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Pharmacokinetics (PK) and Pharmacodynamic (PD) Profiles of Subcutaneous Furosemide (FUR SC) Administered as a 5-hour Infusion and 10-second Injection

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INTRODUCTION

- FUROSCIX 80 mg/10 mL is a buffered furosemide (FUR) formulation delivered subcutaneously (SC) via an On-body- Infusor (OBI) over 5 hours (30 mg in the first hour, then 12.5 mg/hour for 4 hours). A more concentrated 80 mg/mL FUR formulation, FUROSCIX ReadyFlow, is administered SC as a single injection via an autoinjector in less than 10 seconds.
- Both achieved absolute bioavailability (AUC-based bioequivalence) to IV FUR with comparable diuresis, natriuresis, and safety. This analysis summarizes key pharmacokinetic (PK)/pharmacodynamic (PD) similarities and differences between the pivotal PK/PD studies.

Figure 1. Product Illustrations

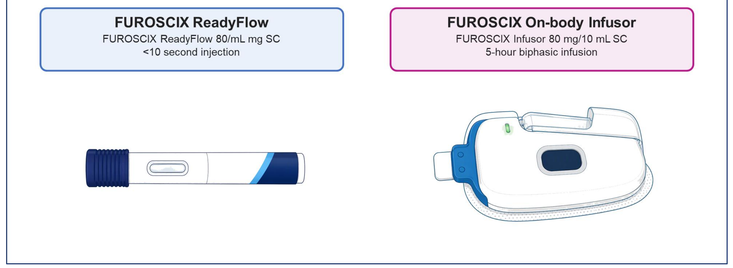
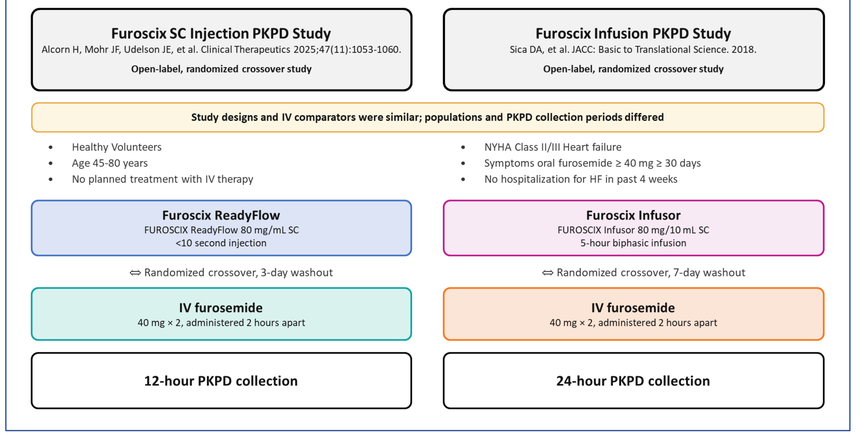


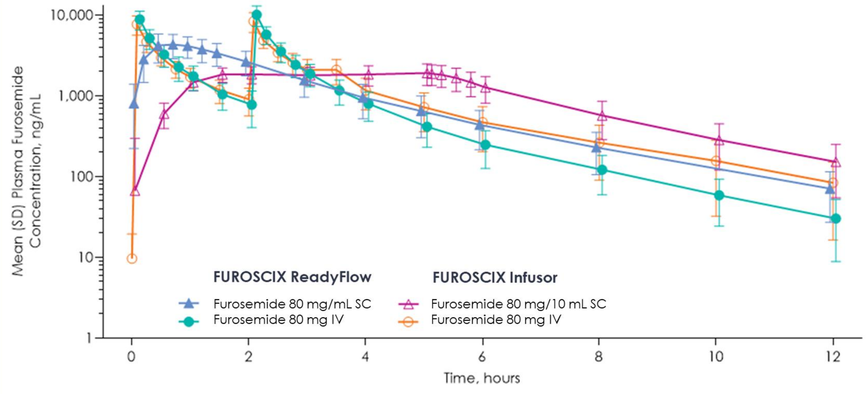
Figure 2. Combined Study Designs and Patient Populations



METHODS

- Both studies were randomized, open-label, crossover studies in which participants received IV FUR 80 mg (two 40mg boluses 2 hours apart) and either the 5-hour SC infusion or SC injection (abdomen injection site). Treatments separated by a wash out period.
- The infusion study enrolled NYHA II/III HF patients (24-hr PK/PD collection), whereas the injection study enrolled healthy participants (12-hr collection).
- Relative BA was assessed using geometric mean ratios for AUC_{last} and AUC_{inf} with BE defined if 90% CIs were within 80-125%.

Figure 3. Least-Squares Mean Plasma vs. Time Concentration Curves



RESULTS

- 15 participants completed the infusion study and 19 completed the injection study. IV dosing produced mean C_{max} values ~4-fold (infusion) and ~2-fold (injection) higher than SC dosing, while AUC values remained similar, confirming similar bioavailability for both formulations.
- Onset of UO occurred within 1st hour for both SC injection and infusion, but urine volume was initially higher with SC injection compared to SC infusion given difference in T_{max}.
- Eight-hour UO and urinary sodium excretion were comparable across SC injection, SC infusion, and IV administration.

Table 1. Summary of PKPD Parameters

	Furoscix SC Injection PKPD Study		FUROSCIX Infusion PKPD Study	
Mean ± SD	Furosemide ReadyFlow (n=19)	IV Furosemide (n=19)	Furoscix Infusor (n=15)[a]	IV Furosemide (n=15)
C_{max} (ng/mL)	4,533 ± 1498	10,088 ± 2805	2,040 ± 449	8,580 ± 2,540
T_{max} (hr)[b]	0.75 (0.5 - 1.50)	2.08 (0.08 - 2.12)	4.00 (1.00 - 5.08)	2.08 (0.08 - 2.08)
AUC_{last} (hr*ng/mL)	12,470 ± 4010	11,684 ± 3453	13,000 ± 4,000	13,000 ± 4,050
AUC_{inf} (hr*ng/mL)	12,714 ± 4117	11,780 ± 3507	13,100 ± 4,010	13,200 ± 4170
$t_{1/2}$ (hr)	2.2 ± 0.3	1.9 ± 0.4	3.2 ± 0.9	2.6 ± 0.3
1-hour urine output (L)	1.03 ± 0.30	1.01 ± 0.35	0.28 ± 0.15	0.64 ± 0.36
8-hour urine output (L)	3.52 ± 0.90	3.19 ± 0.79	2.65± 0.99	2.61 ± 0.77
8-hour Urinary Na Excretion (mmol)	280 ± 118	264 ± 101	284 ± 126	292 ± 111

[a]Administered with Braun Infusion Pump, biphasic regimen (30mg first hour; 12.5mg/h subsequent 4h). [B]median (range). T_{max} values not true comparison given two IV injections, 2 hours apart.

CONCLUSIONS

- Both SC formulations achieved bioequivalence to IV FUR and produced similar diuretic and natriuretic responses.
- Cross-study comparisons should be interpreted cautiously due to differing populations (HF vs. healthy volunteers).
- Both SC modalities provide an IV-equivalent option for outpatient diuresis.

AUC_{inf}, area under the plasma concentration versus time curve from time zero extrapolated to infinity; AUC_{last}, area under the plasma concentration versus time curve from time zero to the time of the last measurable concentration; C_{max}, maximum observed plasma concentration; CRU, clinical research unit; F, absolute bioavailability; h, hour; IV, intravenous; SC, subcutaneous; SD, standard deviation; $t_{1/2}$, terminal-phase half-life; V_d, systemic volume of distribution

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