scPharmaceuticals

STUDY PROTOCOL

Open-label, Single-dose, Randomized, Two-way (two-period) Crossover Study to Compare the Pharmacokinetics and Pharmacodynamics of SCP-111 (furosemide injection) Administered as a Subcutaneous Injection vs Furosemide Administered as an Intravenous Injection in Healthy Volunteers

IND Number:	158047
Protocol Number:	scP-04-001
Study Type:	Phase I
Investigational Drug-Device Combination:	SCP-111 Autoinjector
Original Protocol Date:	04 February 2022
Amendment 1 Date	03 May 2022
Amendment 2 Date	18 November 2022
Amendment 3 Date	06 September 2023
Amendment 4 Date	29 November 2023

SPONSOR CONTACT INFORMATION

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SUMMARY OF CHANGES

Amendment 1: The protocol has been amended to incorporate FDA recommended dosing regimen of 2 x 40 mg intravenous doses given 2 hours apart. The PK sampling points and injection site pain assessment for IV dosing have been revised to account for new dosing regimen.

Amendment 2: The protocol has been amended to update IV furosemide dose administration description, details around Secondary Objectives and remove BD device references. It also clarifies when subjects abstain from caffeine-containing products, the number of subjects enrolled, exclusion criteria and assessment details. Minor administrative changes were made for consistency.

Amendment 3: The protocol has been amended to update exclusion criteria based on FDA feedback. It also includes taking photographs of the injection site prior to injection (baseline) and 4 hours post IV or 6 hours post SC administration and for any AE at injection site at time of event. Adverse event Investigational Product (IP) terminology has been updated to study treatment. A section for documenting AE/SAEs during the washout and Follow-up period has been added. Study drug and study device SCP-111 Autoinjector description updated current common terminology.

Amendment 4: The protocol has been amended to change the inclusion criteria age range to 45 to 80 years of age, extend the study duration to 4 months and expand Introduction description.

Version	Date	Page	Change	Reason for Change
Original	04 Feb 2022	N/A	Original Version	New Document
Amendment 1	03 May 2022	Synopsis, Study Objectives p. 6, Study Treatments p. 8, Section 1.1. p. 15, Section 2. p. 16, Section 3.1. p. 17, Section 3.1.1. p. 18, Section 5.5. p. 23, Section 6.1.1. p. 24, Section 6.2.1.3.2. p. 28, 6.2.1.6.2. p. 29, Appendix 1 p. 49.	Replaced Intravenous (IV) Furosemide injection 80 mg over 2 minutes with dosing regimen of two 40 mg intravenous injections over two minutes, two hours apart.	Updated to FDA recommended IV dosing regimen.
Amendment 1	03 May 2022	Section 6.2.2.6. Pharmacokinetic Assessments – Plasma p. 31-32.	Replaced “5, 15, 30, 45 minutes and 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8 and 12 hours after the IV injection” with First IV and Second IV 2-minute injection dose sampling points.	Revised PK sampling points for IV dosing to account for new dosing regimen.
Amendment 1	03 May 2022	Section 6.2.2.7. Assessment for Injection Site Pain p. 32, Appendix 1 p. 49.	Replaced “immediately after the dose and 15 and 30 minutes and 6 and 12 hours after the dose” with assessments following 1st and 2nd dose.	Revised Pain assessment for IV dosing to account for new dosing regimen.

Version	Date	Page	Change	Reason for Change
Amendment 2	18 Nov 2022	Multiple sections and pages	Modified IV furosemide injection description to “one to two minutes” or “1 to 2.”	Updated to align with IV furosemide dose administration in approved labeling for Listed Drug.
Amendment 2	18 Nov 2022	Multiple sections and pages	Modified assessment “injection site pain/discomfort” to “injection site pain.”	Updated to clarify intensity of pain being measured with rating scale.
Amendment 2	18 Nov 2022	Synopsis, Secondary endpoints p. 9 Section 3.2. p. 22 Section 6.1.1. p. 27	Added titles to Secondary Endpoints, specified time units to “hours”, added injection site pain assessment.	Updated details around Secondary Endpoints.
Amendment 2	18 Nov 2022	Multiple sections and pages	Added subjects instructed to abstain from caffeine-containing products 2 days prior to admission through completion of Crossover Period 2.	To clarify subjects need to maintain <2 gram sodium diet and abstain from caffeine containing products for PK sampling.
Amendment 2	18 Nov 2022	Synopsis, Study Treatments p. 11 Section 3.1.1. p. 20 Figure 1 p. 22 Section 5.2. p. 25	Removed BD Intevia device references, description and figure.	The autoinjector for the study is to be determined.
Amendment 2	18 Nov 2022	Synopsis, Number of Subjects p. 11 Section 8.1. p 42	Updated 21 subjects will be enrolled to ensure 18 subjects complete the study through the Follow-up Phase.	To clarify number of subjects enrolled.
Amendment 2	18 Nov 2022	Synopsis, Subject Population p. 12 Section 4.2. p. 23	Removed Exclusion Criteria #13: “Moderate-to-severe hepatic dysfunction as determined by the investigator.”	Removed because included within Exclusion Criteria #12: Reported history of liver disease, cirrhosis, or ascites.
Amendment 2	18 Nov 2022	Synopsis, Pharmacokinetic and statistical analysis p. 13, Section 8.4 p. 42	Removed “Phoenix® WinNonlin® V8.1 or higher” methods.	The statistical analysis methods to be determined.
Amendment 2	18 Nov 2022	Section 1.4. p. 19	Replaced “electrolyte abnormalities” with ”abnormal serum potassium levels.”	To clarify subjects with abnormal serum potassium levels excluded at screening.

Version	Date	Page	Change	Reason for Change
Amendment 2	18 Nov 2022	Section 3.2.2. p. 22 Section 6.2.1.3.3. p. 31 Section 6.2.1.6.3. p. 32 Section 6.2.2.5. p. 34	Modified urine collection description.	To provide additional details for urine collection.
Amendment 2	18 Nov 2022	Section 6.2. p. 28	Added assessments performed at same time as a PK sample can be performed just prior to PK sample collection.	To provide flexibility for performing assessments scheduled at same time as PK sample collection.
Amendment 2	18 Nov 2022	Section 6.2.1.2. p. 30 Section 6.2.1.5. p. 31 Section 11.1. Appendix 1. p. 51	Added “Subjects will be monitored during the study to ensure a minimum of 100 mL of fluid consumed for every 300 mL of urine output.”	To re-emphasize during Treatment Phase to monitor subjects’ fluid intake.
Amendment 2	18 Nov 2022	Section 3.1.2. Study Schematic p. 21 Section 6.2. p. 28 Section 6.2.1.7. p. 33 Section 11.1. Appendix 1. p. 51	Added “Follow-up visit should occur 24-48 hours after discharge from CRU for Crossover Period 2.”	To clarify timing of Follow-up visit.
Amendment 2	18 Nov 2022	Section 9.1.12 p. 47	Removed that all used study product will be returned from the Subject to the site for accountability.	Removed incorrect accountability instruction.
Amendment 2	18 Nov 2022	Multiple sections and pages	Administrative changes	Added abbreviations, further clarified assessments and modified language for consistency.
Amendment 3	06 Sep 2023	Synopsis, Subject Population p. 14 Section 4.2 p. 26	Removed “ascites” from exclusion #12 and updated exclusion #20 to include tromethamine and benzyl alcohol.	Updated exclusion criteria to align with Prescribing Information based on FDA feedback.
Amendment 3	06 Sep 2023	Synopsis, Study Design and Methodology, p. 12 Section 3.1 p. 22 Section 6.2.1.2 p.32 Section 6.2.1.3.3 p.33 Section 6.2.1.6.1 p. 34	Added Photographs of injection site will be performed prior to IV and SC injection (baseline) and 4 hours post IV or 6 hours post SC administration and for AE at injection site.	Updated to include photographs of the injection site to evaluate AEs related to injection site.

Version	Date	Page	Change	Reason for Change
		Section 6.2.1.6.3 p. 34 Section 6.2.2.8 p. 38 Section 7. p. 38 Section 7.7.4. p.43 Appendix 1 p. 53		
Amendment 3	06 Sep 2023	Multiples sections and pages	Investigational Product (IP) replaced with Study Treatment.	Updated terminology to clarify capture AEs for IV and SC Study Treatments.
Amendment 3	06 Sep 2023	Section 7.7.8 p. 43	Added a section for Adverse Events and Serious Adverse Events during the washout and Follow-up period.	Added to explain how AEs/SAEs during the washout and Follow-up period will be documented.
Amendment 3	06 Sep 2023	Section 9.1.6 p. 47	Revised document retention guidelines to reference clinical trial agreement.	Updated to align with current processes.
Amendment 3	06 Sep 2023	Synopsis, Study Design and Methodology, p. 11 Section 3.1 p. 22	Replaced “plasma” with “blood” samples.	Clarified blood samples collected to measure furosemide plasma concentrations.
Amendment 3	06 Sep 2023	Synopsis, Study Treatment, p. 12 Section 5.2 p.27	Added “isotonic” to describe SCP-111 formulation.	Updated to common terminology.
Amendment 3	06 Sep 2023	Synopsis, Study Treatment, p. 12 Section 3.3 p. 25 Section 5.2 p.27	Modified description for study device SCP-111 Autoinjector.	Updated to common terminology.
Amendment 4	29 Nov 2023	Synopsis, Subject Population p. 13 Section 4.1 p. 26	Changed the inclusion criteria age range to 45 to 80 years of age.	Updated to correlate with intended use population.
Amendment 4	29 Nov 2023	Synopsis, Study Duration p. 11	Extended the study duration to 4 months.	Updated to account for increased enrollment time due to change in age range.
Amendment 4	29 Nov 2023	Introduction, p. 20	Expanded Introduction description of treatment of fluid overload in certain chronic conditions.	Updated to include background on water homeostasis and better align with proposed indication and use.

PROTOCOL APPROVAL PAGE

Study Title:	Open-label, Single-dose, Randomized, Two-way (two-period) Crossover Study to Compare the Pharmacokinetics and Pharmacodynamics of SCP-111 (furosemide injection) Administered as a Subcutaneous Injection vs Furosemide Administered as an Intravenous Injection in Healthy Volunteers
Protocol Number:	scP-04-001
Original Protocol Date of Issue:	04 February 2022
Amendment 1 Date:	03 May 2022
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Amendment 4 Date:	29 November 2023
Sponsor Name and Address:	scPharmaceuticals, Inc. 25 Mall Road, Suite 203 Burlington, MA 01803

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

Approval Section		
	Name/Title	**Signature / Date**
Reviewed and Approved by:	John Mohr, Pharm D SVP, Clinical Development and Medical Affairs	Approvals obtained through MasterControl
Reviewed and Approved by:	Barbara Cornelius Associate Director, Clinical Operations	Approvals obtained through MasterControl
Reviewed and Approved by:	Jen Vandiver VP, Product Development and Engineering	Approvals obtained through MasterControl
Reviewed and Approved by:	Eric Kendig VP, Head of Regulatory Affairs	Approvals obtained through MasterControl
Reviewed and Approved by:	Michelle Whipple VP, Quality	Approvals obtained through MasterControl

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title: Open-label, Single-dose, Randomized, Two-way (two-period) Crossover Study to Compare the Pharmacokinetics and Pharmacodynamics of SCP-111 (furosemide injection) Administered as a Subcutaneous Injection vs Furosemide Administered as an Intravenous Injection in Healthy Volunteers

Protocol Number: scP-04-001 Amendment 4

By my signature, I

- agree to conduct the study in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of Subjects.
- agree to personally conduct or supervise the described investigation(s).
- agree to inform any patients, or any persons used as controls, that the study treatment is being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- agree to report to the Sponsor adverse experiences that occur during the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the Investigator's brochure, including the potential risks and side effects of the study treatment.
- agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without consent from the Sponsor and will not institute those changes in the research protocol until after IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Investigator's Signature Date

Print Name

STUDY SYNOPSIS	
SHORT TITLE	SCP-111 PK/PD
PROTOCOL TITLE	Open-label, Single-dose, Randomized, Two-way (two-period) Crossover Study to Compare the Pharmacokinetics and Pharmacodynamics of SCP-111 (furosemide injection) Administered as a Subcutaneous Injection vs Furosemide Administered as an Intravenous Injection in Healthy Volunteers
PROTOCOL NUMBER	scP-04-001
SPONSOR	scPharmaceuticals, Inc.
INVESTIGATIONAL PRODUCT	SCP-111 (furosemide injection) 80 mg/1 mL for subcutaneous administration via an autoinjector
STUDY OBJECTIVES	**Primary Objective:** • To estimate the bioavailability of SCP-111 80 mg/1 mL administered as a subcutaneous injection via an autoinjector compared with an equivalent dose of furosemide administered as two 40 mg intravenous injections over one to two minutes, two hours apart.
	Secondary Objectives: • To describe the pharmacokinetics and pharmacodynamics of SCP-111 80 mg/1 mL administered as a subcutaneous injection via an autoinjector. • To describe the safety and tolerability of SCP-111 80 mg/1 mL administered as a subcutaneous injection via an autoinjector.

ENDPOINTS	**Primary Endpoints:**
	• Logarithmic transformed geometric mean ratio between 80 mg subcutaneous SCP-111 and 80 mg intravenous furosemide of the:
	  ○ AUC from time 0 (pre-dose) to the last quantifiable time point (AUC_{last})
	  ○ AUC from time 0 (pre-dose) extrapolated to infinity (AUC_{inf})

	Secondary Endpoints: <u>Pharmacokinetics/pharmacodynamics</u> The following pharmacokinetics (PK) parameters will be evaluated for subcutaneous and intravenous furosemide administration: • Maximum observed plasma concentration (C_{max}) • Time to C_{max} (T_{max}) • Terminal phase elimination rate constant (λz), estimated by linear regression of logarithmically transformed concentration versus time data • Terminal elimination half-life (t½) estimated using the equation [ln(2)/λz] • Apparent systemic clearance (CL/F) • Systemic clearance (CL) • Apparent systemic volume of distribution (Vz/F) • Systemic volume of distribution (V) The following pharmacodynamics (PD) parameters will be evaluated for subcutaneous and intravenous furosemide administration: • Urine output (0-6, 0-8, and 0-12 hours) • Urinary sodium excretion (0-6, 0-8, and 0-12 hours) • Urinary potassium excretion (0-6, 0-8, and 0-12 hours) <u>Safety and tolerability</u> <u>Safety</u> Adverse Events (AEs) and Serious Adverse Events (SAEs) will be grouped by body system and summarized. The incidence (number and percentage of subjects) of adverse events and

	serious adverse events will be presented overall and by MedDRA System Organ Class and Preferred Term. <u>Injection Site Pain</u> Injection site pain will be assessed using an 11-point scale where 0 is equivalent to no pain and 10 is equivalent to the worst possible pain. For IV administration, the 11-point pain scale will be performed pre-dose after IV needle placement, immediately after 1st dose and 15 and 30 minutes after 1st dose, immediately after 2nd dose and 15 and 30 minutes and 4 and 10 hours after the 2nd dose. For SC administration, the 11-point pain scale will be performed pre-dose, immediately after dose and 15 and 30 minutes and 6 and 12 hours after dose. Pain requiring treatment, withdrawal from the study or discontinuation of study drug will also be recorded as an adverse event (AE).
STUDY DURATION	4 months
STUDY DESIGN & METHODOLOGY	<u>Study Design:</u> This is an open-label, single-center, single-dose, randomized, two-way (two-period) crossover study in healthy volunteers. Each Subject will complete Screening, Baseline, Treatment, and Follow-up Phases. The Screening Phase will be conducted on an outpatient basis between 14 and 3 days prior to the Baseline visit. Subjects will be instructed to maintain a < 2-gram sodium diet and abstain from caffeine-containing products within 2 days prior to admission to the Clinical Research Unit (CRU). On arrival to the CRU (Day 0), baseline and final qualification assessments will be performed. The Treatment Phase will be comprised of two crossover periods separated by a 3 ± 1 day washout period. During each CRU admission and through the washout period, Subjects will continue a < 2-gram sodium diet and abstain from caffeine-containing products. Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences to receive intravenous (IV) furosemide or subcutaneous (SC) SCP-111 in the abdomen in Crossover Periods (i.e., IV followed by SC or vice versa). Blood samples will be collected to measure furosemide plasma concentrations at pre-dose and for 12 hours post-dose. Prior to dosing in each Treatment Phase, subjects will void their bladder completely and

	urine will be collected starting after the injection through 12 hours post injection to determine total urine output and urinary sodium and potassium excretion. Assessment of injection site pain will be conducted for IV and SC administration using an 11-point pain scale. Photographs of the injection site will be performed prior to the IV and SC injection (baseline) and 4 hours post IV administration and 6 hours post SC administration. In addition, a photograph will be taken of the IV and SC injection site for any AE (i.e., erythema, edema, pruritus, bruising) that occurs at the site at the time of the event. Subjects will remain domiciled in the CRU for each Treatment Phase through 12 hours after administration of study drug. After final assessments are performed, subjects may be discharged from the CRU if safety parameters are acceptable to the Investigator. The Follow-up Phase will occur 24-48 hours (Day 5 ± 1) after discharge from the CRU following Crossover Period 2, completing Subjects' study participation.
STUDY TREATMENTS	Study Drugs: • Intravenous Furosemide (IV Furosemide): Hospira, furosemide injection, solution 10 mg/mL (NDA 018667) (total dose = 80 mg) administered intravenously 40 mg over 1 to 2 minutes by IV injection followed by a second dose of 40 mg over 1 to 2 minutes, 2 hours later (reference treatment). • SCP-111 (furosemide injection), 80 mg/1 mL for subcutaneous administration: Total dose = 80 mg; administered as a subcutaneous injection (test treatment) via an autoinjector. Study Drug: SCP-111, (furosemide injection), 80 mg/1 mL is a proprietary furosemide formulation that is isotonic and buffered to a neutral pH for subcutaneous administration. Study Device: SCP-111 Autoinjector is an investigational single-entity drug-device combination product consisting of a prefilled syringe containing 1 mL of SCP-111 (furosemide injection), preloaded into a fixed single dose, disposable, two step mechanical autoinjector designed to administer the full dose to the subcutaneous tissue.

NUMBER OF SUBJECTS	21 subjects will be enrolled to ensure 18 subjects complete the study through the Follow-up Phase
NUMBER OF SITES	1
PARTICIPATING COUNTRIES	US
SUBJECT POPULATION	Subjects may be enrolled in the study only if all the inclusion criteria and none of the exclusion criteria are met. **Inclusion Criteria:** Female and male subjects are eligible for inclusion only if all the following criteria are met: 1. An Institutional Review Board (IRB) approved informed consent is signed and dated prior to any study-related activities. 2. Male and female subjects 45 to 80 years of age. 3. Has the ability to understand the requirements of the study and is willing to comply with all study procedures. 4. In the opinion of the Investigator, able to participate in the study. **Exclusion Criteria**: A Subject is not eligible for inclusion if any of the following criteria apply: 1. Pregnant or lactating women or women of childbearing age who are not willing to use an adequate form of contraception. 2. Systolic BP (SBP) < 90 mmHg at screening or baseline. 3. Heart rate > 110 beats per minute (BPM) at screening or baseline. 4. Temperature > 38°C (oral or equivalent). 5. Serum potassium ≤ 3.0 or ≥ 5.5 mEq/L at screening. 6. Other significant cardiac abnormalities which may interfere with study participation or study assessments. 7. Current or planned treatment during the study with any IV therapies, including inotropic agents, vasopressors, levosimendan, nesiritide or analogues.

	8. Presence of implanted ventricular assist device, cardiac defibrillator or pacemaker. 9. Severely impaired renal function, defined as an estimated glomerular filtration rate (eGFR) at screening admission < 30 mL/min/1.73m^2, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation. 10. Urinary retention due to bladder emptying disorders and/or urethral narrowing. 11. Presence or need for urinary catheterization. 12. Reported history of hepatic cirrhosis. 13. Administration of intravenous radiographic contrast agent within 72 hours prior to Screening. 14. Concomitant or any use within past 30 days of drugs known to interact with furosemide (aminoglycoside antibiotics, ethacrynic acid, high doses of salicylates, cisplatin, tubocurarine, succinylcholine, chloral hydrate, phenytoin, methotrexate, indomethacin, or lithium). 15. Administration of an investigational drug or implantation of investigational device, or participation in another interventional clinical trial, within 30 days prior to Screening. 16. 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. 17. Positive urine drug screen at Screening or Baseline. 18. Blood alcohol concentration $\geq$ 2 mg/dL (0.02%) at Screening. 19. Alcohol breath test $\geq$ 2 mg/dL (0.02%) on admission to the CRU. 20. History of severe allergic or hypersensitivity reactions to furosemide or any component of the SCP-111 formulation (tromethamine or benzyl alcohol).
PHARMACOKINETIC AND STATISTICAL ANALYSIS	Pharmacokinetic parameters will be estimated using noncompartmental methods. Individual pharmacokinetic parameters for furosemide will be calculated using noncompartmental analysis and will be summarized using descriptive statistics. Bioavailability of SCP-111 will be determined by the logarithmic transformed geometric mean ratios of the SCP-111 to IV furosemide AUC_{last} and AUC_{inf} and 90% Confidence Intervals for the geometric mean ratios (test/reference)

	will be determined and should be within 80% and 125% to establish bioequivalence.

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ABBREVIATIONS

AE	Adverse Event
AUC	Area Under the Curve
AUC_{inf}	Area Under the Curve to infinity
AUC_{last}	Area Under the Curve to last quantifiable time point
βhCG	Beta-human Chorionic Gonadotropin
BMI	Body Mass Index
BPM	Beats per minute
BUN	Blood Urea Nitrogen
C	Celsius
CFR	Code of Federal Regulations
CL	Systemic Clearance
CL/F	Apparent Systemic Clearance
C_{max}	Maximum Plasma Concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CV	Cardiovascular
ECG	Electrocardiogram
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EP	European Pharmacopoeia
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonization
IFU	Instructions for Use
IM	Intramuscular
IN	Inches
IND	Investigational New Drug
IP	Investigational Product
IRB/EC	Institutional Review Board/Ethics Committee
IV	Intravenous
lbs	Pounds
Mg/dL	Milligrams per Deciliter
Min	Minute
mL	Milliliter
mmHg	Millimeters of mercury
mEq/L	Milliequivalent per Liter
OTC	Over-The-Counter
PD	Pharmacodynamics
PK	Pharmacokinetics

SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Subcutaneous
sMDRD	Simplified Modification of Diet in Renal Disease
USP	United States Pharmacopeia
V	Systemic Volume
V_z/F	Apparent Systemic Volume of Distribution

1. INTRODUCTION

Water is a primary constituent of the human body and is responsible for many physiological processes. The balance between fluid gains and fluid losses is regulated through various mechanisms such as neural regulation of thirst, hormonal regulation (vasopressin and natriuretic peptides), management through the skin, hemodynamic changes, and renal control of sodium and water excretion. Chronic diseases that can lead to reduced functionality of organs such as the heart, kidney and liver can lead to an impaired ability to adequately regulate body water and electrolytes. When this occurs, fluid can begin to slowly accumulate in the vasculature and tissues leading to symptoms such as weight gain, swelling, exercise intolerance, dyspnea and fatigue. Diuretics are drugs that pharmacologically tilt the regulation of fluid in favor of the excretion of water and electrolytes by increasing the production and volume of urine and thus affecting water homeostasis. Diuretics are the cornerstone of therapy for managing volume overload in patients with congestive heart failure, liver cirrhosis and kidney disease.

Furosemide, a loop diuretic that was developed in the 1960's, is an anthranilic acid derivative and is available for oral, intravenous (IV), intramuscular (IM) administration as well as a 5-houir subcutaneous infusion via an on-body Infusor. Its mechanism of action is inhibition of the sodium-potassium-2 chloride co-transporter thus decreasing the reabsorption of sodium and chloride in the proximal and distal tubules and in the loop of Henle, thus promoting sodium and water excretion. However, on average, only 50% of an orally administered dose of furosemide is absorbed and oral bioavailability ranges from 10% to 100%, making it a matter of clinical judgement as to how much furosemide to dose in an individual patient, especially in patients with heart failure where absorption can become even further reduced and highly variable.

In the event of worsening symptoms due to fluid overload, administration of IV loop diuretics that bypass the gastrointestinal tract, which are typically administered either in the hospital or an outpatient infusion center if available, are often needed to effectively decrease the excess fluid overload and the associated signs and symptoms. Intravenous (IV) furosemide is indicated for the management of edema associated with heart failure, cirrhosis of the liver and renal disease, including nephrotic syndrome.

SCP-111 (furosemide injection, 80 mg/1 mL) is a pH neutral formulation of furosemide that has been developed for subcutaneous injection. SCP-111 contains the inactive ingredients tromethamine (tris(hydroxymethyl)) aminomethane) and benzyl alcohol and is buffered to a neutral pH with sodium hydroxide and hydrochloric acid.

1.1. Rationale for the Current Study

The proposed study aims to determine the bioavailability and describe the pharmacokinetics and pharmacodynamics of SCP-111 administered as a

subcutaneous injection compared to two 40 mg injections of furosemide administered intravenously over one to two minutes, two hours apart.

In a prior pharmacokinetic study conducted by scPharmaceuticals, the relative bioavailability of furosemide 80 mg/10 mL was 99.6% when administered as a 5-hour, biphasic infusion compared to two 40 mg injections of furosemide administered over two minutes, two hours apart (Sica DA, et al. 2018). The data from this study was used to construct a pharmacokinetic and pharmacodynamic model and simulations of a subcutaneous injection was performed. These simulations demonstrated that subcutaneous injections of furosemide would likely achieve AUC ratios comparable to intravenous furosemide whereby the 90% confidence intervals would fall between 80 and 125% (scPharmaceuticals, Data on file).

1.2. Potential Benefits of Participating in the Study

There are no potential benefits to Subjects beyond the contribution to the development and testing of SCP-111.

1.3. Potential Risks of Participating in the Study

Furosemide is the most widely used diuretic globally and has been used clinically for over 50 years. Intravenous, intramuscular and oral formulations are approved by the Food and Drug Administration. Marked diuresis accompanied by dehydration or a reduction in blood pressure including orthostatic hypotension has been associated with administration of furosemide. In addition, furosemide can cause electrolyte abnormalities (hyponatremia, hypokalemia and hypocalcemia). Subcutaneous administration of furosemide, USP, which has an alkaline pH (8.5-9), has been associated with local skin irritation and infusion site reactions. The furosemide formulation used in this study has been buffered to a neutral pH.

1.4. Risk Management

Subjects will be monitored in the Clinical Research Unit (CRU) for at least 12 hours after dosing with the study treatment and monitored. Subjects will be allowed liquid and solid oral intake ad libitum during the study with a minimum of 100 mL of fluid consumed for every 300 mL of urine output. Subjects with abnormal serum potassium levels at screening will be excluded from the study. Blood pressure and heart rate will be monitored during and after the injections.

2. STUDY OBJECTIVES

The primary objective of the study is:

1.) To estimate the bioavailability of SCP-111 80 mg/1 mL administered as a subcutaneous injection via an autoinjector compared with an equivalent dose of furosemide administered as two 40 mg intravenous injections over one to two minutes, two hours apart.

The secondary objectives of the study are:

1.) To describe the pharmacokinetics and pharmacodynamics of SCP-111 80 mg/1 mL administered as a subcutaneous injection via an autoinjector.

2.) To describe the safety and tolerability of SCP-111 80 mg/1 mL administered as a subcutaneous injection via an autoinjector.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an open-label, single-center, single-dose, randomized, two-way (two-period) crossover study in healthy volunteers. Each Subject will complete Screening, Baseline, Treatment, and Follow-up Phases.

The Screening Phase will be conducted on an outpatient basis between 14 and 3 days prior to the Baseline visit. Subjects will be instructed to maintain a < 2-gram sodium diet and abstain from caffeine-containing products within 2 days prior to admission to the CRU. On arrival to the CRU (Day 0), baseline and final qualification assessments will be performed.

The Treatment Phase will be comprised of two crossover periods separated by a 3 ± 1 day washout period. During each CRU admission and through the washout period, Subjects will continue a < 2-gram sodium diet and abstain from caffeine-containing products. Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences to receive IV furosemide and SC SCP-111 in the abdomen in Crossover Periods (ie, IV followed by SC or vice versa). Blood samples will be collected to measure plasma furosemide concentrations at pre-dose and for 12 hours post-dose. Prior to dosing in each Treatment Phase, subjects will void their bladder completely and urine will be collected starting after the injection through 12 hours post injection to determine total urine output and urinary sodium and potassium excretion. Assessment of injection site pain will be conducted for IV and SC administration using an 11-point pain scale. Photographs of the injection site will be performed prior to the IV and SC injection (baseline) and 4 hours post IV administration and 6 hours post SC administration. In addition, a photograph will be taken of the IV and SC injection site for any AE (i.e., erythema, edema, pruritus, bruising) that occurs at the site at the time of the event. Subjects will remain domiciled in the CRU for each Crossover Period during the Treatment Phase through 12 hours after administration of study drug. After final assessments are performed, Subjects may be discharged from the CRU if safety parameters are acceptable to the Investigator.

The Follow-up Phase will occur 24-48 hours (Day 5 ± 1) after discharge from the CRU following Crossover Period 2, completing Subjects' study participation.

3.1.1. Study Treatment

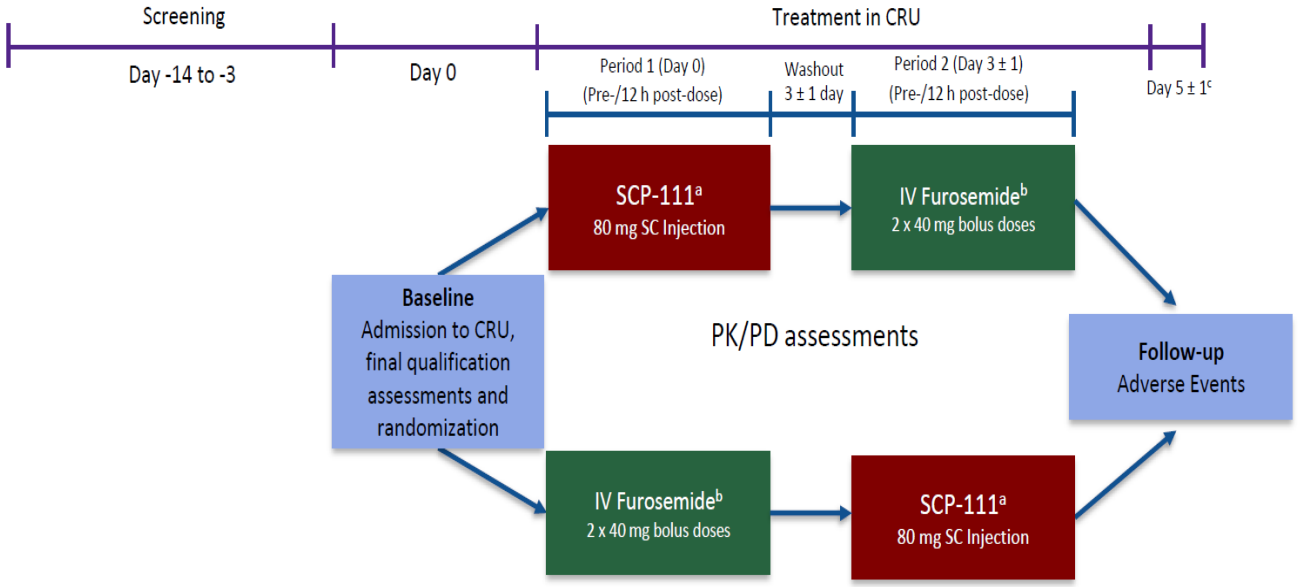
Study Drugs:

- **Furosemide Injection 10 mg/mL, USP:** Hospira, furosemide injection, solution 10 mg/mL (NDA 018667), administered intravenously 40 mg over 1 to 2 minutes by IV injection followed by a second dose of 40 mg administered over 1-2 minutes, 2 hours later (reference treatment).

- **SCP-111 (furosemide injection 80 mg/1 mL):** SCP-111 80 mg/1 mL for subcutaneous administration, (total dose = 80 mg dose) administered as a subcutaneous injection (test treatment) via an autoinjector.

Study drug will be administered at time zero (0) for the purpose of documenting drug administration, PK plasma sampling, urine collection, and AE monitoring according to the Time and Event Schedule. Serial sampling of venous blood for quantitation of furosemide in plasma will be collected over 12 hours according to the schedule of procedures. Urine will be collected from spontaneous voids in 1-hour increments for the first 8 hours and in 2-hour increments up to 12 hours post-dose, for the purpose of determining the total urine volume and urinary sodium and potassium concentration over 12 hours. Plasma samples will be processed and stored according to the instructions in the protocol and assayed using validated bioanalytical methods.

3.1.2. Study Schematic



[a] SCP-111 80 mg SC administered via an autoinjector
[b] Furosemide IV administered as two, 40 mg doses (over 2 minutes) 2 hours apart (80 mg total dose)
CRU=clinical research unit; h=hour; IV=intravenous; min=minute; PK= pharmacokinetics; PD=pharmacodynamics; SC=subcutaneous
[c] Follow-up visit should occur 24-48 hours after discharge from CRU for Crossover Period 2

3.2. Endpoints

3.2.1. Pharmacokinetic Endpoints

Individual pharmacokinetic parameters for furosemide will be summarized with descriptive statistics. Pharmacokinetic parameters including the maximum observed plasma concentration (C_{max}), the area under the plasma concentration versus time curve from time 0 (pre-dose) to the last quantifiable time point (AUC_{last}), the AUC from time 0 (pre-dose) to time infinity (AUC_{inf}), the time to C_{max} (T_{max}), the terminal phase elimination rate constant (λz), the terminal elimination half-life ($t_{½}$) for both SC SCP-111 (test) and IV furosemide (reference), the apparent systemic clearance (CL/F) for SC SCP-111 and systemic clearance (CL) for IV furosemide, the apparent systemic volume of distribution (V_z/F) for SC SCP-111 and systemic volume of distribution (V) for IV furosemide will be calculated using noncompartmental analysis. Bioavailability of SC SCP-111 will be determined based on the logarithmic transformation of the geometric mean ratios of AUC_{last} and AUC_{inf} of IV furosemide (reference) and SC SCP-111 (test) and 90% confidence intervals will be calculated. Compartmental modeling of the pharmacokinetic data may be conducted.

3.2.2. Pharmacodynamic Endpoints

Urine will be collected from spontaneous voids in 1-hour increments for the first 8 hours and in 2-hour increments up to 12 hours post-dose. Total urine output for each time period ((0-1), (1-2), (2-3), (3-4), (4-5), (5-6), (6-7), (7-8), (8-10) and (10-12) hours after initiation of dosing) will be recorded. The 6-hour, 8-hour and 12-hour urine output for IV furosemide and SC SCP-111 will be compared using appropriate statistical tests. In addition, an aliquot of urine will be used from each time period ((0-1), (1-2), (2-3), (3-4), (4-5), (5-6), (6-7), (7-8), (8-10) and (10-12) hours after initiation of dosing) for quantification of urinary sodium and urinary potassium. The 6-hour, 8-hour and 12-hour urinary sodium and potassium excretion will be determined and compared for IV furosemide and SC SCP-111 using appropriate statistical tests.

3.2.3. Safety and Tolerability Endpoints

3.2.3.1. Safety

Incidence of Adverse Events (AEs) and Serious Adverse Events (SAEs) grouped by body system for IV furosemide (reference) and SC SCP-111 (test).

Changes in pre-dose clinical labs, blood pressure and heart rate through CRU discharge will be summarized for IV furosemide (reference) and SC SCP-111 (test).

3.2.3.2. Injection Site Pain

Injection site pain will be assessed using an 11-point scale where 0 is equivalent to no pain and 10 is equivalent to the worst possible pain for IV administration and for SC administration. Pain requiring treatment, withdrawal from the study or discontinuation of study drug will also be recorded as an adverse event (AE) (Appendix 2).

3.3. SCP-111 Autoinjector

The SCP-111 Autoinjector is an investigational single-entity, drug-device combination product containing SCP-111 (furosemide injection), 80 mg/1 mL for subcutaneous use, prefilled in a 1 mL long borosilicate type 1 glass syringe with a 29-gauge, ½ inch stainless steel staked needle, a rigid needle shield, and a FluroTec™ coated butyl rubber stopper, preloaded into a commercially available fixed single dose, disposable, two step, mechanical autoinjector that administers a full dose of drug product into the subcutaneous tissue of the abdomen. It is intended for use by patients, caregivers, or a healthcare professional (HCP) at home or in a clinic setting.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

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

1. An Institutional Review Board (IRB) approved informed consent is signed and dated prior to any study-related activities.
2. Male and female subjects 45 to 80 years of age.
3. Has the ability to understand the requirements of the study and is willing to comply with all study procedures.
4. In the opinion of the Investigator, able to participate in the study.

4.2. Exclusion Criteria

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

1. Pregnant or lactating women or women of childbearing age who are not willing to use an adequate form of contraception.
2. Systolic BP (SBP) < 90 mmHg at screening or baseline.
3. Heart rate > 110 beats per minute (BPM) at screening or baseline.
4. Temperature > 38°C (oral or equivalent).
5. Serum potassium $\leq$ 3.0 or $\geq$ 5.5 mEq/L at screening.
6. Other significant cardiac abnormalities which may interfere with study participation or study assessments.
7. Current or planned treatment during the study with any IV therapies, including inotropic agents, vasopressors, levosimendan, nesiritide or analogues.
8. Presence of implanted ventricular assist device, cardiac defibrillator or pacemaker.
9. Severely impaired renal function, defined as an estimated glomerular filtration rate (eGFR) at screening admission < 30 mL/min/1.73 m^2, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation.

10. Urinary retention due to bladder emptying disorders and/or urethral narrowing.
11. Presence or need for urinary catheterization.
12. Reported history of hepatic cirrhosis.
13. Administration of intravenous radiographic contrast agent within 72 hours prior to Screening.
14. Concomitant or any use within past 30 days of drugs known to interact with furosemide (aminoglycoside antibiotics, ethacrynic acid, high doses of salicylates, cisplatin, tubocurarine, succinylcholine, chloral hydrate, phenytoin, methotrexate, indomethacin or lithium).
15. Administration of an investigational drug or implantation of investigational device, or participation in another interventional clinical trial, within 30 days prior to Screening.
16. 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.
17. Positive urine drug screen at Screening or Baseline.
18. Blood alcohol concentration $\geq$ 2 mg/dL (0.02%) at Screening.
19. Alcohol breath test $\geq$ 2 mg/dL (0.02%) on admission to the CRU.
20. History of severe allergic or hypersensitivity reactions to furosemide or any component of the SCP-111 formulation (tromethamine or benzyl alcohol).

4.3. Removal of Subjects from Therapy/Premature Discontinuation

Subjects will be encouraged to complete the study and all assessments; however, subjects may voluntarily withdraw at any time.

A Subject will be discontinued from the study for the following medical or administrative reasons:

- Subject request
- Pregnancy
- Significant non-compliance with study procedures

The Investigator may discontinue individual subjects from the study at any time.

5. TREATMENTS

5.1. Treatments Administered

Study drugs will be administered by qualified research staff in accordance with the procedures described in this protocol and in the Instructions for Use.

5.2. Identity of Investigational Product

Study Drug: SCP-111 (furosemide injection), 80 mg/1 mL is a proprietary furosemide formulation that is isotonic and buffered to a neutral pH for subcutaneous administration.

SCP-111 (furosemide injection), 1 mL buffered furosemide solution (80 mg/1 mL), is manufactured by Ajinomoto Althea, Inc., 11040 Roselle Street, San Diego, CA 92121, USA, under good manufacturing practice conditions. Each 1 mL of SCP-111 contains 80 mg of furosemide and the following inactive ingredients: 9.7 mg Tromethamine, and 35 mg Benzyl Alcohol and also contains Sodium Hydroxide and Hydrochloric Acid for pH adjustment (pH range: 7.4 to 8.0).

Study Device: SCP-111 Autoinjector is an investigational single-entity drug-device combination product consisting of a prefilled syringe containing 1 mL of SCP-111 (furosemide injection), preloaded into a fixed single dose, disposable, two step mechanical autoinjector designed to administer the full dose to the subcutaneous tissue.

5.2.1. Labeling

80 mg SCP-111 Autoinjector will bear labels that meet applicable laws for an investigational drug-device combination, which may include, but is not limited to, the following information:

- Federal law statement
- Batch number
- Storage information

The Instructions for Use for the SCP-111 Autoinjector as it exists at the time of the study will be available for the Investigator and study staff.

5.2.2 Storage and Handling

Store SCP-111 Autoinjector at controlled room temperature between 20°C and 25°C (68°F and 77°F). Excursions permitted between 15°C and 30°C (59°F and 86°F). Do not refrigerate or freeze. Do not remove the autoinjector from the carton until ready for use. Protect from Light.

5.3. Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences to receive both IV furosemide and SC SCP-111 in the abdomen in Crossover Periods (ie, IV followed by SC or vice versa).

5.4. Selection of Doses in the Study

The dose of 80 mg was selected based in part on the recommended dosage of furosemide injection, 10 mg/mL, USP for the treatment of edema associated with

congestive heart failure, renal disease and liver cirrhosis. The usual initial dose of furosemide IV is 20 to 40 mg given as a single dose slowly over 1 to 2 minutes. If needed, another dose may be administered in the same manner 2 hours later.

5.5. Selection and Timing of Dose for Each Subject

- **Furosemide injection 10 mg/mL, USP:** Hospira furosemide injection, solution 10 mg/mL, (NDA 018667), administered intravenously 40 mg over 1 to 2 minutes by IV injection followed by a second dose of 40 mg administered over 1 to 2 minutes, 2 hours later (reference treatment).
- **SCP-111 (furosemide injection 80 mg/1 mL):** SCP-111, furosemide injection 80 mg/1 mL for subcutaneous administration, (total dose = 80 mg dose) administered as a subcutaneous injection (test treatment) via an autoinjector.

5.6. Procedures for Blinding

This is an open label study.

5.7. Prior and Concomitant Therapy

Prior and concomitant therapy will include all prescription and non-prescription medications including over-the-counter (OTC) weight loss medications and nutritional supplements seven (7) days prior to enrollment. All information on prior and concomitant therapy will be recorded in the Subject's source and on the Subject's electronic case report form (eCRF). Requisite details will include the name of the therapy or drug and duration of the treatment (start and stop dates) and reason for use.

5.8. Prohibited Medications

Concomitant or any use within past 30 days of drugs known to interact with furosemide, including aminoglycoside antibiotics, ethacrynic acid, salicylates, cisplatin and nephrotoxic drugs, paralytic agents, lithium, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, antihypertensive drugs, adrenergic blocking drugs or peripheral adrenergic blocking drugs, norepinephrine, chloral hydrate, methotrexate and other drugs undergoing renal tubular secretion, cephalosporin, cyclosporine, thyroid hormones, phenytoin, or indomethacin is not permitted.

If a Subject is receiving oral furosemide, bumetanide or torsemide, the Subject must discontinue the therapy for 24 hours prior to being dosed with the reference or test treatment.

5.9. Study Stopping Criteria

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

5.10. Treatment Compliance

Study drug will be administered in accordance with the procedures outlined in this protocol. All study medication will be administered by designated study personnel and all information regarding study drug administration will be documented.

5.11. Study Drug Accountability

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.

Study staff authorized to handle and store the study drug will keep an accurate accounting of the receipt and disposition of the study drugs received from the Sponsor. Drug accountability will be assessed by the study monitor during periodic monitoring visits. At the end of the study, following final product reconciliation by the monitor, the study site will be instructed by the Sponsor as to disposition of used and unused study drug and supplies.

6. STUDY PROCEDURES

6.1. Study Measurements and Assessments

6.1.1. Assessment of Efficacy

Efficacy of the SCP-111 autoinjector combination product is being assessed based on the determination of bioavailability of a subcutaneous injection of SCP-111 80 mg compared to furosemide 80 mg administered intravenously as two 40 mg injections over 1 to 2 minutes, 2 hours apart. Urine output and urinary sodium and potassium excretion from time 0-6, 0-8 and 0-12 hours will also be assessed.

6.1.2. Assessment of Safety

Subjects will be monitored for adverse events which will be recorded and reported on the eCRF according to guidelines specified by the United States FDA and detailed in Section 7. Adverse Events. Blood pressure, heart rate, clinical chemistry labs will be collected throughout both treatment phases as outlined in Section 6.2. Study Phases and Procedures. Injection site pain will be assessed as described in Section 6.2.2.7.

6.2. Study Phases and Procedures

The Time and Event Schedule outlining study phases and procedures is provided in Appendix 1.

The Screening Phase will be conducted on an outpatient basis between 14 and 3 days prior to Baseline. Subjects will be instructed to maintain a < 2 gram sodium diet and abstain from caffeine-containing products within 2 days prior to Baseline. Baseline/CRU Admission will occur on Day 0. Study drug will be administered on

Day 0 and Day 3 (± 1 day) with a 3 ± 1 day outpatient fluid washout phase between doses. Subjects will be instructed to continue a < 2-gram sodium diet and abstain from caffeine-containing products through Day 0, the washout phase and Day 3 study drug administration. Follow-up visit will occur 24-48 hours after discharge from the CRU for Crossover Period 2.

Collection of the PK samples should occur as close to the scheduled time point as possible. The actual times of PK sample collections will be recorded. Assessments that are to be performed at the same time as a PK sample is to be drawn may be performed just prior to the collection of PK sample.

6.2.1. Study Phases

6.2.1.1. Screening (Day -14 through -3)

Subjects can be pre-screened ahead of enrollment by telephone and invited to the research center. Upon arrival to the research center, the study procedures will be explained. All Subjects who sign the informed consent form and satisfy the inclusion/exclusion criteria will be enrolled into the study.

The initial Screening visit will be conducted between 14 and 3 days prior to Baseline/CRU Admission on Day 0. The following procedures/assessments will be performed at Screening:

1. Informed consent (must be done prior to **any** of the following procedures, including asking subjects to discontinue prohibited medications)
2. Eligibility review
3. Medical history and demographics
    - Date of birth
    - Sex
    - Race
    - Ethnicity
    - Height (in)
    - Weight (lbs)
    - BMI (calculated from height and weight)
    - Medical History (self-reported; include onset dates)
        - Heart Failure
        - Hypertension
        - Stroke
        - Myocardial infarction
        - Unstable angina
        - Atrial fibrillation/flutter
        - Presence of implanted ventricular assist device, cardiac defibrillator, CardioMEMS™ or pacemaker

- Chronic obstructive pulmonary disease
- Diabetes mellitus
- Hepatic/liver disease
- Chronic Kidney disease (If yes, stage)
    - Stage 1: Normal kidney function (GFR >90 mL/min/1.73 m^2 with urine findings, structural abnormalities, or genetic traits)
    - Stage 2: Mildly reduced kidney function (GFR (60-89 mL/min/1.73 m^2)
    - Stage 3a: Moderately reduced kidney function (GFR (45-59 mL/min/1.73 m^2
    - Stage 3b: Moderately reduced kidney function (GFR 30-44 mL/min/1.73 m^2
    - Stage 4: Severe reduced kidney function (GFR 15-29 mL/min/1.73 m^2)
    - Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis)
- Depression
- Hyperlipidemia
- Obstructive sleep apnea
- Current Smoker (not current smoker if stopped smoking for at least 12 months)

4. Complete/full physical examination as described in Section 6.2.2.1
5. Temperature
6. Blood pressure
7. Heart rate
8. Screening labs will be performed to measure sodium, potassium, calcium, chloride, magnesium, carbon dioxide, blood urea nitrogen, serum creatinine, glucose, hemoglobin, hematocrit and blood alcohol.
9. Urine drug screen
10. Serum pregnancy test (for females of child-bearing potential)
11. 12-Lead ECG as described in 6.2.2.2
12. Prior medication assessment
    - If a Subject is receiving oral furosemide, bumetanide or torsemide, the Subject must discontinue the therapy for 24 hours prior to Baseline/CRU admission.
13. Schedule next study visit (Baseline/CRU admission)

6.2.1.2. Baseline Assessment (Day 0)

Subjects will be admitted to the CRU on Day 0 (the day of study drug administration) for Baseline assessment and procedures. Low sodium diet (< 2 gram per day) and fluid intake ad libitum consisting of water, juice and caffeine free beverages are permitted while domiciled in the CRU. Subjects will be monitored during the study to ensure a minimum of 100 mL of fluid consumed for every 300 mL of urine output.

The following assessments will be completed at Baseline upon CRU admission:

1. Eligibility re-review
2. Limited physical examination as described in Section 6.2.2.1
3. Prior medication assessment
    - Time and date of last dose of oral loop diuretic (if receiving)
4. Weight measurement
5. Temperature
6. Blood pressure
7. Heart rate
8. Clinical laboratory tests as described in Section 6.2.2.3
9. Alcohol breath test
10. Urine drug screen
11. Urine pregnancy test as applicable
12. Randomization to treatment sequence
13. Photograph of Injection Site as described in Section 6.2.2.8

6.2.1.3. Treatment Crossover Period 1 (Day 0)

All subjects will remain domiciled in the CRU through the 12-hour post-dose PK sample. Subjects will be discharged from the CRU if safety parameters are acceptable to the Investigator.

6.2.1.3.1. Pre-dose

The following assessments will be completed prior to dosing:

1. Void bladder immediately before dosing and discard as described in Section 6.2.2.5
2. Plasma sample for pharmacokinetics as described in Section 6.2.2.6
3. Assessment of injection site pain as described in Section 6.2.2.7

6.2.1.3.2. Dosing

For the purpose of assessments and pharmacokinetic sampling times, Day 0, Hour 0 will be defined as the point at which study drug dose is initiated/administered. IV furosemide or SC SCP-111 should be administered according to the randomization schedule. IV furosemide is administered via IV injection as a 40 mg dose over 1 to 2 minutes followed by a second dose of 40 mg over 1 to 2 minutes, 2 hours after the

start of the initial IV dose. SC SCP-111 is administered as a single 80 mg dose via the autoinjector.

6.2.1.3.3. Post-Dose (Hour 0-12)

The following assessments will be completed beginning after the initial dose:

1. Blood pressure (15, 30 minutes and Hour 1, 2, 2.5, 3, 4, 6, 8 and 12)
2. Heart rate (15, 30 minutes and Hour 1, 2, 2.5, 3, 4, 6, 8 and 12)
3. Plasma sample for pharmacokinetics as described in Section 6.2.2.6
4. Clinical laboratory tests as described in Section 6.2.2.3 (Hour 12)
5. Urine collection from spontaneous voids for time periods (0-1), (1-2), (2-3), (3-4), (4-5), (5-6), (6-7), (7-8), (8-10) and (10-12) hours post-dose for urine volume and urinary sodium and potassium as described in Section 6.2.2.5
6. Food, snack and fluid intake and recording as per Time and Event Schedule
7. Assessment of injection site pain as described in Section 6.2.2.7
8. Adverse events
9. Concomitant medications
10. Limited physical examination as described in Section 6.2.2.1 (Hour 12)
11. Weight measurement (Hour 12)
12. Photograph of Injection Site (4 hours post IV administration or 6 hours post SC administration) as described in Section 6.2.2.8
13. Schedule next study visit
14. Discharge from the CRU if safety parameters are acceptable to the investigator (Hour 12)

6.2.1.4. Washout (Days 3 ± 1)

1. Adverse events
2. Concomitant medications
3. Low sodium diet and abstain from caffeine-containing products

6.2.1.5. Pre-Period 2 Assessment (Day 3 ± 1)

Subjects will present to the CRU on Day 3 ±1 for Pre-Period 2 assessment and procedures. Low sodium diet and fluid intake ad libitum consisting of water, juice and caffeine free beverages are permitted while domiciled in the CRU. Subjects will be monitored during the study to ensure a minimum of 100 mL of fluid consumed for every 300 mL of urine output.

The following assessments will be completed at the Pre-period 2 assessment upon CRU admission:

1. Limited physical examination as described in Section 6.2.2.1
2. Concomitant medication assessment

a. Time and date of last dose of oral loop diuretic (if receiving)

3. Weight measurement
4. Temperature
5. Blood pressure
6. Heart rate
7. Clinical laboratory tests as described in Section 6.2.2.3
8. Alcohol breath test
9. Urine drug screen
10. Urine pregnancy test as applicable
11. Adverse events

6.2.1.6. Treatment Crossover Period 2 (Day 3 ± 1)

All subjects will remain domiciled in the CRU through the 12-hour post-dose PK sample. Subjects will be discharged from the CRU if safety parameters are acceptable to the Investigator.

6.2.1.6.1. Pre-dose

The following assessments will be completed prior to dosing:

1. Void bladder immediately before dosing and discard as described in Section 6.2.2.5
2. Plasma sample for pharmacokinetics as described in Section 6.2.2.6
3. Assessment of injection site pain as described in Section 6.2.2.7
4. Photograph of Injection Site as described in Section 6.2.2.8
5. Adverse events

6.2.1.6.2. Dosing

For the purpose of assessments and pharmacokinetic sampling times, Day 3, Hour 0 will be defined as the point at which study drug dose is initiated/administered. IV furosemide or SC SCP-111 should be administered according to the randomization schedule. IV furosemide is administered via IV injection as a 40 mg dose over 1 to 2 minutes followed by a second dose of 40 mg over 1 to 2 minutes, 2 hours after the start of the initial IV dose. SC SCP-111 is administered as a single 80 mg dose via the autoinjector.

6.2.1.6.3. Post-Dose (Hour 0-12)

The following assessments will be completed beginning after the initial dose:

1. Blood pressure (15, 30 minutes and Hour 1, 2, 2.5, 3, 4, 6, 8 and 12)
2. Heart rate (15, 30 minutes and Hour 1, 2, 2.5, 3, 4, 6, 8 and 12)
3. Plasma sample for pharmacokinetics as described in Section 6.2.2.6
4. Clinical laboratory tests as described in Section 6.2.2.3 (Hour 12)

5. Urine collection from spontaneous voids for time periods (0-1), (1-2), (2-3), (3-4), (4-5), (5-6), (6-7), (7-8), (8-10) and (10-12) hours post-dose for urine volume and urinary sodium and potassium as described in Section 6.2.2.5
6. Food, snack and fluid intake and recording as per Time and Event Schedule
7. Assessment of injection site pain as described in Section 6.2.2.7
8. Adverse events
9. Concomitant medications
10. Limited physical examination as described in Section 6.2.2.1 (Hour 12)
11. Weight measurement (Hour 12)
12. Photograph of Injection Site (4 hours post IV administration or 6 hours post SC administration) as described in Section 6.2.2.8
13. Schedule next study visit
14. Discharge from the CRU if safety parameters are acceptable to the investigator (Hour 12)

6.2.1.7. Follow-Up (Day 5 ± 1)

Follow-up visit should occur 24-48 hours after discharge from CRU for Crossover Period 2.

1. Complete/full physical examination as described in Section 6.2.2.1
2. Weight measurement
3. Blood pressure
4. Heart rate
5. Adverse events
6. Concomitant medications

6.2.2. Study Procedures

6.2.2.1. Physical Examination

At Screening and Follow-up, a complete/full physical examination should be performed. At Baseline assessment Day 0 and on Day 3 a limited physical examination may be performed consisting of assessments of the skin, lungs/chest, heart, extremities, abdomen and any other abnormalities detected during the study period. Post-dose physical examination on Day 0 and Day 3 should be performed 12 hours after the study drug is administered.

6.2.2.2. 12-lead ECG

At Screening a 12-lead ECG will be performed after the Subject has rested quietly for at least 5 minutes in a supine position.

6.2.2.3. Clinical Laboratory Tests

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

6.2.2.3.1 Screening:

Blood Clinical Chemistry: sodium, potassium, calcium, chloride, magnesium, carbon dioxide, blood urea nitrogen, serum creatinine, glucose, hemoglobin, hematocrit, and blood alcohol.

Serum pregnancy test in females of childbearing potential: beta hCG

Urine Drug Screen: Subjects with positive urine drug screen test results will be excluded from the study.

6.2.2.3.2 Pre-Dose and Post-Dose

Blood Clinical Chemistry: sodium, potassium, calcium, chloride, magnesium, carbon dioxide, blood urea nitrogen, serum creatinine, glucose, hemoglobin, hematocrit.

Post-dose clinical labs on Day 0 and Day 3 should be performed 12 hours after the study drug is administered.

The Investigator is responsible for determining if out of range laboratory values are clinically significant or not. All clinically significant values will be followed until stabilization, resolution, or loss to follow-up.

6.2.2.4. Temperature, Blood Pressure and Heart Rate

Temperature (oral or equivalent) will be taken. Blood pressure (mmHg) and heart rate (bpm) will be measured in the supine position after the Subject has rested comfortably for at least 5 minutes.

Height and weight will be collected and BMI will be calculated. Height collected at Screening only.

6.2.2.5. Urine Collection

Subjects will be instructed to void in order to empty their bladder immediately before dosing (pre-dose urine). The pre-dose urine will be **discarded**. Dosing should not commence if the Subject has not emptied their bladder in the previous 60 minutes. Urine from spontaneous voids during the post-dose phases will be collected and pooled, measured, recorded for time periods (0-1), (1-2), (2-3), (3-4), (4-5), (5-6), (6-7), (7-8), (8-10) and (10-12) hours after initiation of dosing. Urine for each collection period must be collected in a single vessel and refrigerated until the end of the collection period. An aliquot of urine from each time period will be collected and sent for urinary sodium and urinary potassium. Urinary sodium and urinary potassium concentration for each collection interval over the 12-hour urine collection period will be analyzed by standard lab biochemistry test. The 6-hour, 8-hour and 12-hour urinary sodium and potassium excretion will be determined and compared for each treatment group. Total urine output volume will be documented for each collection period.

6.2.2.6. Pharmacokinetic Assessments – Plasma

PK blood samples will be obtained by either direct venipuncture or use of an indwelling catheter. Collection of PK samples should occur as close to the scheduled time point as possible. The actual time of PK sample collection will be recorded.

For IV administration of furosemide injection, USP (reference), PK blood samples will be collected as follows:

- First IV 1 to 2-minute injection dose
  - Pre-dose
  - 5, 15, 30, 45 minutes and 1, 1.5, 2 hours after **start** of first IV dose. The sample taken at 2 hours will be drawn immediately prior to the start of the second IV dose.
- Second IV 1 to 2-minute injection dose (new clock for PK sampling starts upon the start of administration of second IV dose):
  - 5, 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8 and 10 hours after **start** of second IV dose.

For the SC administration of SCP-111 (test), PK blood samples will be collected as follows:

- Pre-dose
- 5, 15, 30, 45 minutes and 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8 and 12 hours after the SC injection

A minimum of 2 mL of blood will be collected in pre-labeled tubes. Blood samples will be processed into plasma and the plasma samples will be stored in appropriately labeled cryotubes at minus 70˚C until shipped to the bioanalytical laboratory. Plasma samples will be assayed for furosemide using a validated LC-MS/MS analytical method.

Blood samples will be drawn and processed for plasma as described in a separate document supplied to the CRU. The plasma samples will be split into two aliquots after processing, and one shipped to the bioanalytical laboratory. The other plasma aliquot will be stored at the site at minus 70˚C.

6.2.2.7. Assessment for Injection Site Pain

Pain will be assessed using an 11-point scale where 0 is equivalent to no pain and 10 is equivalent to the worst possible pain. (Appendix 2)

For IV administration of furosemide injection, USP (reference), assessment of injection site pain will be conducted pre-dose, after placement of the IV needle, immediately after the 1st dose,15 and 30 minutes after the 1st dose, immediately after the 2nd dose and 15 and 30 minutes and 4 and 10 hours after the 2nd dose.

For the SC administration of SCP-111 (test), assessment of injection site pain will be conducted pre-dose, immediately after the dose and 15 and 30 minutes and 6 and 12 hours after the dose.

6.2.2.8. Photograph of Injection Site

Photographs of the injection site will be performed prior to the IV and SC injection (baseline) and 4 hours post IV administration or 6 hours post SC administration. In addition, a photograph will be taken of the IV and SC injection site for any AE (i.e., erythema, edema, pruritus, bruising) that occurs at the site at the time of the event.

6.2.2.9. Alcohol and Caffeine

Subjects will abstain from alcohol and caffeine-containing products (including decaffeinated coffee), from 2 days prior to the Baseline visit, during both Crossover Periods and the washout period and until completion of procedures in Crossover Period 2. Subjects will undergo an alcohol breath test at each CRU admission.

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. AEs will be assessed continuously through the last study visit unless the nature of the AE or SAE requires continued monitoring. All AEs are recorded as mild, moderate or severe, and as Not Related, Possibly Related, Probably Related, or Definitely Related to the Study Treatment. A photograph will be taken of the IV and SC injection site for any AE (i.e., erythema, edema, pruritus, bruising) that occurs at the site at the time of the event.

7.1. Definition of an Adverse Event

An Adverse Event (AE) is any untoward medical occurrence associated with the use of a Study Treatment or Study Drug (refer Section 3.1.1 for study treatment definitions) in humans, whether considered related to the Study Treatment. An adverse event (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a Study Treatment and does not imply any judgment about causality. An adverse event can arise with any use of the Study Treatment (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

A “pre-existing” condition is one that is present prior to administration of study treatment and is reported as part of the Subject’s medical history. Pre-existing conditions should be reported as AEs only if the frequency, intensity, or character of the pre-existing condition worsens during the study.

Laboratory or functional test abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms or require medical intervention.

A laboratory abnormality (e.g., a clinically significant change detected on clinical chemistry, hematology, urinalysis) or functional test abnormality (e.g., a clinically significant change detected on ECG, pulse oximetry, or spirometry) that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to treatment interruption or discontinuation, must be considered an AE.

All AEs judged to be clinically significant, including clinically significant laboratory results, ECG and functional test abnormalities, will be followed until resolution or return to baseline or until no further improvement is expected.

An AE **does** include any:

- Exacerbation of a pre-existing illness.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study treatment placement and/or drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE **does not** include 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 an Unexpected Adverse Event

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

7.3. 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 (ie, 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.

7.4. Severity of Adverse Events and Serious Adverse Events

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.

7.5. Outcome of Adverse Events and Serious Adverse Events

- **Not Recovered/Not Resolved:** One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated.
- **Recovered/Resolved:** One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated.
- **Recovered/Resolved with Sequelae:** One of the possible results of an adverse event outcome where the Subject recuperated but retained pathological conditions resulting from the prior disease or injury.
- **Recovering/Resolving:** One of the possible results of an adverse event outcome that indicates that the event is improving.
- **Unknown:** Not known, not observed, not recorded, or refused.
- **Fatal:** The termination of life as a result of an adverse event

7.6. Assessment of Relatedness to Study Treatment

The Investigator will assess each AE and SAE for causality based on their best medical judgment, the observed symptoms associated with the event, and the available information on the study treatment. The relatedness guidance provided below can be used to assist in determining the relationship of the study treatment to the AE or SAE. However, it is ultimately the investigator's responsibility to determine the relationship based on their best medical judgment, knowledge, and experience.

- **Not Related:** Based upon available information regarding Subject history, disease process, relationship of adverse event to dosing and drug pharmacology, there is no reasonable relationship between the study treatment and the adverse event.

- **Possibly Related:** Relationship exists between the adverse event and study treatment, when the adverse event follows a reasonable sequence from the time of the study treatment administration, but could also have been produced by the Subject's clinical state or by other drugs administered to the patient.

- **Probably Related:** Relationship exists between the adverse event and the study treatment when the adverse event follows a reasonable sequence from the time of the study treatment administration, follows a known response

pattern of the drug class, is confirmed by improvement on stopping the study treatment and the study treatment is the most likely of all causes.

- **Definitely Related:** Relationship exists between the adverse event and the study treatment when the adverse event follows a reasonable sequence from the time of the study treatment administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the study treatment and no other reasonable cause exists.

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

At appropriate intervals, Subjects should be assessed for AEs and SAEs as in Section 6.2.

7.7.1. Timeframes for Reporting Serious Adverse Events

Prompt notification of the sponsor regarding SAEs is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. The Investigator must report SAEs according to the following time frames:

- Initial notification of all SAEs based on the available information must be provided to the sponsor or designee **within 24 hours** of the investigational site learning of the event. **(Initial notification within 24 hours of Death and life-threatening events is extremely important).**
    - Follow-up information when available must be sent to the sponsor or designee **within 48 hours** of receipt of the information by the investigational site.

7.7.2. Serious Adverse Event Information to Report

At a minimum, SAE reports must contain the Subject ID, the serious adverse event term, onset date, relationship to study treatment, and a brief narrative of the event. Please note that **relationship to study treatment/causality is very important** and must be included in the initial report as it may impact expedited regulatory reporting requirements for the event.

Copies of medical records will be requested. **However, it is not acceptable for the Investigator to send photocopies of the Subject's medical records in lieu of completion of the appropriate AE/SAE pages**. For medical records submitted, all Subject personal identifiers must be completely and thoroughly redacted prior to submission.

7.7.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

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

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

7.7.4. Documenting Adverse Events and Serious Adverse Events

All adverse events, including SAEs that occur after dosing of study treatment must be documented in the Subject's medical records and on the CRF.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE term.

A photograph will be taken of the IV and SC injection site for any AE (i.e., erythema, edema, pruritus, bruising) that occurs at the site at the time of the event.

7.7.5. Regulatory Ethics and Reporting Requirements

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

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

All AEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts. AEs and SAEs will be followed until the last study visit unless the nature of the AE or SAE requires continued monitoring. If a Subject dies during participation in the study or during a recognized follow-up period, a copy of any post-mortem findings, including histopathology, should be obtained, if available, and forwarded to scPharmaceuticals or designee. New or updated information will be recorded on the originally completed SAE Report Form with all changes electronically signed/dated by the Investigator or designee.

7.7.7. Post-study Adverse Events and Serious Adverse Events

Should the Investigator learn of an AE or SAE occurring within 30 days after a Subject completes the study, the event should be reported if it is considered related to study treatment.

7.7.8. Adverse Events and Serious Adverse Events during the Washout and Follow-up Period

If AEs emerge during the washout or Follow-up period, the causal relationship will be assessed in relation to the study treatment administered in the time preceding the washout or Follow-up period.

7.7.9. Medical Monitor

SAEs and other medical matters can be discussed with the Medical Monitor.

8. STATISTICS

8.1. Determination of Sample Size

In one study, the average coefficient of variation for furosemide AUC_{inf} following a 20 mg dose by the intravenous, oral, and sublingual routes of administration were 50%, 25%, and 33%, respectively (Haegeli, et al. 2007). In another study, the coefficient of variation for AUC_{inf} following 2-40 mg intravenous doses 2-hours apart was 31.6% and 30.6% for an 80 mg, 5-hour subcutaneous infusion (Sica DA, et al. 2018).

Assuming an intra-subject variability is approximately ½ of total variability for the primary pharmacokinetic parameter AUC_{inf} and the test reference would fall within 95% to 105% at a significance level of 0.05, a minimum sample size of 18 subjects would be required to establish bioequivalence between test and reference products (defined as 90% CI for AUC_{inf} Geometric mean ratio SC injection to IV injection of furosemide within 80-125% interval) with a priori statistical power of at least 90%.

21 subjects will be enrolled to ensure 18 subjects complete the study through the Follow-up Phase.

8.2. Analysis Populations

Three analysis populations will be defined as follows:

- **PK Population** will include all randomized subjects who receive full 80 mg dose of furosemide study drug AND have sufficient samples collected for estimation of pharmacokinetic parameters.
- **Bioavailability Population** will include all subjects in the PK population who have a sufficient number of samples collected for estimation of pharmacokinetic parameters after receiving BOTH IV furosemide and SC SCP-111.
- **Safety Population** will include all randomized subjects who received at least 1 dose of either study drug and provided at least 1 post-baseline safety assessment.

8.3. Baseline Characteristics and Subject Disposition

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

8.4. Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters will be estimated using noncompartmental methods. Compartmental modeling of the pharmacokinetic data may be conducted.

Furosemide concentrations will be summarized using descriptive statistics (including N, mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum) for each treatment.

The following PK parameters in table below will be estimated by noncompartmental methods from plasma samples. Actual elapsed time from dosing will be used to estimate all individual PK parameters.

C_{max}	Maximum observed plasma concentration
T_{max}	Time of maximum concentration (h), obtained directly from the observed concentration versus time data.
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration
AUC_{inf}	Area under the plasma concentration-time curve from 0-time extrapolated to infinity
AUC_{ext}	The percentage of the AUC that is extrapolated beyond the last measurable concentration
λz	Apparent plasma terminal-phase elimination rate constant
$t_{½}$	Terminal-phase half life
Vz/F	Apparent volume of distribution, terminal phase, for SCP-111
V	Systemic volume of distribution, terminal phase, for IV furosemide
CL/F	Apparent systemic clearance for SCP-111
CL	Systemic clearance for IV furosemide
F	Bioavailability ([AUC_{inf} / Dose SC SCP-111] / [AUC_{inf} / Dose IV furosemide])

Derived plasma PK descriptive statistics will be tabulated by dosing group and summary statistics. Descriptive statistics for PK parameters (C_{max}, T_{max}, AUC_{last}, AUC_{inf}, λ_z, $t_{½}$, V, Vz/F, CL and CL/F) will include the arithmetic and geometric mean (for C_{max}, AUC_{last}, and AUC_{inf}, only), CV%, SD of the arithmetic mean, median, minimum, maximum, and N.

Bioavailability of SC SCP-111 will be determined by the logarithmic transformation of the geometric mean ratios of the SC SCP-111 to IV furosemide AUC_{last} and AUC_{inf}

and 90% Confidence Intervals will be determined and should be within 80% and 125% to establish bioequivalence.

8.5. Pharmacodynamic Analysis

Total urine output, total urinary sodium excretion and total urinary potassium excretion from times 0-6, 0-8 and 0-12 hours will be tabulated and compared using descriptive statistical analysis stratified by treatment group.

8.6. Safety and Tolerability Analysis

Adverse events, clinical laboratory assessments, blood pressure and heart rate will be summarized with descriptive statistics.

Injection site pain assessments will be conducted as described in 6.2.2.7. All findings will be tabulated and assessed using descriptive statistical analysis stratified by treatment group; incidence rates will also be analyzed and reported in the final clinical study report.

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. For studies conducted under a United States IND, 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 and Independent Ethics Committee Approval

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

All information about the nature of the proposed investigation provided by the Sponsor or study monitor to the Principal Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the Subject, or the appropriate regulatory authority) must be kept in confidence by the Principal Investigator.

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. Compensation, Insurance and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

9.1.6. Study Files and Retention of Records

The Investigator 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 including (although not limited to) the following: (1) Investigator's study file, and (2) Subject clinical source documents.

The Investigator's study file will contain the protocol/amendments, IRB/EC approval, informed consent, drug accountability records, staff curriculum vitae, medical licenses as applicable, financial disclosure forms, local laboratory documentation, screening and enrollment log, 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, laboratory reports, worksheets, consultant letters, etc.

All clinical study documents must be retained by the Investigator until the number of years specified in the clinical trial agreement. The Investigator must notify scPharmaceuticals prior to destroying any clinical study records.

Should the Investigator wish to move study records to another location, arrangements must be made to store these in sealed containers so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the Subject, appropriate copies should be made for storage outside of the site.

9.1.7. Case Report Forms

For each Subject who signs informed consent, a CRF must be completed and signed (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 AE, thorough efforts should be made to clearly document the outcome.

9.1.8. Protocol Deviations

Neither the Investigator nor the Sponsor is permitted to intentionally deviate from the protocol without proper notification to the FDA or to other relevant regulatory authorities in the form of a protocol amendment. Protocol deviations that occur during the study must be documented.

The Investigator will not alter this study protocol without obtaining the written agreement from the sponsor. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol and will require re-approval of the Institutional Review Board (IRB/Independent Ethics Committee (IEC).

9.1.9. Disclosure of Data

The Principal Investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the name of the Principal Investigator, their addresses, qualifications and extent of involvement. It is understood that the Principal Investigator is required to provide scPharmaceuticals with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the US FDA and other regulatory authorities, by scPharmaceuticals and its designees, and the IRB as appropriate. At a Subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during this study is confidential and disclosure to third parties other than those noted above is prohibited.

9.1.10. Financial Disclosure

The US FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require Sponsors to obtain certain financial information from Investigators participating in covered clinical studies; each Principal Investigator and Sub-investigator is required to provide the required financial information and to promptly update scPharmaceuticals with any relevant changes to their financial information throughout the course of the clinical study and for up to 1 year after its completion. This rule applies to all Principal Investigators and Sub-investigators participating in covered clinical studies to be submitted to the FDA in support of an application for market approval.

9.1.11. Study Completion

scPharmaceuticals requires the following data and materials before a study can be considered complete or terminated:

1. All clinical data and special test results from screening through the end of the study.
2. eCRFs properly completed by appropriate study personnel and signed and dated by the Principal Investigator.
3. Complete Product Accountability records.
4. Copies of protocol amendments and IRB approval/notification/closure if appropriate.

9.1.12. Drug and Device Product Accountability

The Investigator or designee (pharmacist) is responsible for ensuring adequate accountability of all used and unused study treatment. This includes acknowledgment of receipt of each shipment of study treatment (quantity and condition) and Subject dispensing records and return. Dispensing records will document quantities received and quantities dispensed to Subjects, including lot number, date dispensed, Subject identifier number and the initials of the person dispensing the medication.

At the end of the study, following final product reconciliation by the monitor, the Sponsor will instruct the study site the handling of all used and unused study drugs and materials.

9.1.13. Inspections

The Investigator will provide access to source documents and all study records for this trial to appropriately qualified personnel from scPharmaceuticals or its representatives, and to regulatory authority inspectors.

9.2. Sponsor Responsibilities

9.2.1. Study Materials and Instructions

It is the Sponsor's responsibility to ensure that the Investigator is provided with the documents and other study materials necessary to conduct the study. Examples of those materials include, but are not limited to protocol, Investigator's Brochure, study treatments, CRF, logs, etc. The Sponsor or designee will also provide training and oversight through site and medical monitoring.

9.2.2. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study Subjects, will be made by Sponsor-initiated amendment. IRB approval must be obtained before changes can be implemented.

9.3. Joint Investigator and Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

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

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered. The monitor should have access to any Subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

9.3.2. Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs and IECs. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the Subjects' interests.

10. REFERENCES

Haegeli, Laurent; Brunner-La Rocca, Hans Peter; Wenk, Markus; Pfisterer, Matthias; Drewe, Jurgen; Krahenbuhl, Stephan (2007): Sublingual administration of furosemide: new application of an old drug. In *British journal of clinical pharmacology* 64 (6), pp. 804–809. DOI: 10.1111/j.1365-2125.2007.03035.x.

Sica, D. A., Muntendam, P., Myers, R. L., Ter Maaten, J. M., Sale, M. E., de Boer, R. A., & Pitt, B. (2018). Subcutaneous Furosemide in Heart Failure: Pharmacokinetic Characteristics of a Newly Buffered Solution. *JACC Basic Transl Sci, 3*(1), 25-34. doi:10.1016/j.jacbts.2017.10.001

11. APPENDICES

11.1. Appendix 1. Time and Event Schedule

	Screening Phase Day –14 to –3	Baseline Phase Assessment Day 0	Treatment Phase								Follow-Up Phase
			Crossover Period 1			Washout Period (3 ± 1 Days)	Pre-Period 2 Assessment Day 3 ± 1	Crossover Period 2			
			Day 0					Day 3 ± 1			Day 5 ± 1[14]
			Pre-dose	Dosing	Post-dose			Pre-dose	Dosing	Post-Dose	
Sign Informed Consent	X										
Confirmation of Eligibility	X	X									
Med History & Demographics	X										
Complete Physical Examination[1]	X										X
Limited Physical Examination[1]		X			X		X			X	
Screening Labs for Eligibility[2]	X										
Weight	X	X			X		X			X	X
Height (Screening only)[3]	X										
Blood Alcohol Test	X										
Alcohol Breath Test		X					X				
Temperature	X	X					X				
Blood Pressure and Heart Rate	X	X			X		X			X	X
Clinical Laboratory Tests[4]		X			X		X			X	
Urine Drug Screen	X	X					X				
Serum Pregnancy Test[5]	X										
Urine Pregnancy Test[5]		X					X				
12-lead ECG	X										
Admission to CRU		X					X				
Randomization to Treatment Sequence		X									
Study Treatment Administration[6]				X					X		
Plasma for Pharmacokinetics[7]			X		X			X		X	
Void Bladder[8]			X					X			
Urine Collection[8]					X					X	
Food and Fluid intake[9]					X					X	
Assessment of Injection Site Pain[10]			X		X			X		X	
Photograph of Injection Site[11]			X		X			X		X	
Adverse Events[12]					X	X	X	X		X	X
Prior Medication Assessment	X	X									
Concomitant Medications					X	X	X			X	X
Schedule Next Study Visit	X				X					X	

Discharge from CRU[13]							X					X		

[1] A complete/full physical examination should be performed at Screening and Follow-up. On Days 0 and 3 a limited physical examination may be performed consisting of assessments of the skin, lungs/chest, heart, extremities and abdomen and any other abnormalities detected during the study period. Post-dose physical examination on Day 0 and Day 3 should be performed 12 hours after the study drug is administered.

[2] Screening labs include sodium, potassium, calcium, chloride, magnesium, carbon dioxide, blood urea nitrogen (BUN), serum creatinine, glucose, hemoglobin, hematocrit and blood alcohol.

[3] Height and weight collected for calculation of BMI. Height collected at Screening only.

[4] Clinical labs include sodium, potassium, calcium, chloride, magnesium, carbon dioxide, blood urea nitrogen (BUN), serum creatinine, glucose, hemoglobin, and hematocrit. Post-dose clinical labs on Day 0 and Day 3 should be performed 12 hours after the study drug is administered.

[5] Pregnancy test for females of child-bearing potential.

[6] Intravenous furosemide is administered as 40 mg over 1 to 2 minutes followed by a second dose of 40 mg over 1 to 2 minutes, 2 hours apart by IV injection. SCP-111 is administered as a single, 80-mg dose by subcutaneous injection via an autoinjector.

[7] Pharmacokinetic sampling per instructions in 6.2.2.6

[8] Subjects will be instructed to void immediately before dosing (pre-dose urine) and this sample will be discarded. Urine from spontaneous voids during post-dose phases will be collected and pooled, measured, recorded for time periods (0-1), (1-2), (2-3), (3-4), (4-5), (5-6), (6-7), (7-8), (8-10) and (10-12) hours after initiation of dosing. Urine from each collection period must be collected in a single vessel and refrigerated until the end of the collection period. Urinary sodium and urinary potassium concentrations for each collection interval over the 12-hour urine collection period will be analyzed by standard lab biochemistry test. Total urine output volume will be documented for each collection period.

[9] Low sodium snacks and meals as well as water, juice, and caffeine free beverages will be allowed ad libitum, and the amount measured and recorded over the post-dose phases. Subjects will be monitored to ensure a minimum of 100 mL of fluid consumed for every 300 mL of urine output.

[10] Assessment of injection site pain for IV administration performed pre-dose after IV needle placement, immediately after 1st dose and 15 and 30 minutes after 1st dose, immediately after 2nd dose and 15 and 30 minutes and 4 and 10 hours after the 2nd dose. For SC administration, injection site pain conducted pre-dose, immediately after dose and 15 and 30 minutes and 6 and 12 hours after dose.

[11] Photographs of the injection site will be performed prior to the IV and SC injection (baseline) and 4 hours post IV administration or 6 hours post SC administration. In addition, a photograph will be taken of the IV and SC injection site for any AE (i.e., erythema, edema, pruritus, bruising) that occurs at the site at the time of the event.

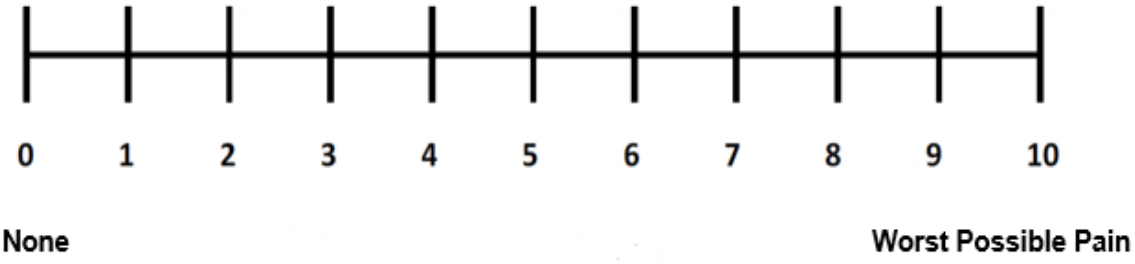
[12] AEs will be assessed continuously during administration of study drug and during the post-dose phase. AEs and SAEs will be followed until resolution if the nature of the AE or SAE requires continued monitoring at the discretion of the Investigator.

[13] Discharge from the CRU after the last assessment per protocol if safety parameters acceptable to Investigator.

[14] Follow-up should occur 24-48 hours after discharge from CRU for Crossover Period 2.

11.2. Appendix 2. Assessment of Injection Site Pain

INJECTION SITE PAIN ASSESSMENT 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 None and 10 being the worst possible pain.