (time of consent)
- Review of concomitant cardiovascular medications, diuretics and electrolyte supplementation
- Baseline NTpro-BNP or BNP, creatinine, BUN, and electrolytes (local laboratory), pregnancy test (if female and if not done during hospitalization)
- Numerical rating score (0-10 point NRS) for symptoms **(**see **Appendix B)**

Assessments and labs done as usual care within 4 hours of enrollment may be collected and entered into the eCRF for the study.

Once the baseline data points have been collected, a member of the study team will teach the subject about the subcutaneous pump and the infusion will be started.

10.1.1 Study Days 1-2

For study days 1-2 the following will be collected daily:

- Physical examination focused on signs and symptoms of congestion
- Daily AM weight post void
- Numerical rating score (0-10 point NRS) for symptoms
- Total inputs and outputs (i.e. fluid balance)
- Daily furosemide dose plus any rescue therapy (i.e. need for additional diuretics)
- Need for electrolyte supplementation and dose
- Lab values for basic metabolic panel (only if done per standard of care)
- Assessment for adverse events

10.1.2 Study Day 9

There will be a phone visit for all subjects 9 days (+2 days to allow for arranging the call on a weekday) post enrollment.

Assessments during this phone call will include:

- Assessment for adverse events

Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits

10.2 Baseline Evaluation: Outpatient Pilot

At the time of enrollment, all study subjects will undergo:

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including weight)
- NYHA Classification prior to decompensation
- Concomitant cardiovascular medications, diuretics and electrolyte supplementation
- Baseline creatinine, BUN, NT-proBNP or BNP, and electrolytes (local laboratory, standard of care), pregnancy test (if female of child bearing potential and not done during hospitalization)
- Numerical rating score (0-10 point NRS) for symptoms **(**see **Appendix B)**
- Assessment for adverse events

Assessments and labs done as usual care within 12 hours prior to enrollment may be collected and entered into the eCRF for the study.

Once the baseline data points have been collected, and prior to discharge, a member of the study team will teach the subject on the use of the subcutaneous pump and the subject will apply it for their first dose while supervised.

10.2.1 Study Days 1 through 7

For study days 1-7, the following will be collected daily. These data will be recorded daily by the subject and reported to the study site during phone contacts:

- Daily AM weight (from chart if subject in hospital, self weigh if home). Subjects will be instructed to collect an AM post-void weight and record this information.
- Numerical rating score (0-10 point NRS) for symptoms (subject recorded)
- Total diuretic dose
- Electrolyte supplementation (type and dose)
- Assessment for adverse events
- Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits

10.2.2 D1, D3 & D5 Phone Call

There will be a phone visit for all subjects 1, 3, and 5 days post enrollment.

Assessments during each phone call will include:

- Weight (patient reported)
- Numerical rating score (0-10 point NRS) for symptoms (patient reported)
- Changes in diuretic dose
- Electrolyte supplementation
- Assessment for adverse events
- Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits
- Any problems with the pump use or drug

10.2.3 D2 Lab Visit

On study day 2 (window: + 2 days), subjects will undergo laboratory testing of BUN, creatinine, and electrolytes. Labs can be done at the study site or via home laboratory testing that is set up by study site prior to discharge if assurances are made that results will be sent to the study team in a timely manner (<24 hours).

10.2.4 D7 Clinic Visit

There will be a protocol specified clinic visit for all subjects who have been discharged. This will occur on day 7 (+ 2 days to allow for arranging clinic visit on a weekday) post enrollment. Out-patient subjects may not continue subcutaneous therapy beyond day 7.

Assessments will include:

- Directed history and physical examination, focused on signs and symptoms of congestion.
- Vital signs (including weight)
- Numerical rating score (0-10 point NRS) for symptoms
- Creatinine, BUN, and electrolytes
- Changes in cardiovascular medications
- Assessment for adverse events
- Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits
- Blood sample for BNP or NT-proBNP (local)
- Total diuretic dose
- Electrolyte supplementation (type and dose)
- Any problems with the pump use or drug
- Return pump and all used and unused vials, cartridges and diary

10.2.5 D14 Phone Call

There will be a phone visit for all subjects 14 days (+2 days to allow for arranging the call on a weekday) post enrollment.

Assessments during this phone call will include:

Assessment for adverse events
Assessment for interval hospitalizations, ED visits, or unscheduled clinic visits

11.0 PARTICIPANT SAFETY AND ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a subject whether or not considered drug or biologic related. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a pharmaceutical product or biologic.

11.1.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” suggests there is a causal relationship between the drug and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.3 Serious Adverse Events

An AE or SAR is considered serious if the Investigator or sponsor believes any of the following outcomes may occur:

- Death
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of hospitalization.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event 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 above.

This determination is based on the opinion of either the investigator or sponsor (e.g., if either believes it is serious, it must be considered serious).

11.1.4 Laboratory Test Abnormalities

For laboratory test abnormalities that meet the definition of a serious adverse event (SAE), which required the subject to have the investigational product discontinued or interrupted, or required the subject to received specific corrective therapy, the clinical diagnosis rather than the laboratory term will be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

11.1.5 Assessment of Severity

The determination of adverse event severity rests on medical judgment of a medically qualified investigator. The intensity of AEs will be graded using the following definitions:

Mild: awareness of sign, symptom, or event but easily tolerated.
Moderate: discomfort enough to cause interference with usual activity and may warrant intervention.
Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

11.1.6 Assessment of Causal Relationship

A medically-qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Not related:** There is not a reasonable causal relationship to the investigational product and the adverse event.
- **Unlikely related:** No temporal association or the cause of the event has been identified, or the drug or biologic cannot be implicated.
- **Possibly related:** There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
- **Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

The Investigator reports causality, but the sponsor retains the final decision on causality when filing to the FDA.

11.1.7 Expectedness

The expectedness of an AE or SAR shall be determined according to the specified reference document containing safety information (e.g., most current product label). Any AE that is not identified in nature, severity, or specificity in the current study drug reference document(s) is considered unexpected. Events that are mentioned in the product label as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

11.2 Suspected Unexpected Serious Adverse Reaction

AEs that meet the criteria of serious, related to study drug, and unexpected per investigator brochure, qualify for expedited reporting to the regulatory authorities. The sponsor or their designee will notify the FDA and all participating investigators in a written IND safety report of an SAR that is serious and is unexpected, as determined by the sponsor. The reporting will occur as soon as possible, but not later than 15 calendar days after sponsor determines that it qualifies for expedited reporting. The sponsor will identify all safety reports concerning a similar SAR, and will analyze the significance of the SAR in light of the previous, similar reports. Follow-up reports will be sent to investigators to inform and update them about an important suspected adverse reaction if it significantly affects the care of the participants or conduct of the study.

11.2.1 Day Zero

Day zero (0) is the calendar day that the sponsor is first notified of an event. Day zero can also be the date the event qualified for expedited reporting as determined by the sponsor.

11.2.2 Pregnancy

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to DCRI within the same timelines as a serious adverse event. The pregnancy will be recorded on the appropriate paper pregnancy tracking form. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur to the mother or

fetus will be recorded in the AE/SAE eCRF, within the study database.

11.3 Recording and Reporting of Adverse Events

The Site Investigator is responsible for monitoring the safety of participants enrolled into the study at the study sites. Non-serious AEs that occur from the time of informed consent and up to 7 days post last product use will be collected in the study database. These events should be documented in the source documents and followed until clinically resolved.

SAEs, except for those anticipated AEs listed above, occurring from *signed informed consent* to the 7 days post last product use will be captured on the SAE form. Unless exempted as described above**,** all SAEs, whether or not deemed drug-related or expected, must be reported to the sponsor (or designee) by the investigator or qualified designee within 24 hours of first becoming aware of the event. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the study database, which will automatically result in distribution of the information to the sponsor or their designee (e.g. DCRI Safety Surveillance). If the study database system is temporarily unavailable, the event, including the investigator-determined causality to study drug should be reported via the back-up paper SAE form to the sponsor or their designee. Upon return of the availability of the electronic data capture (EDC) system, the SAE information must be entered into the study database.

11.4 Follow-up

When additional relevant information becomes available, the Investigator will record follow-up information according to the same process used for reporting the initial event as described above. The Investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

The sponsor or their designee will follow all SAEs until resolution, stabilization, until otherwise explained or until the subject completes the final follow-up, whichever occurs first.

Investigators are also responsible for promptly reporting AEs and SAEs to their reviewing IRB/EC in accordance with local requirements.

The DSMB will review detailed safety data approximately every 6 months throughout the study.

11.5 *Anticipated Disease Related Adverse Events*

The following AEs are anticipated, disease-related events in patients admitted with AHF:

- **Arrhythmias:** This refers to both atrial and ventricular arrhythmias.
- **Sudden Cardiac Death:** This refers to witnessed cardiac arrests and sudden deaths without an otherwise apparent cause such as trauma or malignancy.

- **Acute Coronary Syndrome:** This refers to unstable angina, non ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial (STEMI).
- **Cerebrovascular Event:** This refers to cerebrovascular accidents (stroke) of any cause (hemorrhagic, ischemic, or embolic) and transient ischemic attack (TIA).
- **Venous Thromboembolism:** This includes both deep venous thrombosis and pulmonary embolus.
- **Lightheadedness, Presyncope, or Syncope:** This includes dizziness, lightheadedness, or fainting from any cause.
- **Acute kidney injury as defined by KDOQI guidelines:** Acute kidney injury, typically defined as a rise in creatinine > 0.3 mg/dL over 48 hours, or progressive loss of renal function over time.
- **Worsening HF:** Worsening of symptoms and signs of heart failure requiring intensification of IV therapy or initiation of mechanical therapy.
- **Hypokalemia** (K^+ <3.5 mmol/L)
- **Hypomagnesemia** (Mg <1.0 mEq/L or <0.70 mmol/L)

All anticipated disease related events, will not be captured as AEs/SAEs during the study, but will be entered on the appropriate eCRF module.

11.6 Summary of the Risks

Experience with subcutaneous furosemide injection has been limited. Although preclinical studies did not suggest any local irritation or reaction from administration of the study drug, local discomfort or irritation following administration of the study drug cannot be excluded.
The subcutaneous administration of furosemide is expected to be associated with the same systemic adverse experience profile as the intravenous and intramuscular administration. The systemic adverse experience profile for intravenous and intramuscular furosemide is listed below.

11.6.1 Drug Adverse Reactions

General
Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possibly vascular thrombosis and embolism, particularly in elderly patients. As with any effective diuretic, electrolyte depletion may occur during furosemide therapy, especially in patients receiving higher doses and a restricted salt intake. Hypokalemia may develop with furosemide, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids, ACTH, licorice in large amounts, or prolonged use of laxatives may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

All patients receiving furosemide therapy should be observed for these signs or symptoms of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, or hypocalcemia): dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting. Increases in blood glucose and alterations in glucose tolerance tests (with abnormalities of the fasting and 2-hour postprandial sugar) have been observed, and rarely, precipitation of diabetes mellitus has been reported. In patients with severe symptoms of urinary retention (because of bladder emptying

disorders, prostatic hyperplasia, urethral narrowing), the administration of furosemide can cause acute urinary retention related to increased production and retention of urine. Thus, these patients require careful monitoring, especially during the initial stages of treatment. In patients at high risk for radiocontrast nephropathy, furosemide can lead to a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast. In patients with hypoproteinemia (e.g., associated with nephrotic syndrome) the effect of furosemide may be weakened and its ototoxicity potentiated. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Patients allergic to sulfonamides may also be allergic to furosemide. The possibility exists of exacerbation or activation of systemic lupus erythematosus. As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver or kidney damage, or other idiosyncratic reactions.

11.6.2 Information for Patients

Patients receiving furosemide should be advised that they may experience symptoms from excessive fluid and/or electrolyte losses. The postural hypotension that sometimes occurs can usually be managed by getting up slowly. Potassium supplements and/or dietary measures may be needed to control or avoid hypokalemia.

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.
Hypertensive patients should avoid medications that may increase blood pressure, including over-the counter products for appetite suppression and cold symptoms.

Adverse Reactions

Adverse reactions are categorized below by organ system and listed by decreasing severity.

Gastrointestinal System Reactions
(1) Hepatic encephalopathy in patients with hepatocellular insufficiency (2) Pancreatitis (3) jaundice (intrahepatic cholestatic jaundice) (4) increased liver enzymes (5) anorexia (6) oral and gastric irritation (7) cramping (8) diarrhea (9) constipation (10) nausea (11) vomiting.

Systemic Hypersensitivity Reactions
(1) Severe anaphylactic or anaphylactoid reactions (e.g., with shock) (2) Systemic vasculitis (3) interstitial nephritis (4) necrotizing angiitis.

Central Nervous System Reactions
(1) Tinnitus and hearing loss (2) paresthesias (3) vertigo (4) dizziness (5) headache (6) blurred vision (7) xanthopsia.

Hematologic Reactions
(1) Aplastic anemia (2) thrombocytopenia (3) agranulocytosis (4) hemolytic anemia (5) leukopenia (6) anemia (7) eosinophilia.

Dermatologic-Hypersensitivity Reactions
(1) Exfoliative dermatitis (2) bullous pemphigoid (3) erythema multiforme (4) purpura (5) photosensitivity (6) urticaria (7) rash (8) pruritus (9) Stevens-Johnson Syndrome (10) toxic epidermal necrolysis.

Cardiovascular Reaction
(1) Orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics, (2) Increase in cholesterol and triglyceride serum levels.

Other Reactions
(1) Hyperglycemia (2) glycosuria (3) hyperuricemia (4) muscle spasm (5) weakness (6) restlessness (7) urinary bladder spasm (8) thrombophlebitis (9) transient injection site pain (10) fever.

11.6.3 Device Adverse Reactions

SC2Wear System
Mild skin irritation such as redness, itching and edema or skin trauma and abrasion may occur during exposure or removal of the adhesive. Removal of the device may be uncomfortable or painful. Rarely, allergic reactions to the adhesive may occur. If the subject knows they are sensitive or allergic to medical adhesive tape, they should not participate in the study.

The needle used to inject the drug into the subcutaneous tissue is automatically inserted at the beginning of the infusion cycle, and automatically retracted at the end. The needle is 27 gauge and 8.5 mm. Common risks with needle injection include pain or discomfort upon needle injection, or minor bruising from needle movement. Injection site reactions were minimal and limited to very slight edema and very slight to definite erythema. An accidental needle stick injury may occur if (a) the needle appears before the Pump is placed on the body or (b) the Pump falls off the body while it is pumping. If either of the above happens, the Pump should be handled carefully.

As with all devices that use medical adhesives for adherence the usual risks are: it is possible that there may be instances of complete or near complete dislodgement of the device from the abdominal skin. In a previous study designed to look at adhesive effectiveness in combination with the sc2Wear device, 2 out of 132 device applications (1.5%) became completely detached from the skin. In the same study 6 subjects (4.5%) had evidence of medical adhesive-related skin injury (MARSI). The finding of rare cases of dislodgement and rare cases of MARSI indicate that the objective to find an adhesive with the optimal balance between adhesive strength and skin tolerability has been achieved. Using more aggressive adhesive would increase the risk of MARSI which carries a risk of infection and may reduce the patient acceptance of this treatment. Should dislodgement occur, there would be minimal risk to the patient, as it would be obvious and clearly discoverable by the patient being treated. In such instances, the patients will be instructed to call their healthcare provider. In this study, patients are instructed to contact the study team in cased of complete dislodgement or if leakage is detected.

12.0 STATISTICAL CONSIDERATIONS AND DATA MANAGEMENT PROCEDURES

12.1 Overview

There will be no formal hypothesis tested, and statistical analysis will be descriptive in nature.

12.2 Analysis of Safety Data and Statistical Monitoring Plan

Interim data analysis for efficacy and futility will not be conducted due to relatively small size and short duration of this clinical trial. Safety data will be assessed at the completion of the pilot study by the NHLBI-appointed DSMB. The safety analyses will be based on the entire ITT population. Safety will be evaluated by comparing the rates of occurrence and severity of AEs of the study population to expected rates of occurrences.

12.3 Overview of Data Management

The CC will have primary responsibility for data management, including the development of data collection systems, data monitoring processes, and data storage and back up. State-of-the-art technology will be used for the management of the network's data.

The CC team will develop modules necessary for this study. Common fields and data elements will be used across the HFN trials to promote data standardization and facilitate cross-network analyses. Study components may include an enrollment and demographics form; forms for recording relevant history, HF symptoms, physical exam results, laboratory results, baseline biomarker levels, and other baseline presenting characteristics; follow-up forms for use during regular follow-up visits; forms to track the participant's clinical course over time; and event forms for recording the circumstances and details surrounding the occurrence of a death or hospitalization.

The data will be collected in a validated, 21 CFR Part 11-compliant EDC system. The DCRI has an internal team of skilled data managers and programmers that will design and produce a tailored network system that provides operational efficiency and meaningful reporting of metrics.

12.3.1 Data Management Process

The EDC system will be used for data entry and may be used for simple reports. All data will be entered into the eCRF by personnel at the clinical sites. The system allows for both automatic and manual queries.

The CC may create reports to identify trends in the data that may require additional clarification and training. The CC may perform internal database quality-control checks during the study to identify systematic deviations requiring corrections.

12.3.2 Data Quality Control

A two-step approach to data quality control will be implemented.

1. Training: Prior to the start of enrollment, the Investigators and Study Coordinators will be trained on the clinical protocol and data collection procedures. Recent site surveys indicate that most Coordinators are very familiar with the EDC system, so training is typically targeted to a specific protocol. For Coordinators new to the InForm database, the CC will be available to provide training with hands-on database interaction and demonstration of key EDC system functionality as needed. Personnel at the clinical sites

will enter the data mandated by the protocol into the eCRFs. The data will be extracted from the participant's medical charts and other source documents. The CC will conduct follow-up training and training for new study personnel as needed.

2. Monitoring: A CC monitor will visit sites during the enrollment period to ensure that data collection is being handled properly, to provide in-service training, and to address questions from site investigators and coordinators. Additional details will be outlined in the Clinical Monitoring Plan.

12.4 Data Security

Access to databases will be controlled centrally by the CC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by a firewall and through controlled physical access. Database back-up will be performed daily using standard procedures in place at the CC. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

12.5 Publication Policy

Dissemination of preliminary information can adversely affect the objectivity of study data. For this reason, Investigators will be prohibited from performing subset analyses at any point prior to the conclusion of the study, and any data, other than safety data, cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB or HFN Steering Committee.

13 STUDY ADMINISTRATION

13.1 Data and Safety Monitoring Board (DSMB)

A DSMB has been appointed by the NHLBI for the HFN. This committee consists of a group of highly experienced individuals with extensive pertinent expertise in HF and clinical trials. The DSMB will advise the HFN Steering Committee regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. Safety data, summarized at the treatment level, will be assessed approximately every 6 months by the DSMB. The safety analyses will be based on the entire ITT population. During the evaluation phase, safety will be evaluated by comparing the occurrence of AEs and changes in laboratory values between study strategies.

13.2 Coordinating Center

The Duke Clinical Research Institute will function as the CC for this trial as specified by the National Institute of Health and NHLBI HFN grant.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and applicable national and local regulations. This will ensure adherence to Good Clinical Practice, as described in the following documents:

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

Participating investigators agree to adhere to the instructions and procedures described in the protocol and thereby to adhere to the principles of Good Clinical Practice to which it conforms.

14.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be provided to the CC before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

14.3 Informed Consent

The investigator or designee must explain to each participant (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The informed consent form(s) must be submitted by the investigator for IRB/IEC approval. The Coordinating Center will supply template informed consent forms, which comply with regulatory requirements, and are appropriate for the study. Any changes to the template consent form suggested by the Investigator must be agreed to by the Coordinating Center before submission to the IRB/IEC, and a copy of the approved version must be provided to the Coordinating Center after IRB/IEC approval.

14.4 Confidentiality and HIPAA Requirements

All information collected on study participants will be stored in a confidential manner using the procedures in place at each participating center. Only approved study personnel will have access to data collected as part of the study. Study participants will be identified by a participant ID number on all study documents. Data will be transmitted to the CC in a secure manner, and stored securely at the CC using standard Duke Clinical Research Institute operating procedures.

15.0 MONITORING

The study will be monitored remotely by representatives of the Duke Clinical Research Institute or its designee according to the prospective clinical monitoring plan for the following purposes:

- To enable real-time monitoring of compliance with study protocol inclusion and exclusion criteria; this will be enabled via triggers and range checks programmed in the InForm database.
- To assist site personnel who will verify data identified within query reports against source documents through frequent telephone and email contact.
- To verify that written informed consent was obtained before initiation of any screening procedures that are performed solely for determining eligibility for the clinical study and/or prior to any tests or procedures.

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17.0 APPENDICES

17.1 Appendix A. Schedule of Assessments

Inpatient Pilot

	D0	D1	D2	D9 (+2d)
Inpatient	x	x	x	
Phone Call				x
Vitals	x	x	x	
Weight	x	x	x	
I/O	x	x	x	
Diuretic dose and electrolyte supplementation[1]	x	x	x	
Medical History	x			
PE/Congestions Assessment	x	x	x	
Symptom Rating (NRS)	x	x	x	
AEs/SAEs	x	x	x	x
Electrolytes[2] & Renal Function	x	x	x	
BNP or NTproBNP	x			
Pregnancy test (females only)	x			

1Potassium and magnesium supplementation changes from pre-hospitalization.
2For the basic metabolic panel, all available lab values performed as standard of care will be collected. However, the protocol driven lab values are: sodium, potassium, chloride, BUN, creatinine, calcium, glucose, and magnesium.

Outpatient Pilot

	D0	D1	D2 (+2d)	D3	D4	D5	D6	D7 (+2d)	D14 (+2d)
Inpatient	x								
Clinic Visit								x	
Phone Call		x		x		x			x
Vital Signs(includes weight)	x							x	
Weight		x[3]	x[3]	x[3]	x[3]	x[3]	x[3]		
Diuretic dose and electrolyte supplementation[1]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x	
Medical History	x								
Physical Exam/Congestion Assessment	x							x	
Symptom Rating (NRS)	x	x[3]	x[3]	x[3]	x[3]	x[3]	x[3]	x	
AEs/SAEs	x	x		x		x		x	
Electrolytes[2] & Renal Function	x		x					x	
BNP or NT-Pro BNP	x							x	
Pregnancy Test (females only)	x								

1Potassium and magnesium supplementation changes from pre-hospitalization.

2For the basic metabolic panel, all available lab values that were performed for standard of care will be collected. However, the protocol driven lab values are: sodium, potassium, chloride, BUN, creatinine, calcium, glucose, and magnesium.

3Subject to record daily and report to coordinator on call and return diary at Day 7 visit.

17.2 Appendix B. Numerical Rating Scale for Breathlessness

On a scale from 0 to 10

Indicate how much shortness of breath you are having right now.

With 0=no shortness of breath

And 10=shortness of breath as bad as can be

Circle the number:

0 1 2 3 4 5 6 7 8 9 10

17.3 Appendix C. Guidelines for Remote Adjustment of Diuretics during outpatient Subcutaneous treatment

This document provides a framework for remote decision-making (I.e., assessing and adjusting therapy in the absence of a face-to-face encounter with the patient) to guide the use and adjustment of outpatient diuretics during outpatient treatment with subcutaneous diuretics therapy. It is intended to provide general guidance rather than specific instructions, and the guidelines herein will have to interpreted and applied in the context of good clinical judgment. Data from laboratory testing (renal function, electrolytes, etc.) will also inform decision-making.

Assessments will generally include consideration of the following variables:

- Patient reported weight/change in weight relative to best "dry weight" as determined at time of study enrollment
- Blood pressure and heart rate (patient reported)
- Presence and/or change in-patient reported symptoms and/or signs related to congestion (dyspnea, orthopnea, edema, abdominal distension).
- Presence and/or change in symptoms related to intravascular volume depletion (dizziness, lightheadedness, pre-syncope, syncope etc.)
- Patients subjective report of adequacy of diuresis

Recommend continue current strategy without change:
Persistent signs/symptoms of congestion
Weight still >=5 lbs. above dry weight
Blood pressure and heart rate within acceptable range (will vary by patient)
No signs of suggestive of intravascular volume depletion
Subjectively adequate diuresis

Recommend increase diuretic regimen or clinic visit
Persistent or worsening signs symptoms of congestion
Weight still >=5 lbs above dry weight or increasing
Blood pressure and heart rate within acceptable range (will vary by patient)
No signs of suggestive of intravascular volume depletion
Subjectively inadequate diuresis

Recommend transition to oral diuretics
Signs or symptoms of congestion at or near baseline
Weight within 3 lbs. of dry weight
Blood pressure and heart rate within acceptable range (will vary by patient)
No signs of suggestive of intravascular volume depletion
Subjectively adequate diuresis

Recommend clinic visit
Clinically important changes in blood pressure or heart rate (will vary by patient)
Signs or symptoms of intravascular depletion
Any other evidence of clinical instability