Pharmacokinetics (PK) and Pharmacodynamics (PD) of a Subcutaneous (SC) Injection of a Novel-Formulation of furosemide (FUR)

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ABSTRACT

Background. Furoscix 80 mg/10 mL is a buffered formulation of FUR that is self-administered SC via an On-body Infusor over 5 hrs. Furoscix 80 mg/mL, a novel-formulation of FUR administered as a single dose via an autoinjector (FUR SC), is in development. This Phase 1 study aimed to characterize bioavailability (BA), PK, and PD of FUR 80 mg/mL SC via an autoinjector compared to the equivalent intravenous (IV) dose of FUR.

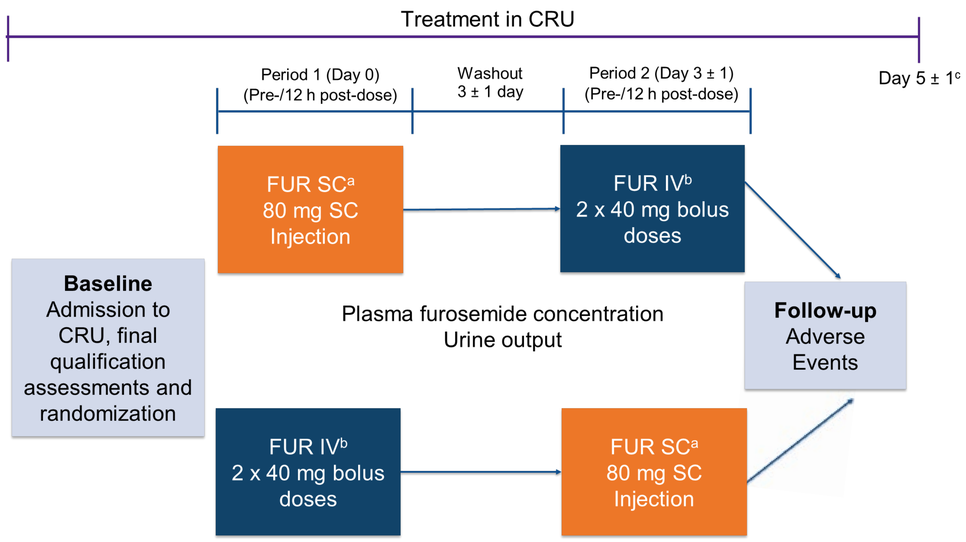
Methods. Randomized, open-label, single-center crossover study. Healthy participants were randomized 1:1 to 1 of 2 treatment sequences (FUR IV 80 mg [two IV 40-mg boluses 2 hours apart] or FUR SC 80 mg/mL via autoinjector into abdomen). Opposite treatment was administered after 3-day washout. Blood was collected pre-dose and for 12 hours post-dose to determine FUR plasma concentrations. BA was estimated by least squares mean ratios of AUC_{last} and AUC_{inf} between FUR SC and IV. Urine was collected for 12 hours post-dose to determine urine output (UO) and urinary Na+ and K+ excretion. Pain scores were calculated using 11-point numeric rating scale (NRS). Safety was assessed through Day 5 ±1 of study.

Results. 21 subjects were randomized to FUR SC/FUR IV (N=10) or FUR IV/FUR SC sequences (N=11). BA for FUR SC based on AUC_{last} and AUC_{inf} was 106.1 (90% CI: 102.7, 109.6) and 107.3 (90% CI: 103.9, 110.8), respectively, indicating similar BA. Although C_{max} was ~2-fold higher following 40 mg IV boluses compared to 80 mg SC (10,088 vs 4,533 ng/mL), total UO and cumulative urinary Na+ and K+ excretion were similar following SC and IV for 0-6, 0-8, and 0-12 time intervals. Adverse events (AE)s involving injection site were more common with FUR SC than FUR IV (42.9 vs. 10%). Median (range) pain score immediately post-dose was 0 (0, 3) for FUR SC and 0 (0, 2) for FUR IV (IV pain score was same as after needle placement). One subject experienced a serious AE of hyponatremia that was moderate in severity and possibly related to SC administration and resolved in 2 days.

Conclusions. FUR SC administered via autoinjector demonstrated equivalent relative BA compared to FUR IV, with similar UO, natriuresis, and kaliuresis. SC FUR was generally safe and well-tolerated.

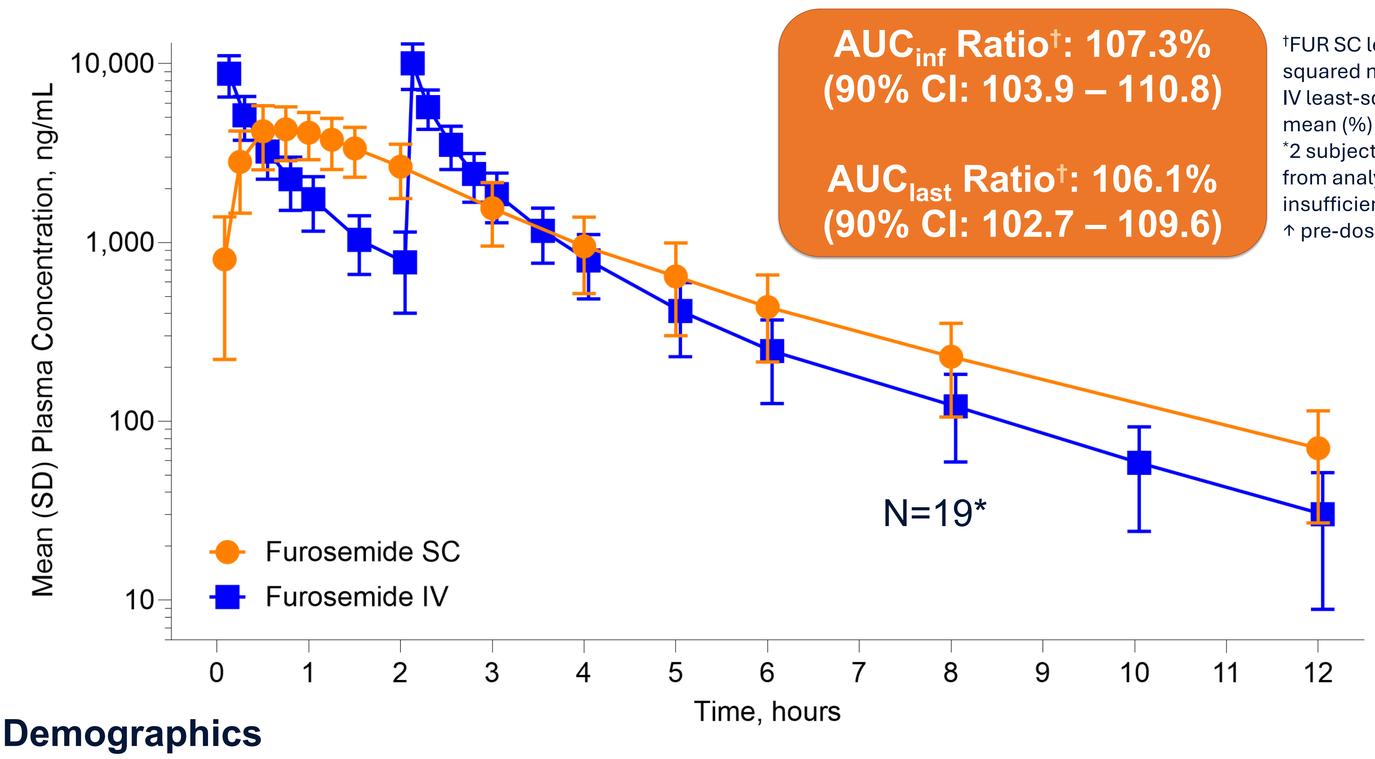
METHODS

- Open-label, single center, single dose, randomized two-way (two period) crossover study
- Primary objective: Estimate BA of FUR SC 80 mg/mL via autoinjector vs. FUR IV 40 mg x 2 doses, 2 hours apart
- Secondary objectives:
  - Describe PK and PD of FUR SC
  - Describe safety and tolerability of FUR SC



[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); [C] Follow-up visit should occur 24-48 hours after discharge from CRU for Crossover Period 2; CRU=clinical research unit.

RESULTS



Demographics

- Age: 56 (45-71); 71.4% Female; 19% African American; 23.8% Hispanic/Latino
- BMI, 27.4 (19.3, 51.4) kg/m^2; eGFR, 79 (56, 138) mL/min/1.73 m^2

PK and PD

Mean (SD)	FUR IV N=19	FUR SC N=19
C_{max} (ng/mL)	10,088 (2,805)	4,533 (1,498)
AUC_{last} (hr*ng/mL)	11,684 (3,453)	12,470 (4,010)
AUC_{inf} (hr*ng/mL)	11,780 (3,507)	12,714 (4,117)
$t_{1/2}$ (hr)	1.9 (0.4)	2.2 (0.3)
CL (L/hr)	7.32 (1.97)	6.87 (2.00)
V_d (L)	19.8 (4.8)	21.5 (5.6)

Mean (SD)	FUR IV N=19	FUR SC N=19	p-value
UO, Liters			
0-6 hours	2.91 (0.72)	3.19 (0.88)	0.27
0-8 hours	3.19 (0.79)	3.52 (0.90)	0.23
0-12 hours	3.70 (0.95)	3.99 (0.96)	0.32
Urinary Na+, mmol			
0-6 hours	258 (99)	276 (111)	0.59
0-8 hours	264 (101)	280 (118)[#]	0.75
0-12 hours	273 (103)	288 (121)[#]	0.77
Urinary K+, mEq			
0-6 hours	39.3 (14.6)	41.8 (10.5)	0.40
0-8 hours	44.5 (16.1)	47.0 (11.6)[#]	0.63
0-12 hours	52.6 (17.9)	55.1 (14.1)[#]	0.70

[#]n=18

Safety

- AEs occurred in 11 (54.2%) subjects in FUR SC and 7 (35.0%) in FUR IV
- Most common AE with FUR SC were associated with injection site (pain, bruising, erythema and pruritis)
- Systemic AEs with FUR SC were those reported for IV and oral furosemide (muscle spasms, hyponatremia, nausea, vomiting)
- All AEs mild or moderate; 66.7% and 9.5%, respectively
- 1 FUR SC subject developed moderate hyponatremia with muscle cramps nausea, vomiting that was assessed as serious

CONCLUSIONS

- FUR SC demonstrated equivalent bioavailability compared to FUR IV
- FUR SC had similar total urine output, Na and K excretion compared to FUR IV
- FUR SC was generally safe and well tolerated