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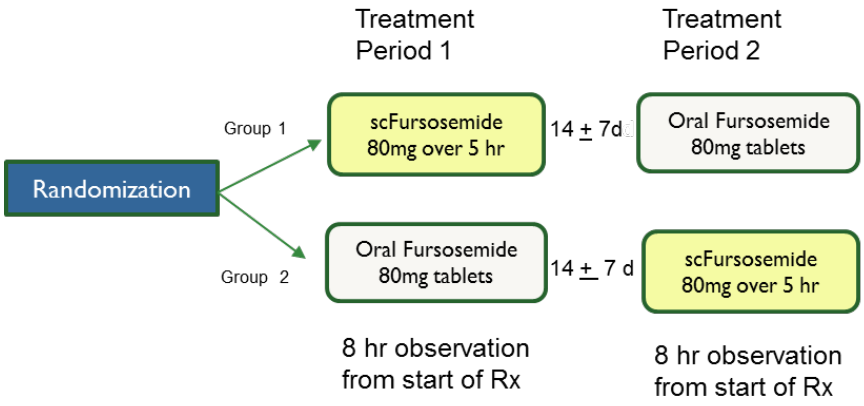
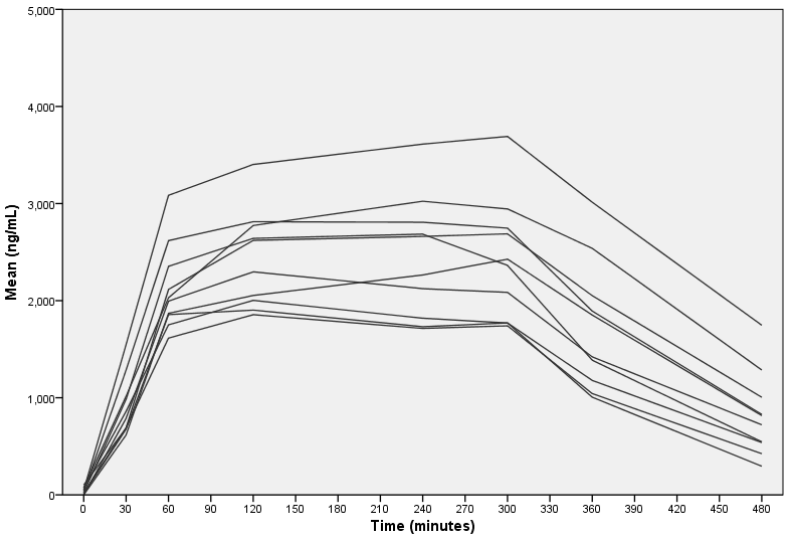
SYNOPSIS REPORT

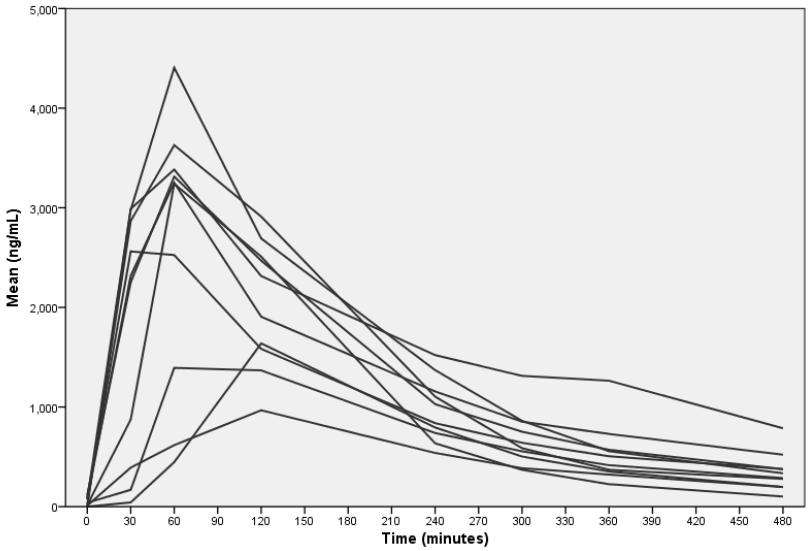
Name of Sponsor Company: scPharmaceuticals, Inc. **Name of Investigational Product:** Furosemide Injection Solution (SCP-101)	
Title of Study:	A single center, randomized, open-label, cross-over exploratory study to evaluate the pharmacodynamic and pharmacokinetic response to a subcutaneous administration or oral administration of furosemide in subjects with heart failure presenting with chronic fluid overload
Investigator(s) and Study Center:	Rudolf A. de Boer, MD, PhD University Medical Center Groningen (UMCG), Groningen, The Netherlands
Protocol Number:	SCP-01-001
Phase of Development:	Phase I/II
Study Design:	This was a single center, randomized, open-label, cross-over exploratory study in heart failure subjects with chronic fluid overload as indicated by the presence of symptoms of heart failure and elevated levels of natriuretic peptides (NT-proBNP). Subjects visiting the heart failure outpatient clinic were assessed for eligibility criteria for the study as part of their routine care. If the subject appeared to be eligible, the subject was informed of the study, invited to participate, and provided with study information to review at home. Subjects were instructed to contact the clinic approximately 7 days later and if they agreed to participate, they were scheduled for a screening visit. The informed consent was reviewed and signed at the screening visit and a number of assessments were done to further evaluate eligibility. Eligible subjects were invited for the first study period if they agreed to participate. Following the start of treatment, subjects remained at the clinic and participated in a treatment evaluation period of 8 hours. After 14 ±7 days (Figure 1), subjects returned for the second, in-clinic 8-hour treatment period. Blood samples were taken at protocol-specified intervals for pharmacokinetic (PK) analyses. Urine specimens were collected for assessment of diuresis, natriuresis, creatinine clearance and to determine urinary excretion of furosemide.

	Figure 1 Study Design 
Study Period:	**First subject screened:** 17 December 2014 **Last subject completed:** 08 April 2015
Objectives:	Primary • To assess the effects of a 5-hour, subcutaneous abdominal delivery of furosemide 80 mg compared to furosemide 80 mg administered orally in subjects with chronic, heart failure with chronic fluid overload Secondary • To obtain plasma samples following subcutaneous and oral furosemide administration for pharmacokinetic analyses and treatment comparison • To investigate injection site reactions and discomfort during subcutaneous administration of furosemide 80 mg • To assess the effects of subcutaneous and oral furosemide 80 mg on signs and symptoms of heart failure (e.g. dyspnea) • To assess the effects of subcutaneous and oral furosemide 80 mg on natriuresis • To investigate if furosemide induced diuresis correlates with changes in bioimpedance parameters • To investigate if pretreatment bioimpedance measurements predict diuretic response to furosemide
Number of Subjects (Planned vs. Actual):	The study was planned to enroll up to 10 subjects. Subsequently, 10 subjects were enrolled, all 10 subjects completed the study, and all 10 subjects were evaluable.
Main Inclusion Criteria	The main subject inclusion criteria for this study were as follows:

	1. Written informed consent before performing any study assessments 2. Male and female subjects >18 years of age, with body weight <120 kg and body mass index (BMI) <30 kg/m^2 3. Females who were at least 2 years post-menopausal 4. Prior treatment with oral furosemide (40 mg oid or bid) or therapeutic equivalent (e.g. bumetanide 1 mg oid or bid) for a period of at least 90 days before first dose of study medication 5. History of chronic heart failure according to 2012 ESC guidelines with presence of moderate symptoms of chronic fluid overload. Chronic fluid overload was defined as the presence of relatively stable signs and symptoms of heart failure and congestion, like dyspnea at mild or minimal exertion, pulmonary congestion and/or peripheral edema at the time of presentation in combination with elevated levels on natriuretic peptides (NT-proBNP >300 ng/L) 6. In the opinion of the investigator, was able to participate in the study
Test Device, Substance Administered, Dose and Mode of Administration, Batch Number(s):	Participants were administered both the subcutaneous and oral furosemide formulations with a treatment interval of 14 ±7 days between the two treatment periods. Subjects meeting the study enrollment criteria were randomized 1:1 to receive 1 of 2 sequence groups (Group 1 or Group 2). Subjects allocated to sequence 2 received oral Lasix® first, followed by subcutaneous Furosemide treatment, and vice versa for subjects allocated to sequence 1. The study treatments were: • Subcutaneous Administration: 80 mg of a novel Subcutaneous Furosemide Injection Solution (SCP-101) (8 mg/mL) administered over 5 hours – 30 mg during the first hour followed by a 12.5 mg/hour infusion for 4 hours. • Oral Administration: 80 mg Lasix® (furosemide) tablets Subcutaneous Furosemide: 10 mL of undiluted solution (8 mg/mL) was administered in the abdominal area via standard subcutaneous infusion set with the use of a commercial infusion pump. Oral Lasix® Tablet: Two (2) 40 mg tablets administered with 100 mL of water. Furosemide Injection Solution Lot Number: 006E14 Lasix® Tablet Formulation Lot Number: 14K12_023

Duration of Treatment:	The study duration included a screening visit, and two treatment visits on separate days. Each treatment visit required a maximum duration of 8 hours from the start of the treatment. The treatment visits were separated by 14 ±7 days. The active treatment period completed at the conclusion of the second treatment visit. Participants were subsequently monitored by telephone interview for SAEs through 30 days post study completion.
Disposition of Study Population:	Ten (10) subjects were enrolled in this randomized, open-label, cross-over exploratory study to evaluate the pharmacodynamic and pharmacokinetic response of subcutaneous vs. oral administration of furosemide in subjects with heart failure presenting with chronic fluid overload. The average age of the subjects was 69.9 ±8.6 years, 20% were female, and the mean BMI was 27.5 ±4.5 kg/m^2. All 10 subjects were evaluated as New York Heart Association (NYHA) Class II. Relevant medical history included 5 (50%) subjects with ischemic heart disease, 6 (60%) subjects with an implantable cardioverter defibrillator (ICD) and 2 (20%) subjects with a cardiac resynchronization therapy device (CRT-D). All 10 of the subjects completed the study.
Criteria for Evaluation	To minimize confounding variables on diuresis, food, water and salt intake were to be standardized during the treatment period and instructions provided regarding food and drink intake during the 48 hours preceding each of the two treatment periods. However, in practice, fluid intake during the study was ad libitum (range 1,175-2,000 mL over 8 hours interval). This routine was not compliant with the protocol and impacted interpretation of many variables being collected. These include the following: • Pharmacodynamic Assessments i.e. diuresis, natriuresis • Dyspnea Score • Heart Failure Symptom Score • Measurement of Thirst and Thirst Intensity • Measurement of Bioimpedance However, plasma furosemide levels, adverse event (AE) and serious adverse event (SAE) observations are unlikely affected by fluid intake. **Pharmacokinetic Assessment (both study treatments):** Plasma samples collected at time 0 (pre-dose), and at 30, 60, 120, 240, 300, 360 and 480 minutes post-dose were assayed for furosemide levels using a validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) analytical method. These data were used to graphically illustrate mean and individual furosemide concentration-time profiles.

Statistical Methods	Safety evaluations that were performed at screening, baseline and at the end of each treatment period included physical examination evaluations, weight and temperature measurements and blood chemistry and hematology evaluations. Safety evaluations that were performed at baseline, during each treatment period and at the end of each treatment period included injection site inspections that were documented using digital imaging, vital sign measurements (also performed at screening), and AE/SAE monitoring.
Pharmacodynamic Results	Pharmacodynamic results generally appear to be compromised because of ad libitum fluid intake, which ranged from 1,175 mL to 2,000 mL over the 8 hour observation period. This was based on a misunderstanding by the investigator. The protocol prescribed a standardized fluid intake of 100 mL per hour which the study staff interpreted to mean 100 mL in addition to ad libitum fluid intake.
Pharmacokinetic Results	The pharmacokinetic results support proof of concept for subcutaneous administration of the novel furosemide formulation. All participants achieved plasma furosemide levels of over 1000 ng/mL within one hour of start of subcutaneous infusion as illustrated in the figure below (furosemide levels in ng/mL are plotted using the y-axis and time in minutes is plotted on the x-axis). Plasma levels in the plateau phase (60-300 minutes) show little variability (i.e. constant rate of absorption).  In comparison, orally administered furosemide was rapidly absorbed with mean peak levels observed at the 60-minute post dose timepoint followed by a rapid decline in plasma levels to <1000 ng/mL. Following subcutaneous administration plasma levels over 1,000 ng/mL were maintained over a longer period of time compared to orally administered furosemide.



Safety Results

The overall incidence of subjects who had 1 or more AE following subcutaneous administration of the investigational product and AEs listed by the Medical Dictionary for Regulatory Activity (MedDRA) system organ class (SOC) and verbatim term are summarized in the table below using the Safety Population:

SOC/ Verbatim Term	SC Treatment Group (N=10) n (%)
Number of Subjects with AEs	6 (60)
General Disorders and Administration Site Conditions	
Bruise at injection site	1 (10)
Burning/stinging sensation at/around injection site	4 (40)
Exhausted	1 (10)
Red discharge	1 (10)
Infections and Infestations	
Flu	1 (10)
Musculoskeletal and Connective Tissue Disorders	
Cramps both legs	1 (10)
Respiratory, Thoracic and Mediastinal Disorders	
Exacerbated COPD	1 (10)
Bronchitis	1 (10)
Vascular Disorders	
Stroke	1 (10)
Source: Summary of Adverse Events (Data on File)	

Six (60%) of the 10 subjects who received subcutaneous furosemide 80 mg experienced a total of 12 AEs. For the same group of 10 subjects, there were no reports of AEs when they were administered oral furosemide 80 mg. The only AE that was reported by more than 1 (10%) subject following subcutaneous furosemide administration was

"burning/stinging sensation at/around injection site", which was reported by 4 (40%) subjects. Overall, AEs associated with the administration site accounted for 6 of the 12 AEs that were reported.

AEs severity, and relatedness to IP, the infusion procedure, underlying disease and any other procedure was evaluated. These data for AE's following administration are summarized in the following tabular display. The table also summarizes subjects requiring treatment for an AE, AE outcome and the incidence of serious adverse events (SAEs).

Parameter/ Level	SC n (%)	PO n (%)	Occurred Outside Treatment n (%)
Safety Analysis Set	10	10	10
Subjects with AEs	6 (60)	0 (0)	3 (30)
Subjects with AEs by Severity			
No event	4 (40)	10 (100)	7 (70)
Mild	6 (60)	0 (0)	0 (0)
Moderate	0 (0)	0 (0)	2 (20)
Severe	0 (0)	0 (0)	1 (10)
Subjects with AEs Related to IP			
No event	4 (40)	10 (100)	7 (70)
Unrelated	0 (0)	0 (0)	3 (30)
Related	6 (60)	0 (0)	0 (0)
Subjects with AEs Related to Infusion Procedure			
No event	4 (40)	10 (100)	7 (70)
Unrelated	1 (10)	0 (0)	3 (30)
Related	5 (50)	0 (0)	0 (0)
Subjects with AEs Related to Underlying Disease			
No event	4 (40)	10 (100)	7 (70)
Unrelated	6 (60)	0 (0)	0 (0)
Related	0 (0)	0 (0)	3 (30)
Subjects with AEs Related to Other Procedure			
No event	4 (40)	10 (100)	7 (70)
Unrelated	6 (60)	0 (0)	2 (20)
Related	0 (0)	0 (0)	1 (10)
Treatment Required			
No Event	4 (40)	10 (100)	7 (70)
None	6 (60)	0 (0)	0 (0)
Medication	0 (0)	0 (0)	2 (20)
Non-drug Treatment	0 (0)	0 (0)	0 (0)
Hospitalization	0 (0)	0 (0)	1 (10)
Outcome			
No Event	4 (40)	10 (100)	7 (70)
Resolved	6 (60)	0 (0)	2 (20)
Resolved with Sequelae	0 (0)	0 (0)	1 (10)
Continuing	0 (0)	0 (0)	0 (0)
Lost to Follow-up	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)

Subjects with SAEs			
No Event	4 (40)	10 (100)	7 (70)
Non-serious	6 (60)	0 (0)	2 (20)
Serious	0 (0)	0 (0)	1 (10)

AE=adverse event; IP=investigational product; SAE=serious adverse event; SC=subcutaneous; PO=oral
Subjects experiencing more than one AE counted under maximum severity/causality/outcome experienced across events.

For the 6 (60%) subjects who reported at least 1 AE following administration of subcutaneous furosemide, all were of mild severity and all were considered by the Investigator to be related to treatment with the IP. Treatment was not required for any of the AEs, and all AEs that occurred following administration of subcutaneous furosemide resolved.

There was one SAE that occurred outside of the treatment period that was related to an underlying disease and required hospitalization. Subject 007 was 81-years-old male with a history of chronic obstructive pulmonary disease (COPD). The subject was enrolled in the SCP-01-001 study and as per study protocol, received a dose of 80 mg oral furosemide on 14 February 2015 and a dose of investigational product (80 mg subcutaneous furosemide) on 24 February 2015. On 02 March 2015, the subject presented to the emergency department with dyspnea, and productive cough. The subject was admitted to the hospital with COPD exacerbation secondary to an upper respiratory tract infection. The subject's chest x-ray revealed possible infiltrate in the paravertebral right lower lobe. A sputum culture was positive for *Staphylococcus aureus* and *Klebsiella pneumoniae*. The subject was treated with prednisone and Augmentin® and recovered quickly, and was discharged from the hospital on 05 March 2015. The investigator determined that the SAE was unrelated to investigational product or procedures and related to the subject's underlying disease.

Summary and Conclusions:

In terms of proof of concept, the following observations were made regarding administration of subcutaneous furosemide in the current study:

- Therapeutic levels of furosemide were achieved within 30 minutes in all subjects (range: 617 to 1548 ng/mL)
- Therapeutic levels of furosemide were maintained over a period of 5 hours
- Constant plasma levels in plateau phase with 100% of the subjects maintaining levels of 1000 ng/mL for a minimum of 5 hours following subcutaneous administration vs. 10% of subjects following oral administration
- Subcutaneous furosemide was well-tolerated with no sign of drug-induced skin reactions

In terms of safety and tolerability, but keeping in mind the small number of subjects administered each treatment, the following observations can

	be made regarding administration of subcutaneous furosemide in the current study. • Overall, subcutaneous furosemide was well-tolerated. All AEs that were related to the IP or the infusion procedure were reported as "mild" • AE incidence, primarily due to AEs associated with the administration site, was higher following subcutaneous furosemide administration compared to AE incidence following oral furosemide administration.
Date of Report:	21 March 2017

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SYNOPSIS REPORT APPROVAL PAGE

Study Title:	A single center, randomized, open-label, cross-over exploratory study to evaluate the pharmacodynamic and pharmacokinetic response to a subcutaneous administration or oral administration of furosemide in subjects with heart failure presenting with chronic fluid overload
Protocol Number:	SCP-01-001
Original Protocol Date of Issue:	September 30, 2014
Amendment 1 Date of Issue:	November 17, 2014
Sponsor Name and Address:	scPharmaceuticals, Inc. 131 Hartwell Avenue, Suite 215 Lexington, MA 02421

I, the undersigned, have read and approve this synopsis report and agree on its content.

Approval Section			
	Name/Title	**Signature**	**Date**
Prepared and Approved by:	Rene Myers, PhD VP Clinical Affairs		23 MAR 2017
Prepared and Approved by:	Pieter Muntendam, MD Medical Consultant		23 Mar 2017