Poster #211

# A Creative Cocktail Drug-Drug Interaction Study to Evaluate the Effect of Sparsentan at Steady State on the PK of CYP & Transporter Substrates


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## BACKGROUND

- Sparsentan is a first-in-class, dual-acting antagonist of endothelin type A and angiotensin II subtype 1 receptors (“DEARA”), currently marketed in the US and Europe for the treatment of primary immunoglobulin A nephropathy
- *In vitro* studies indicated that sparsentan can both inhibit and induce CYP3A, but in a clinical DDI study sparsentan at steady state did not alter the PK of midazolam, a sensitive CYP3A substrate
- The potential of a single dose of sparsentan for direct CYP3A inhibition was assessed in this DDI study
- *In vitro* data also indicated that sparsentan can induce CYP2C9 and CYP2C19 and inhibit the transporters P-gp and BCRP.
- The potential of sparsentan to induce CYP2C9 and CYP2C19 and inhibit P-gp and BCRP at steady state was also evaluated in this cocktail DDI study

## METHODS

- Open-label, two-part DDI study utilized a two-treatment, fixed-sequence, cocktail dosing approach design for each part in healthy subjects.
- Part 1 (42 subjects): see Figure 1; Part 2 (32 subjects): see Figure 2
- Pre- and post-dose blood samples were collected for analysis of the plasma PK of midazolam (up to 24 hrs), tolbutamide (up to 48 hrs) and omeprazole (up to 12 hrs) and their metabolites as well as for digoxin (up to 144 hrs) and rosuvastatin (up to 96 hrs)
- Geometric LSMs were calculated for AUC0-t, AUC0-inv and Cmax, and treatment GMRs of LSMs with 90% CIs were assessed
- A 90% CI outside the 80–125% range was considered an interaction

Figure 1. Schematic of Part 1 Design

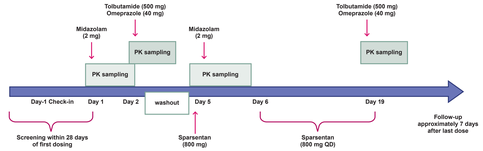
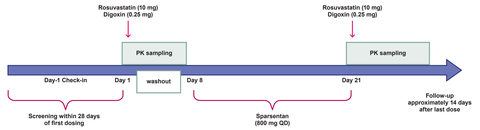



Figure 2. Schematic of Part 2 Design




## RESULTS

- PK versus time profiles of individual substrates are depicted in Figures 3-7
- A statistical comparison of plasma PK is shown in Table 1
- After a single dose of sparsentan:
  - Midazolam AUC0-t and Cmax were approximately 66% and 36% higher, respectively
  - 1-OH-midazolam MRs were decreased
- At steady state sparsentan:
  - AUCs of tolbutamide and omeprazole were decreased by approximately 25% and 61% and their Cmax by 9% and 49%, respectively
  - AUC0-t, AUC0-inf and Cmax of digoxin were increased by 34%, 18% and 61%, respectively
  - Rosuvastatin Cmax was increased by 64%, but AUCs were unaffected
  - 4-OH-tolbutamide MRs were increased
  - 5-OH-omeprazole MRs were increased
- A summary of metabolite PK is shown in Table 2

Figure 3. Midazolam (CYP3A substrate)

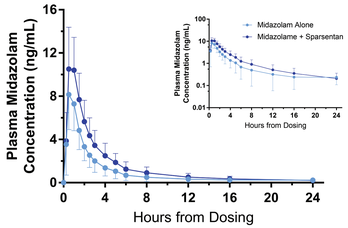



Figure 4. Tolbutamide (CYP2C9 substrate)

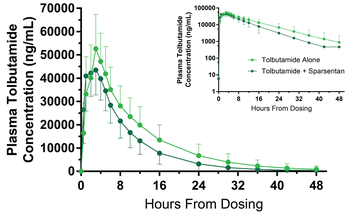



Figure 5. Omeprazole (CYP2C19 substrate)

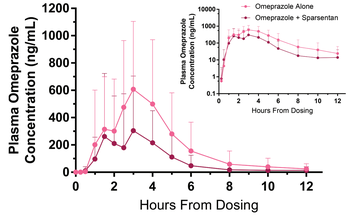



Figure 6. Digoxin (P-gp substrate)

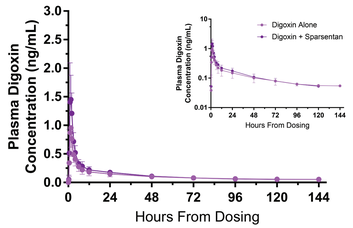
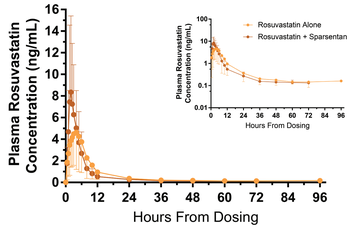



Figure 7. Rosuvastatin (BCRP substrate)




### Drug Probes:

- CYP3A: Midazolam
- CYP2C9: Tolbutamide
- CYP2C19: Omeprazole
- P-gp: Digoxin
- BCRP: Rosuvastatin

### Abbreviations:

- AUC0-inf: Area under the concentration-time curve from time 0 to infinity
- AUC0-t: Area under the concentration-time curve from time 0 to last measurable concentration
- BCRP: Breast cancer resistance protein
- CI: Confidence interval
- Cmax: Maximum concentration
- CYP: Cytochrome P450
- DDI: Drug-drug interaction
- GMR: Geometric mean ratio
- LSM: Least squares mean
- MR: Metabolite-to-parent ratio
- P-gp: P-glycoprotein
- PK: Pharmacokinetics
- QD: Once daily
- Stddev: Standard deviation

Table 1: Substrate PK parameters

| Substrate | Geometric LSM AUC0-t values (ng*hr/mL) | | GMR (%) (90% CI) | Geometric LSM AUC0-inf values (ng*hr/mL) | | GMR (%) (90% CI) | Geometric LSM Cmax (ng/mL) | | GMR (%) (90% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | Substrate alone | Substrate + sparsentan | | Substrate alone | Substrate + sparsentan | | Substrate alone | Substrate + sparsentan | |
| Midazolam | 19.50 | 32.31 | 165.68 (153.39 - 178.95) * | 20.69 | 33.85 | 163.59 (151.64 - 176.49) * | 8.211 | 11.20 | 136.46 (126.46 - 147.25) * |
| Tolbutamide | 570000 | 429100 | 75.29 (70.23 - 80.70) * | 578100 | 431000 | 74.56 (69.53 - 79.94) * | 55390 | 50610 | 91.38 (84.31 - 99.03) * |
| Omeprazole | 1730 | 673.8 | 38.96 (35.09 - 43.26) * | 1744 | 696.1 | 39.91 (35.78 - 44.51) * | 770.5 | 390.6 | 50.69 (43.00 - 59.77) * |
| Digoxin | 10.45 | 13.96 | 133.55 (118.69 - 150.26) * | 14.81 | 17.43 | 117.70 (107.77 - 128.54) * | 0.999 | 1.606 | 160.73 (142.42 - 181.40) * |
| Rosuvastatin | 41.31 | 38.22 | 92.51 (83.72 - 102.22) | 45.11 | 41.74 | 92.53 (83.94 - 101.99) | 4.345 | 7.144 | 164.44 (141.38 - 191.26) * |

*Outside the 80-120% range*

Table 2: Metabolite PK parameters

| Metabolite | Mean AUC0-t (Stddev) (ng*hr/mL) | | Mean AUC0-inf (Stddev) (ng*hr/mL) | | Mean Cmax (Stddev) (ng/mL) | | Mean t½ (Stddev) (hr) | | MR AUC0 inf (Stddev) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Substrate alone | Substrate + Sparsentan | Substrate alone | Substrate + Sparsentan | Substrate alone | Substrate + Sparsentan | Substrate alone | Substrate + Sparsentan | Substrate alone | Substrate + Sparsentan |
| 1-OH-midazolam | 8.045 (31.1) | 9.204 (32.1) | 8.818 (32.5) | 10.17 (35.1) | 0.504 (0.50, 1.02) | 0.998 (0.50, 1.50) | 4.384 (2.5453) | 6.705 (4.8081) | 0.4463 (0.18528) | 0.3203 (0.13824) |
| 4-OH-tolbutamide | 7893 (35.3) | 7987 (26.2) | 8770 (30.7) | 8757 (23.2) | 3.018 (1.01, 6.02) | 3.000 (0.99, 6.00) | 7.671 (2.4085) | 6.107 (1.8900) | 0.01520 (0.0050324) | 0.02042 (0.0069306) |
| 5-OH-omeprazole | 1061 (26.4) | 702.0 (24.1) | 1077 (25.8) | 705.5 (23.7) | 3.002 (1.00, 5.07) | 2.998 (1.00, 5.04) | 1.577 (0.5025) | 1.256 (0.2567) | 0.7642 (0.49498) | 1.143 (0.69165) |

## CONCLUSION

- The cocktail design approach in this DDI study allowed for the simultaneous evaluation of multiple drug interactions, improving efficiency and minimizing the number of subjects required
- Overall results demonstrate that sparsentan (single dose) is a weak inhibitor of CYP3A4
- At steady state, sparsentan is a weak inducer of CYP2C9, a moderate inducer of CYP2C19 and a weak inhibitor of P-gp
- Sparsentan is not likely to affect overall exposure to BCRP substrates

TRAVERE THERAPEUTICS