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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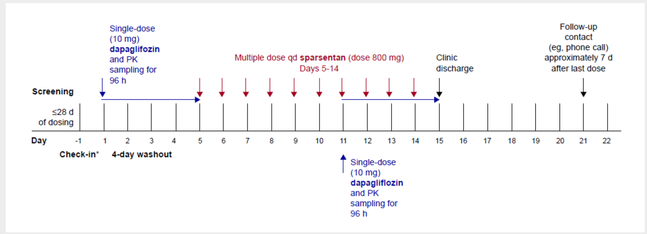
BACKGROUND

- Sparsentan (SPAR) is a first-in-class, novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA) under investigation for the treatment of immunoglobulin A nephropathy (IgAN) and focal segmental glomerulosclerosis (FSGS)[1]
- Sodium-glucose cotransporter 2 inhibitors (SGLT2is), such as dapagliflozin (DAPA), have recently been indicated for chronic kidney disease[2-4]
  - DAPA has been shown to attenuate estimated glomerular filtration rate (eGFR) for patients with FSGS when used concomitantly with renin-angiotensin-aldosterone system inhibitors[5]
  - DAPA has also been shown to improve outcomes for patients with IgAN treated concomitantly with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker[6]
- Therefore, it is important to determine any drug-drug interactions (DDIs) between SPAR and DAPA that may affect DAPA pharmacokinetics (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

METHODS

- This open-label DDI study included 2 periods (**Figure 1**)
  - 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

Figure 1. Study design



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

- 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 analysis of variance (ANOVA) mixed-model analysis of DAPA and dapagliflozin-3-O-glucuronide ln-transformed area under the concentration-time curve from time zero to last observed nonzero concentration (AUC_{0-t}), area under the concentration-time curve from time zero extrapolated to infinity (AUC_{0-inf}), and the maximum observed concentration (C_{max}) following DAPA+SPAR vs DAPA alone
- Treatment-emergent adverse events (TEAEs) were summarized

RESULTS

- The study enrolled 22 adults, and 20 patients completed both treatment periods
- Per the statistical analysis plan, only subjects with data for both dapagliflozin (DAPA) + sparsentan (SPAR) and DAPA were included in the statistical analysis
  - One subject vomited within the 2 hours following DAPA dosing and, therefore, was excluded from the statistical analysis of both DAPA+SPAR and DAPA
- 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 (differences of ~8% or less; **Table 1**)
  - The 90% confidence intervals (CIs) of DAPA + SPAR relative to DAPA geometric mean ratios (GMRs) for C_{max} and AUC fell entirely within the 80%-125% range

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] (n=20)	Geometric LSMs[c] (n=20)			
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

[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.
AUC_{0-inf}, area under the concentration-time curve from time zero extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time zero to last observed nonzero concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; DAPA, dapagliflozin; GLSMR, geometric least-squares mean ratio; LSMs, least-squares means; PK, pharmacokinetics; SPAR, sparsentan.

- 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**)
  - While the lower limit of the 90% CI for C_{max} was outside the 80%-125% range, all other 90% CIs fell within that range

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

[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.
AUC_{0-inf}, area under the concentration-time curve from time zero extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time zero to last observed nonzero concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; DAPA, dapagliflozin; GLSMR, geometric least-squares mean ratio; LSM, least-squares mean; PK, pharmacokinetics; SPAR, sparsentan.

- There were no deaths, serious adverse events, or unusual adverse events during the study
- TEAEs were reported by 14 (63.6%) subjects
  - Most frequent were headache (6 [27.3%]) and nausea (5 [22.7%])
  - Preprandial asymptomatic hypoglycemia (5 [22.7%]) was also experienced following SPAR alone
    - Treatment protocol difference: oral 20% glucose solution not provided with SPAR treatment, with ≥10-hour fasting
    - Subjects did not report symptoms; hypoglycemia was observed by blood glucose analysis (Day 5, Period 2)
  - The majority of TEAEs were mild in severity; none of the TEAEs were severe

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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Disclosures

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

References

1. Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016;310(10):R877-R84.
2. FARXIGA® (dapagliflozin) tablets, for oral use [prescribing information]. AstraZeneca Pharmaceuticals LP; 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.
6. Wheeler DC, et al. *Kidney Int.* 2021;100(1):215-24.

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