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Effect of Multiple Doses of Sparsentan on the Single-Dose Pharmacokinetics of Dapagliflozin: Open-label Drug-Drug Interaction Study in Healthy Adults

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TRAVERE™ THERAPEUTICS

DISCLOSURES

- **SCC, DC, CW, NV, PP:** Employee and equity ownership, Travere Therapeutics, Inc.

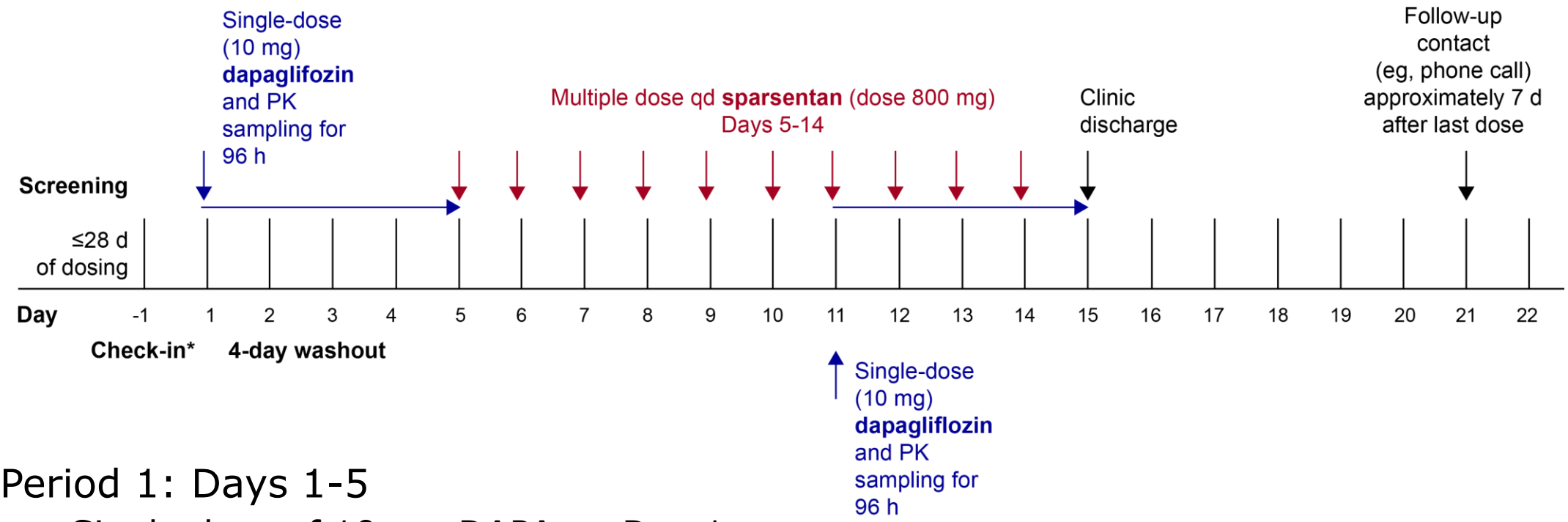
- SPAR is a first-in-class, novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA) under investigation for the treatment of immunoglobulin A nephropathy and focal segmental glomerulosclerosis[1]
- Sodium-glucose cotransporter 2 inhibitors, such as DAPA, have recently been indicated for chronic kidney disease[2-5]
- It is important to determine any drug-drug interactions between SPAR and DAPA that may affect DAPA PK
- This phase 1 study examined the effect of multiple-dose SPAR on single-dose DAPA PK and assessed the safety and tolerability of single-dose DAPA when coadministered after multiple doses of SPAR in healthy adults

DAPA, dapagliflozin; PK, pharmacokinetics; SPAR, sparsentan.

1. Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(10):R877-R84. **2.** AstraZeneca Pharmaceuticals LP. FARXIGA® (dapagliflozin) tablets, for oral use [prescribing information]. Wilmington, DE July 2022. **3.** Boeckhaus J, Gross O. *Cells*. 2021;10(7):1815. **4.** Food and Drug Administration. 2022. https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-chronic-kidney-disease. **5.** Wheeler DC, et al. *Nephrol Dial Transplant*. 2022;37(9):1647-56.

METHODS

Study Design



- Period 1: Days 1-5
  - Single dose of 10 mg DAPA on Day 1
  - DAPA and dapagliflozin-3-O-glucuronide PK sampling before dosing and up to 96 hours after dosing
- Period 2: Days 5-14
  - SPAR 800 mg once daily for 10 days with single dose of 10 mg DAPA coadministered on Day 11
  - DAPA and dapagliflozin-3-O-glucuronide PK sampling before dosing and up to 96 hours after dosing on Day 11

*Subjects may be admitted earlier for COVID-19 procedures. DAPA, dapagliflozin; PK, pharmacokinetics; qd, once daily.

METHODS

- To avoid hypoglycemic events with DAPA, subjects received 240 mL of an oral 20% glucose solution in water with the DAPA dose and every ~15 minutes up to 4 hours after dosing
- Plasma concentrations and PK parameters of DAPA and dapagliflozin-3-O-glucuronide were summarized
- Subjects with evaluable data for both periods were included in an ANOVA mixed-model analysis of DAPA and dapagliflozin-3-O-glucuronide $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} following DAPA+SPAR vs DAPA alone
- TEAEs were summarized

$AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{0\text{-}t}$, ln-transformed area under the concentration-time curve from time zero to last observed nonzero concentration; ANOVA, analysis of variance; C_{max}, maximum observed concentration; TEAE, treatment-emergent adverse event.

RESULTS

- The study enrolled 22 adults, and 20 patients completed both treatment periods
- Geometric mean peak and extent of DAPA exposure (C_{max} and AUC) values were similar following 10 mg DAPA alone and 10 mg DAPA plus 800 mg SPAR (**Table 1**)
- Geometric mean peak and extent of dapagliflozin-3-O-glucuronide exposure (C_{max} and AUC) were 11%-14% lower following 10 mg DAPA plus 800 mg SPAR compared to 10 mg DAPA alone (**Table 2**)
- There were no deaths, SAEs, or unusual AEs during the study
- TEAEs were reported by 14 (63.6%) subjects
  - Most frequent were headache (6 [27.3%]) and nausea (5 [22.7%])
  - The majority of TEAEs were mild in severity

AE, adverse event; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{0\text{-}t}$, ln-transformed area under the concentration-time curve from time zero to last observed nonzero concentration; C_{max}, maximum observed concentration SAE, serious adverse event.

Table 1. Statistical Comparisons of Plasma DAPA PK Parameters Following DAPA+SPAR Versus DAPA Alone

	DAPA[a]	DAPA+SPAR[b]	GLSMR (%)[d]	90% CI	Intrasubject CV%[e]
	Geometric LSMs[c]	Geometric LSMs[c]			
AUC_{0-t} (ng*h/mL)	508.8	526.1	103.4	99.9-107.0	6.3
AUC_{0-inf} (ng*h/mL)[f]	533.7	565.4	105.9	103.1-108.9	4.4
C_{max} (ng/mL)	73.9	79.9	108.2	96.0-121.8	22.0

Per statistical analysis plan, only subjects with data for both DAPA+SPAR and DAPA were included in the statistical analysis. Subject 2 vomited within the 2 hours following DAPA dosing, and therefore, was excluded from the statistical analysis of both DAPA+SPAR and DAPA.

[a]A single oral dose of 10 mg DAPA (1×10 mg tablet) administered at Hour 0 on Day 1 of Period 1. [b]Multiple oral doses of 800 mg SPAR (2×400 mg tablets) administered once daily on Days 5-14 of Period 2, with a single oral dose of 10 mg DAPA (1×10 mg tablet) coadministered at Hour 0 on Day 11 of Period 2. [c]Geometric LSMs are calculated by exponentiating the LSMs from the ANOVA. [d]Geometric LSM ratio (%) = 100 × (test/reference). [e]Intrasubject CV% = 100 × square root(exp[MSE]-1), where MSE = residual variance from ANOVA. [f]n=16 for both treatment groups.

CV, coefficient of variation; GLSMR, geometric least-squares mean ratio; LSM, least-squares mean.

RESULTS

Table 2. Statistical Comparisons of Plasma Dapagliflozin-3-O-Glucuronide PK Parameters Following 10 mg DAPA Alone and 10 mg DAPA plus 800 mg SPAR

	DAPA[a]	DAPA+SPAR[b]	GLSMR (%)[d]	90% CI	Intrasubject CV%[e]
	Geometric LSMs[c]	Geometric LSMs[c]			
AUC_{0-t} (ng*h/mL)	706.7	623.9	88.3	85.1-91.6	6.7
AUC_{0-inf} (ng*h/mL)[f]	729.3	645.6	88.5	85.0-92.2	7.03
C_{max} (ng/mL)	109.4	94.5	86.3	76.8-97.1	21.7

Per statistical analysis plan, only subjects with data for both DAPA+SPAR and DAPA were included in the statistical analysis. Subject 2 vomited within the 2 hours following DAPA dosing, and therefore, was excluded from the statistical analysis of both DAPA+SPAR and DAPA.

[a]A single oral dose of 10 mg DAPA (1×10 mg tablet) administered at Hour 0 on Day 1 of Period 1. [b]Multiple oral doses of 800 mg SPAR (2×400 mg tablets) administered once daily on Days 5-14 of Period 2, with a single oral dose of 10 mg DAPA (1×10 mg tablet) coadministered at Hour 0 on Day 11 of Period 2. [c]Geometric LSMs are calculated by exponentiating the LSMs from the ANOVA. [d]Geometric LSM ratio (%) = 100 × (test/reference). [e]Intrasubject CV% = 100 × square root(exp[MSE]-1), where MSE = residual variance from ANOVA. [f]n=18 for both treatment groups.

CONCLUSIONS

- In healthy adults, SPAR coadministration did not affect DAPA PK, suggesting that dose adjustments may not be necessary. However, further research in patients with CKD is needed.
- Mean peak and extent of exposure values of DAPA were similar following administration of 10 mg DAPA alone and 10 mg DAPA plus 800 mg SPAR (differences of ~8% or less)
- The 90% CIs of DAPA + SPAR relative to DAPA GMRs for C_{max} and AUCs fell within the 80%-125% range
- DAPA is metabolized to dapagliflozin-3-O-glucuronide mediated by UGT1A9. The PK for dapagliflozin-3-O-glucuronide suggests that UGT1A9 was not affected by the SPAR treatment.
- Mean peak and extent of exposure values of dapagliflozin-3-O-glucuronide were approximately 11%-14% lower following administration of 10 mg DAPA plus 800 mg SPAR compared to 10 mg DAPA alone
- With the exception of the lower limit of C_{max}, the 90% CIs of GMRs fell entirely within the 80%-125% range
- Single-dose DAPA coadministered with multiple doses of SPAR appeared to be safe and well tolerated by healthy adults in this study

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