Pharmacokinetics (PK) and Pharmacodynamics (PD) of SC Furosemide (Furoscix) in Patients with Heart Failure (HF) and Obesity

Tamas Alexy[1], Katie H. Luepke[2], Phanisyam Kamineni[2], Matthew M. Goodwin[2], Barbara Cornelius[2], John F. Mohr[2]

[1]Department of Medicine, Division of Cardiology, University of Minnesota, Minneapolis, MN; [2]scPharmaceuticals, Inc., Burlington, MA

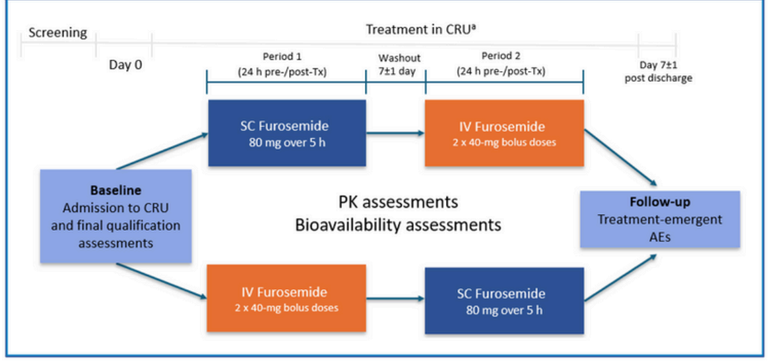
INTRODUCTION AND OBJECTIVES

- Up to 49% of patients with HF are obese, and obesity is extremely common (>80%) in HF patients with preserved ejection fraction[1].
- Oral diuretics are the cornerstone of treatment, yet blunted absorption in the setting of fluid overload contributes to diuretic resistance[2,3].
- Furoscix (SC furosemide) is a pH-neutral formulation of furosemide that is FDA-approved as a self-administered 5-hour subcutaneous infusion for treatment of congestion due to fluid overload in adult patients with chronic HF.
- In a pivotal PK/PD study, bioavailability of SC furosemide was 99.6% compared to IV furosemide, with similar diuresis and natriuresis[4].
- The purpose of this analysis was to evaluate the PK/PD of SC furosemide based on Body Mass Index (BMI).

METHODS

- An overview of the methodology for the PK/PD study is depicted in Figure 1.
- A post-hoc analysis of the study was conducted to compare PK and urine output (UO) to IV furosemide, stratified by BMI.

Figure 1. Pivotal PK/PD Study Methodology



[a]Patients discontinued oral furosemide >24 h prior to administration of study drug for each crossover period.
AE=adverse event; CRU=clinical research unit; h=hour; IV=intravenous; min=minute; PK= pharmacokinetics; SC=subcutaneous

- SC furosemide 80 mg was administered via 5-hour biphasic regimen (30 mg hour 1, 12.5 mg/hr hours 2-5). IV furosemide was given as two 40 mg bolus doses 2 hours apart.
- Plasma was collected for determination of furosemide concentrations and urine output was quantified over 24-hour study period.
- PK/PD parameter assessments and determination of SC bioavailability were previously described; of note AUC was utilized for bioavailability determination given differences in Cmax between IV and SC routes [(AUC∞/SC furosemide dose) / (AUC∞/IV furosemide dose)].
- Patients with a BMI > 38 kg/m² were excluded from the study.

RESULTS

- 17 patients were enrolled, and 15 patients were available for analysis. The median BMI was 31.2 kg/m² (range 23.2-37.9).
- Baseline characteristics are listed in Table 1.

Pharmacokinetics

- Peak plasma furosemide concentration (Cmax) was lower in the BMI >31.2 kg/m² group with no difference in half-life. There was no difference in any of the variables between the SC and IV agents across the BMI spectrum (Table 2).

Table 1. Baseline Characteristics

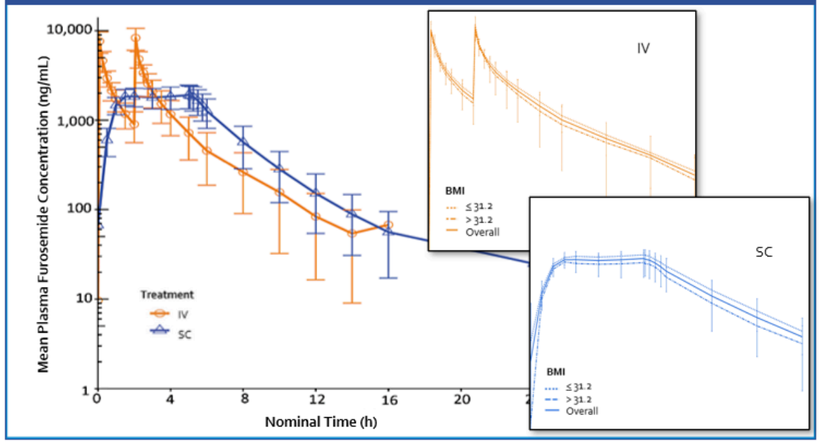
Characteristic	n=17
Age (years)	68 ± 9.5
Male (%)	88.2
Weight (kg)	96.6 ± 15.6
Body Mass Index (kg/m²)	31 ± 4.6
NYHA functional class II/III (%)	76.5/23.5
eGFR^,*	60 (41-98)
Baseline furosemide dose (mg/day)*	40 ± 0

Mean ± SD, %, or median (range). ^mL/min/1.73m². *17 enrolled; 15 in statistical analysis (1 withdrew, 1 had high pre-dose concentration).

Table 2. Furosemide Noncompartmental PK parameters after SC and IV Administration

Route	SC			IV		
BMI (kg/m²)	≤ 31.2 n=7	> 31.2 n=8	Overall n=15	≤ 31.2 n=7	> 31.2 n=8	Overall n=15
C_{max} (ng/mL)	2,360 (1930, 2780)	1,740 (1340, 2230)	2040 (449)	8,450 (6,610, 11,600)	7,835 (5,060, 13,800)	8,580 (2,540)
AUC_{∞} (h*ng/mL)	16,000 (10600, 21100)	10,740 (7610, 16800)	13,100 (4010)	14,200 (12,100, 20,900)	10,650 (6,600, 19,300)	13,200 (4170)
$t_{1/2}$ (h)	3.2 (2.62, 4.64)	3.1 (1.78, 4.69)	3.16 (0.91)	2.52 (2.00, 3.18)	2.53 (2.12, 3.13)	2.55 (0.34)
CL (L/h)	6.2 (3.84, 7.73)	6.5 (4.82, 10.6)	6.71 (2.21)	6.2 (3.83, 6.6)	6.87 (4.14, 2.1)	6.71 (2.31)

Figure 2. IV vs SC Furosemide Concentration-Time Profiles by BMI



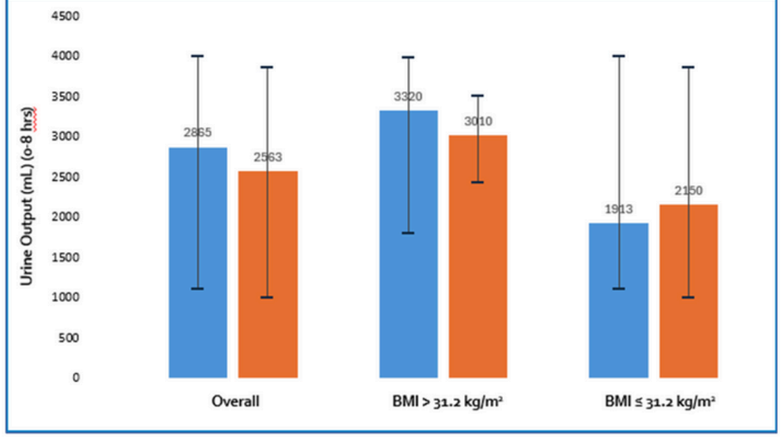
Data reported as mean (SD). ^mL/min/1.73 m²; Cmax, peak plasma concentration; t1/2, half-life; AUC∞, plasma concentration to infinity; CL, clearance.

RESULTS, CONT.

- Figure 2 contains the concentration-time curve for overall population (99.6% bioavailability for SC based on AUC) and by BMI
- As expected, the furosemide serum concentration was slightly lower with increased BMI, but changes in serum concentration based on BMI were consistent across IV and SC administration.

- Median (min, max) 8-hour UO in patients with BMI >31.2 and ⩽ 31.2 kg/m² from SC was 3320 (2425, 3500) and 1913 (1095, 3885) mL, respectively.
- 8-hour UO was higher in patients with BMI >31.2 kg/m² with both SC and IV administration (Figure 3).

Figure 3. 8-Hour Urine Output by Route and BMI



SUMMARY AND CONCLUSIONS

- Compared to the overall population, furosemide exposure from both SC and IV administration was slightly decreased in patients with BMI > 31.2 kg/m².
- Despite decreased serum concentration, UO in patients with BMI >31.2 kg/m² was higher compared to patients with BMI ⩽ 31.2 kg/m², which illustrates attainment of threshold required for diuresis.
- Future research is needed in patients with BMI > 38 kg/m², and also to explore mechanisms behind increased UO in patients with a higher BMI.

References: 1. Progress in Cardiovascular Diseases 2020;63(5): 561-569. 2. Ann Intern Med 1985;102(3):314-318. 3. J Am Coll Cardiol: Basic Trans Science. 2018;3(1):25-34 4. J Otolaryngology. 1982;11(2):127-133.

Study funded by scPharmaceuticals Inc.