STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: Furoscix in Heart Failure Patients with Diuretic Resistance

NCT number: NCT05528588

IRB Approved date: 07-22-24

Form A

IRB #	STU-2022-0768

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

The purpose of this study is to assess the diuretic efficiency of subcutaneous furosemide (Furoscix) compared to oral diuretic therapy for patients post heart failure (HF) hospitalization and evaluate the impact of diuretic resistance as identified by the BAN-ADHF (**B**lood urea nitrogen, cre**A**tinine, **N**atriuretic Peptide levels, **A**trial fibrillation**, D**iastolic blood pressure, **H**ypertension and **H**ome diuretic dose, and **H**eart Failure hospitalization) risk score.

Key Outcomes:

1. Post-treatment urine output over 8 hours. This will be assessed in mL per mg of treatment (Furoscix vs. oral diuretic).
2. Post-treatment urine sodium. Urine sodium will be assessed hourly over 8 hours post-treatment.

Safety Outcome Measures:

1. Number of participants with post-intervention need for emergency department visit or hospitalization. The count of participants with post-intervention need for emergency department visit or hospitalization for worsening heart failure is assessed.

Goals: Successful completion of this project will establish proof of concept that Furoscix provides more effective post-hospitalization diuresis than the traditional oral dose in a diuretic resistance patient population. This study will provide pilot data to guide the design of larger studies involving a diuretic-resistant heart failure population.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Introduction

Heart failure is one of the leading causes of hospitalization in the United States, contributing to over 1 million emergency department visits and nearly 1 million hospitalizations for HF annually.[1] The estimated mean cost for HF was $11,552 in 2014, totaling an estimated $11 billion.[2] Thus, strategies to reduce the burden of acute care use for patients with heart failure are necessary. Acute decompensation of heart failure is characterized by volume overload and is primarily treated with intravenous diuretics. However, inefficient and ineffective diuresis both during hospitalization and in the post-discharge environment predispose patients to frequent readmission and a worse prognosis.[3] Importantly, there is heterogeneity in patient response to intravenous diuresis, with an estimated 20-50% of patients having poor response to initial IV diuretic therapy.[3] Patients who are resistant to intravenous diuresis have increased risk of re-hospitalization and mortality. Importantly, our group recently derived an integer-based risk score (BAN-ADHF score) to predict patients with low diuretic efficiency, with the research winning the NHLBI Heart Failure Data Challenge.[4,5]

As part of patient's standard of care, they receive oral diuretics, including furosemide or torsemide, which are FDA approved for treating congestion and volume overload from heart failure. However, some patients are "resistant" to oral diuretics and have higher risk of repeat hospitalization. Therefore, purpose of this study is to evaluate treatment with subcutaneous furosemide (Furoscix) compared with oral diuretic therapy for patients with recent heart failure hospitalization either with or without diuretic resistance.

Furoscix (Furosemide Injection) is FDA approved for subcutaneous administration for the treatment of congestion due to fluid overload in adult patients with New York Heart Association (NYHA) Class II and Class III chronic heart failure who display reduced responsiveness to oral diuretics and who do not require hospitalization.[6] The research team is collecting safety and efficacy data on this drug.

This drug is administered via a device called the Infusor (Note: The research team is not studying the device component). The Infusor delivers 80 mg of Furoscix. Per Sponsor: "The infusor is a compact, ethylene oxide (EtO) sterilized, single-use, electro-mechanical (battery powered, micro-processor controlled), on-body subcutaneous delivery system based on the SmartDose® Gen II 10 mL (West Pharmaceutical Services). The Infusor is applied to the abdomen via a medical grade adhesive and delivers a subcutaneous infusion of Furoscix through a pre-programmed, biphasic delivery profile with 30 mg (3.75 mL) administered over the first hour, followed by 12.5 mg (1.56 mL) per hour for the subsequent 4 hours (Total dose is 80 mg (10 mL) over 5 hours)."[7]

References:

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation*. 2021;143:e254-e743. doi: 10.1161/CIR.0000000000000950
2. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. *Circ Heart Fail*. 2018;11:e004873. doi: 10.1161/CIRCHEARTFAILURE.117.004873
3. Gupta R, Testani J, Collins S. Diuretic Resistance in Heart Failure. *Curr Heart Fail Rep*. 2019;16:57-66. doi: 10.1007/s11897-019-0424-1
4. Chaikijurajai T, Segar MW, Pandey A, Tang WHW. Validation Of The BAN-ADHF Risk Score And Risk Of Long-term Mortality In Patients With Acute Decompensated Heart Failure. *Journal of Cardiac Failure*. 2022;28:S36-S37. doi: https://doi.org/10.1016/j.cardfail.2022.03.098
5. Parsa S, Segar M, Butler J, Willett D, Tang WHW, Pandey A. PREDICTION OF DIURETIC RESISTANCE IN PATIENTS WITH CHRONIC STABLE HEART FAILURE: THE BAN-ADHF RISK SCORE. *Journal of the American College of Cardiology*. 2022;79:293-293. doi: doi:10.1016/S0735-1097(22)01284-0
6. Furoscix (furosemide injection). Burlington, MA. scPharmaceuticals, 2022.
7. scPharmaceuticals, 2022. Confidential document.

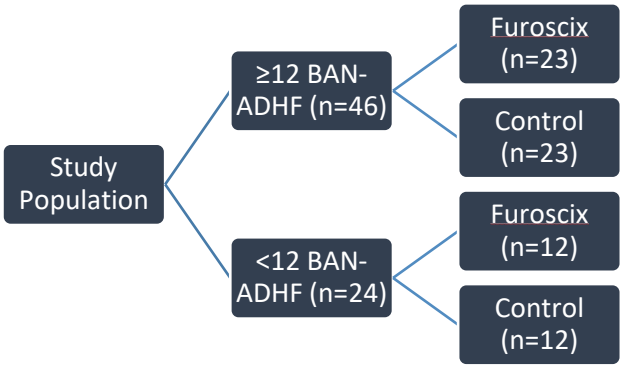
b. Current practice

After discharge, current practice is to transition patients back to a home oral diuretic regimen in hopes that this will provide sufficient diuresis to prevent re-hospitalization.

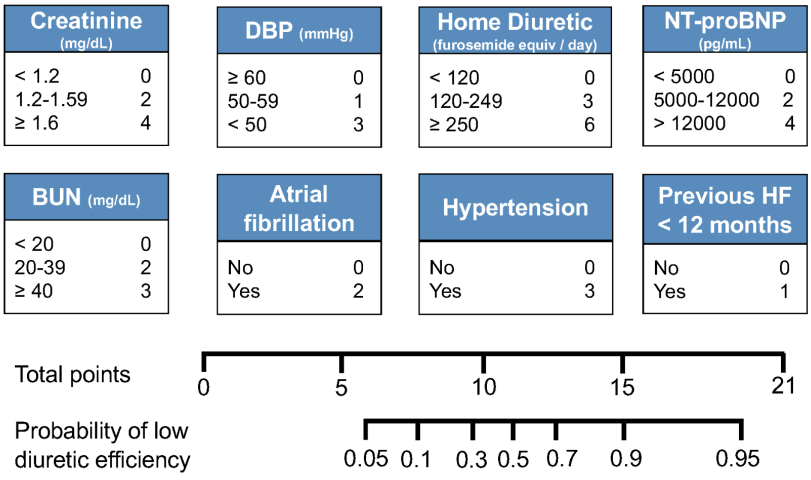
3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

This will be a randomized, open-label pilot study of 70 patients with and without diuretic resistance who were recently admitted and discharged for acute decompensated heart failure with an oral diuretic regimen testing whether Furoscix is more effective at achieving post-discharge outpatient diuresis than standard of care.

Schema:



Visual description of the BAN-ADHF Score



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4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Inclusion and Exclusion Criteria:

Eligibility criteria are shown in the following table:

Inclusion Criteria	Exclusion Criteria
• English speaking patients discharged after ward hospitalization for acute decompensated heart failure • Able to be screened and enrolled within 14 days of discharge • Recent echocardiogram (6 months or less) • Discharged with diuretic therapy	• Chronic kidney disease stage 5 (GFR<20) or End Stage Kidney Disease • Systolic blood pressure <100 • ICU hospitalization within 3 months • Inotrope use within last 3 months • Home inotropes • Electrolyte abnormalities on discharge • Inadequate data for BAN-ADHF score • Pregnant • Prior heart transplantation or left ventricular assist device • Low-output heart failure • Concurrent use of non-loop diuretic • Advanced liver disease • Severe malnutrition • Skin/Soft tissue condition precluding Furoscix • Inability to collect urine • Non-English-speaking patients

Intervention, Setting, and Design: We are recruiting patients from UTSW and Parkland. All of the research procedures in this study will take place at the Clinical Research Unit in the Aston Building at UT Southwestern Medical Center. This will be a randomized, open-label pilot study of 70 patients with and without diuretic resistance who were recently admitted and discharged for acute decompensated heart failure with an oral diuretic regimen testing whether Furoscix is more effective at achieving post-discharge outpatient diuresis than oral diuretics. Diuretic resistance will be identified using the BAN-ADHF (**B**lood urea nitrogen, cre**A**tinine, **N**atriuretic Peptide levels, **A**trial fibrillation**, D**iastolic blood pressure, **H**ypertension and **H**ome diuretic dose, and **H**eart Failure hospitalization) score which has been integrated into the electronic health record. The score is integer-based with a score of ≥ 12 indicating diuretic resistance with high likelihood of poor outcomes.

Screening:

- We are requesting a partial HIPAA waiver to review electronic health records and confirm their eligibility in the study. Pre-screening will occur through the electronic health record to evaluate for inclusion and exclusion criteria and to assess if women of child-bearing potential have a pregnancy test to confirm they are not pregnant. Lab testing will be reviewed. These include review of urine drug screen, alcohol screen (if clinically indicated), NT-proBNP, creatinine clearance.
- BAN-ADHF score will be calculated.

- After patients are screened, patients will be approached for potential participation. If patients are interested, they will be scheduled for an in-person randomization visit optimally within 1-7 days of hospital discharge, although patients will be eligible up to 14 days after discharge.
- At the research appointment, patients will be asked if they are interested in voluntarily participating in this study.

Research Visit:

Pre-Randomization:
- Confirm eligibility
- Obtain informed consent
- Physical exam including vital signs assessment.
- Prior and concomitant medication assessment.

Randomization:
If patients still meet all eligibility criteria and sign informed consent, they will undergo stratified randomization based on BAN-ADHF score (≥12 vs. <12). Within each stratum, patients will be randomized in a 1:1 ratio (intervention: control) during the research visit. Patients will be informed via telephone prior to visit to not take home oral dose of diuretic on the day of the visit and will be instructed to hold any caffeine products such as coffee or any other drugs that could increase urine output on the day of the visit.

- **Intervention: Furoscix** – administration of subcutaneous furosemide (Furoscix) during study visit. It will be administered using the Furoscix Infusor. Per information from the Sponsor, "The Infusor is placed on the patient's abdomen for subcutaneous infusion. Furoscix is delivered subcutaneously through a small, 27-gauge, 6 mm needle. The Infusor is preprogramed to deliver 80 mg (10 mL) furosemide over 5 hours using a biphasic delivery profile of 30 mg furosemide (3.75 mL) over the first hour and 12.5 mg furosemide (1.56 mL) per hour over the subsequent 4 hours."[7]
- **Control: Oral Diuretic** - administration of oral diuretic during study visit. Patients will bring their home prescription of oral diuretic and will take the oral formulation while in the visit. If the patient did not bring their home dose, an equivalent oral dose will be provided from the UT Southwestern Investigational Drug Service.

The intervention arm (Furoscix over 5 hours at 8 mg/mL) will be compared to a usual care group (home oral diuretic dose prescribed by discharge physician). Patients will be monitored for 8 hours in the Clinical Research Unit post-drug administration for clinical safety and to measure clinical response.

Other research procedures:
- Patients will be instructed to void immediately before dosing (pre-dose urine) and this sample will be discarded. After medication administration, urine from spontaneous voids during post-dose phases will be collected and recorded. Urine sodium measurements will be obtained at hourly intervals. Urine from each collection period must be refrigerated until the end of the collection period. Total volume of urine produced will be assessed over 8 hours post-study drug administration. 5 mL of each hourly urine sample will be sent for a urine sodium lab test in a yellow round bottom tube.
- Collect approximately 10 mL of blood for a blood test to check patient's electrolytes. This will be done at the end of the research visit.
- Call participants in 7 days after their research visit to assess if patient has had a presentation to urgent care, emergency department, or is re-hospitalized for acute exacerbation in heart failure.

Compensation:
To account for a full day of research monitoring, patients will be compensated $250 for their participation in the study with the UTSW ClinCard.

Data Safety and Monitoring:
Patient safety will be tracked over the study. For any adverse events (AE) that occur during their participation in the study, medical care will be provided and patients will be followed until resolution. See Form D for more details.

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Privacy and Confidentiality:
To protect patient's privacy and confidentiality, we will ensure the consent process takes place in a private area and conduct research in secure areas where others will not have access to their PHI. All PHI collected during the study will be coded with a Subject ID using a randomized code. The key to the code will be kept on a password database in the research coordinator's locked office. Only authorized personnel listed on Form B will have access to the data. Any hard copy documents such as the signed consent form will be kept in the research coordinator's locked office.

Statistical Analysis:
This study will assess the primary outcomes of greater diuretic efficiency as measured by total urine output and urine sodium. As the Furoscix group will receive 80 mg of subcutaneous furosemide and the control group will take a home dose of oral diuretic, urine output will be normalized per mg of treatment administered. Differences in total urine produced will be compared between Furoscix versus oral diuretic groups. The urine sodium will be assessed hourly, and will be compared across the two groups.

As this study is a preliminary pilot study to assess the effect of Furoscix on diuretic efficacy, we have chosen a convenience sample of 70 patients to allow for a comparison between patients who receive Furoscix and those who do not receive Furoscix. The results of this trial will serve as a precursor for a larger, multicenter trial of Furoscix in patients with diuretic resistance.

4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	Furoscix (Furosemide subcutaneous)	☒ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes
2	Insert study intervention 2 here	☐ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

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4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

4.c.
Study Intervention #1
Furoscix (Furosemide subcutaneous)

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
Intervention arm (Furoscix)	Participants will not personally benefit from this study. Their participation may provide data that will help prevention of future heart failure hospitalizations.

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

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4.c.
Study Intervention #1
Insert name used in 4.b.

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

4.d. List ALL other research procedures or components not listed in table 4.b.
The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.

Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)

#	Research component • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Screening for Eligibility in Medical Records**	N/A	Multiple Times	Breach of confidentiality; not serious and less likely
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
2	**CRU visit**			
	Screening Procedures	N/A	Once	N/A-See risks in the consent form
	Urine samples	N/A	Multiple times	N/A-See risks in the consent form
	10 mL blood draw		Once	N/A-See risks in the consent form
3	**Post-CRU visit follow-up**			
	Call patient to assess whether they were hospitalized in 7 days post discharge	N/A	Once	N/A-See risks in the consent form
	Insert procedure here			
	Insert procedure here			
4	**Insert component 4 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Risks and side effects related to Furoscix include those which are:

Likely, some may be Serious

In 100 people, approximately 21-100 may have:

- Dehydration
- Electrolyte depletion, including low potassium (hypokalemia), low sodium (hyponatremia), low magnesium (hypomagnesemia), low calcium (hypocalcemia).
- Dry mouth
- Thirst

- Weakness
- Muscle pains or cramps
- Low blood pressure
- High heart rate
- Arrythmia
- Nausea or vomiting

Less Likely, some may be Serious
In 100 people, approximately 2-20 may have:

- Deterioration in kidney function
- Increased uric acid and gout
- Urine bladder spasm
- Transient injection site pain
- Fever
- Restlessness

Rare and Serious
In 100 people, approximately 1 or less may have:

- Exacerbation of systemic lupus erythematosus
- Allergy to furosemide/Systemic hypersensitivity reactions
- Liver or kidney damage
- Tinnitus and hearing loss
- Aplastic anemia, thrombocytopenia, agranulocytosis
- Skin hypersensitivity reactions

Risks and side effects related to Oral Diuretic Therapy:

Likely, some may be Serious
In 100 people, approximately 21-100 may have:

- Dehydration
- Electrolyte depletion, including low potassium (hypokalemia), low sodium (hyponatremia), low magnesium (hypomagnesemia), low calcium (hypocalcemia).
- Dry mouth
- Thirst
- Weakness
- Muscle pains or cramps
- Low blood pressure
- High heart rate
- Dizziness

Less Likely, some may be Serious
In 100 people, approximately 2-20 may have:

- Deterioration in kidney function or an acute kidney injury
- Increased uric acid and gout
- Urine bladder spasm

Rare and Serious
In 100 people, approximately 1 or less may have:

- Exacerbation of systemic lupus erythematosus
- Allergy to furosemide or torsemide/Systemic hypersensitivity reactions
- Liver or kidney damage
- Tinnitus and hearing loss
- Aplastic anemia (bone marrow failure), thrombocytopenia (low blood platelet count), agranulocytosis (low white blood cell count)
- Skin hypersensitivity reactions such as skin rash

Furoscix is a specific subcutaneous formulation of furosemide. Patients are required to be taking home diuretics as eligibility criteria; therefore we anticipate very few side effects associated with the medication. Skin reactions may occur with administration of Furoscix, although this is a rare side effect. Patients will be monitored for 8 hours post medication administration, with a serum potassium check performed after the study visit to ensure stable serum electrolytes.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

A physician will be always available during the study visits. A research nurse will be monitoring the patient throughout the research visit. We will also follow up with patients over the phone in a week after their study visit.

Should any AE's occur, it will be documented and medical care will be provided. The team will follow patient's AE until resolution. See Form D for more information.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

N/A