Pharmacokinetics (PK) and Pharmacodynamics (PD) of SC Furosemide (Furoscix) in Chronic Kidney Disease (CKD): A New Option for Outpatient Diuresis

Christian W. Mende[1], Katie H. Luepke[2], Phanisyam Kamineni[2], Matthew M. Goodwin[2], John F. Mohr[2], Barbara Cornelius[2]

[1]University of California San Diego, La Jolla, CA; [2]scPharmaceuticals, Inc., Burlington, MA

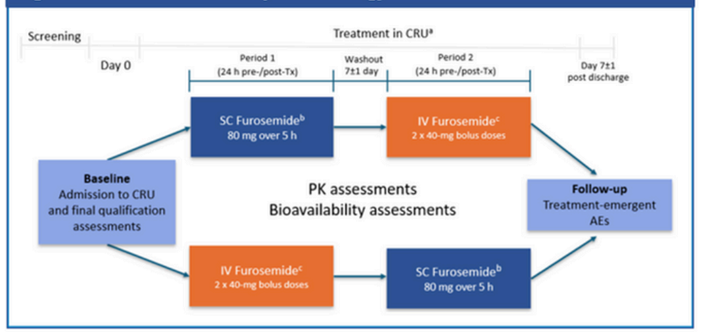
INTRODUCTION AND OBJECTIVES

- Fluid overload affects 40-50% patients with CKD and can lead to further eGFR decline, cardiovascular complications, and increased mortality[1,2,3].
- Oral diuretics are the cornerstone of treatment, yet blunted absorption from fluid overload contributes to diuretic resistance[4,5].
- 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 heart failure (HF).
- In a pivotal PK/PD study, bioavailability of SC furosemide was 99.6% compared to IV furosemide, with similar diuresis and natriuresis[6].
- The purpose of this analysis was to evaluate PK/PD of SC furosemide based on eGFR.

METHODS

- 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 eGFR.

Figure 1. Pivotal PK/PD Study Methodology



[a]Patients discontinued oral furosemide >24 h prior to administration of study drug for each crossover period.
[b]Administered with Braun Infusion Pump, biphasic regimen (30 mg first hour; 12.5 mg/h subsequent 4 h).
[c]Administered as two, 40-mg bolus doses (over 2 min) 2 h apart. 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)].
- Renal function was estimated using the Modification of Diet in Renal Diseases (MDRD) equation and results were stratified by eGFR < 60 and ≥ 60 mL/min/1.73 m² using descriptive statistics.
- Patients with eGFR <45 mL/min/1.73m² were excluded from the study.

References: 1. J Am Heart Assoc. 2015;4:1-12. 2. PLoS ONE. 2016;11(7):e0159335. 3. Clin J Am Soc Nephrol. 2015;10:39-46. 4. N Eng J Med. 2017;377:1964-1975. 5. Ann Intern Med 1985;102(3):314-318. 6. J Am Coll Cardiol: Basic Trans Science. 2018;3(1):25-34 7. J Otolaryngology. 1982;11(2):127-133.

RESULTS

- 15 patients were available for analysis. Despite exclusion criteria, 2 patients were enrolled with eGFR <45 mL/min/1.73 m².
- Baseline characteristics are listed in Table 1. The median eGFR was 60, and most patients had eGFR between 30-59 and 60-89 mL/min/1.73 m² (7 each).

Pharmacokinetics

- As renal function declined, furosemide plasma levels increased but mean Cmax values from SC were lower than IV bolus administration (Table 2).
- Regardless of renal function, neither SC nor IV resulted in Cmax associated with ototoxicity (>50,000-100,000 ng/mL)[7].

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).

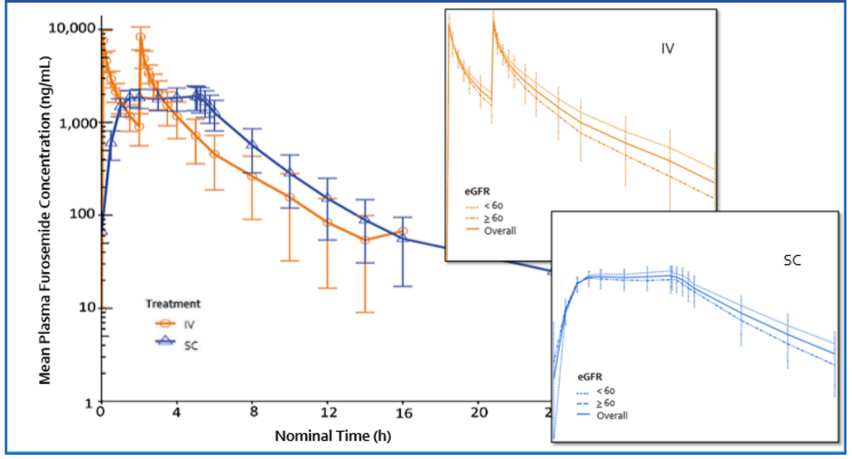
Table 2. Furosemide Noncompartmental PK parameters after SC and IV Administration

Route	SC			IV
eGFR^	≥ 60 n=8	< 60 n=7	Overall n=15	Overall n=15
C_{max} (ng/mL)	1835 (418)	2269 (383)	2040 (449)	8,580 (2,540)
AUC_{∞} (h*ng/mL)	11,444 (3494)	15,411 (3810)	13,100 (4010)	13,200 (4170)
$t_{1/2}$ (h)	2.92 (0.88)	3.45 (0.91)	3.16 (0.91)	2.55 (0.34)
CL (L/h)	7.59 (2.27)	5.51 (1.52)	6.71 (2.21)	6.71 (2.31)

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.

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

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



RESULTS, CONT.

- Mean hourly urine output for the overall population is in Figure 3. IV compared to SC had an earlier onset of action, but both resulted in similar diuresis between 0-8 hours (2,718 + 654 ml and 2,663 + 1,021 ml); IV and SC, respectively.

Figure 3. IV vs SC Furosemide Hourly Urine Output

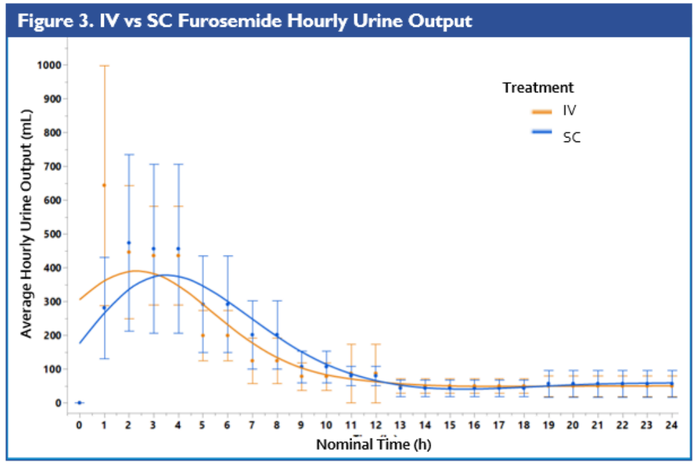
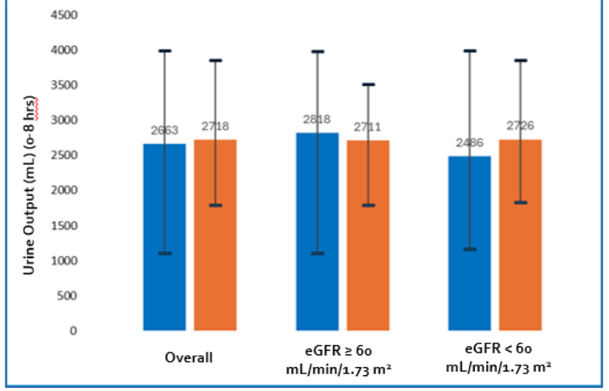


Figure 4. 8-Hour Urine Output by Route and eGFR



- Mean (SD) 8-hour urine output in patients with eGFR > 60 and <60 mL/min/1.73 m² from SC administration was 2818 (1034) and 2486 (1057) mL, respectively. 8-hour urine output was consistent between SC and IV regardless of renal function (Figure 4).

SUMMARY AND CONCLUSIONS

- As renal function declined, furosemide exposure from SC increased but remained below the threshold for ototoxicity.
- Urine output between SC and IV remained consistent regardless of eGFR.
- SC furosemide is a new IV-equivalent, outpatient option for patients with CKD who experience fluid overload.
- Future research is needed with SC furosemide in patients with eGFR <45 mL/min/1.73m².

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