

A Cocktail Drug-Drug Interaction Study to Evaluate the Effect of Single and Chronic Sparsentan Dosing on the PK of CYP and Transporter Substrates



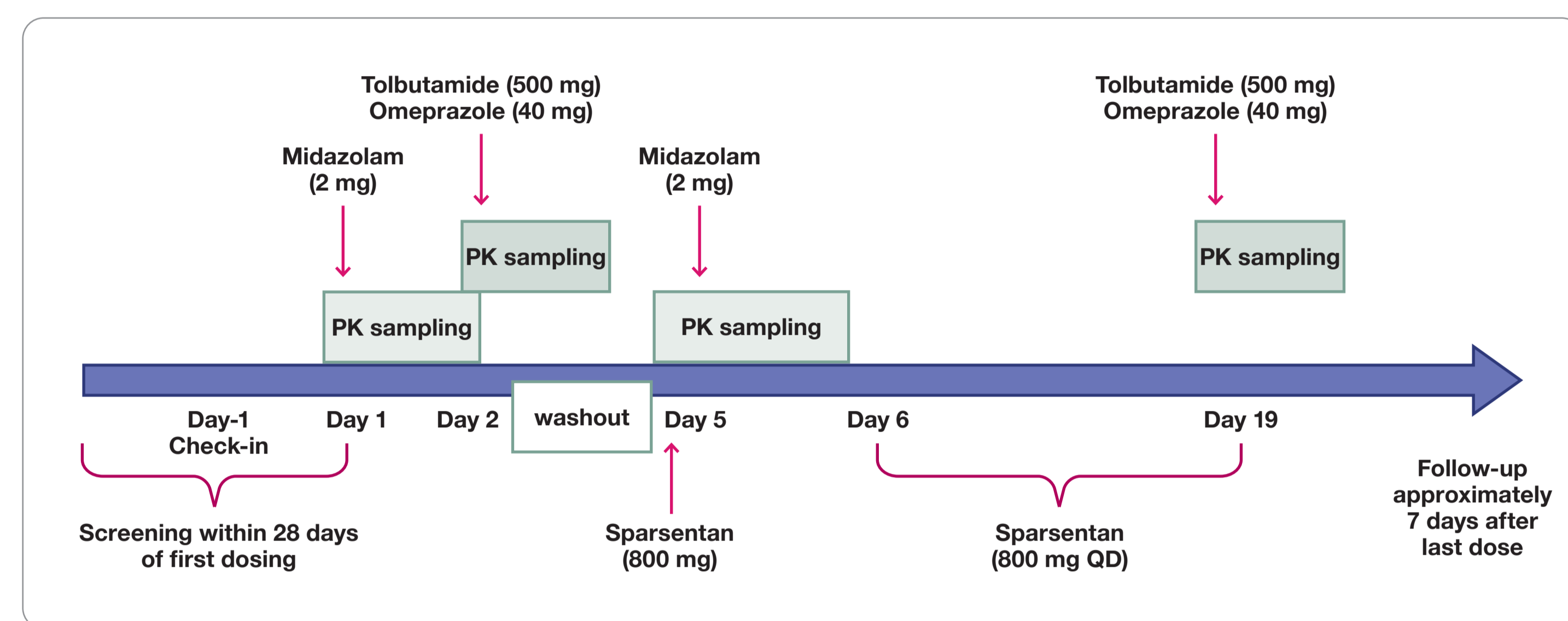
Aernout van Haarst, PhD
Senior Director, Scientific Affairs
aernout.vanhaarst@celerion.com

Aernout D. van Haarst¹, Kristina Z. Denic², Samer Haddad¹, Niamh Dean¹, Colin W.H. Cheng¹, David Balderson², Suresh Katragadda²
¹Celerion, ²Traverse Therapeutics, Inc.

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 SD 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

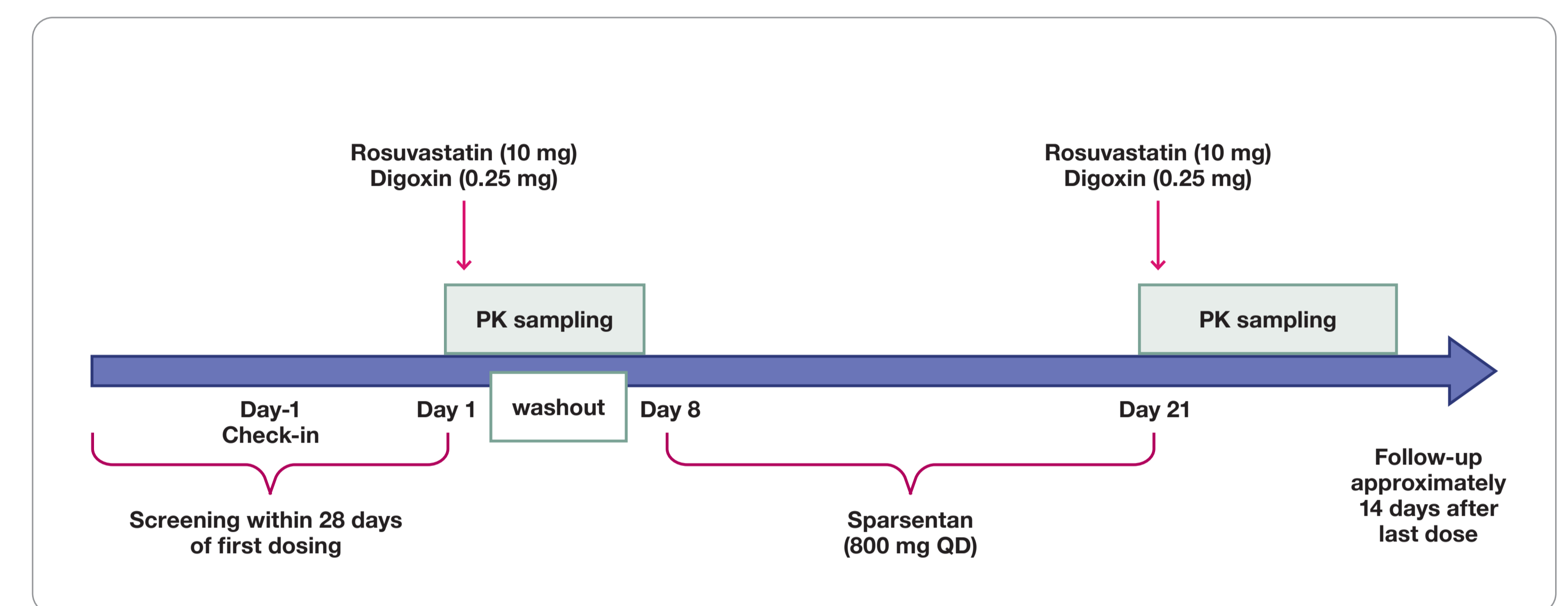
Figure 1. Schematic of Part 1 Design



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 AUC_{0-t}, AUC_{0-inf} and C_{max}. The LSM for C_{max} and AUCs, along with treatment LSM ratios and their 90% CIs, were assessed
- A 90% CI outside the 80–125% range was considered an interaction

Figure 2. Schematic of Part 2 Design



Drug Probes:

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

RESULTS

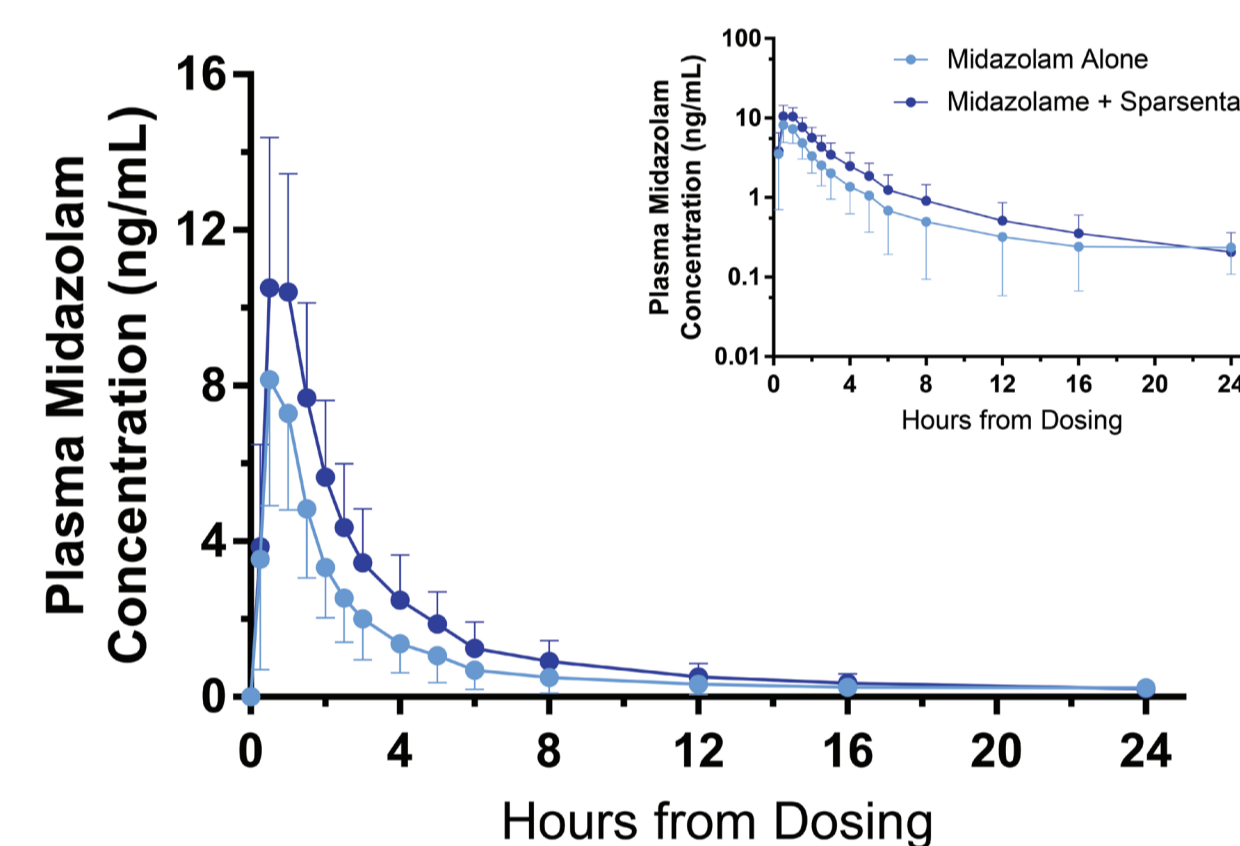


Figure 3. Midazolam (CYP3A substrate)

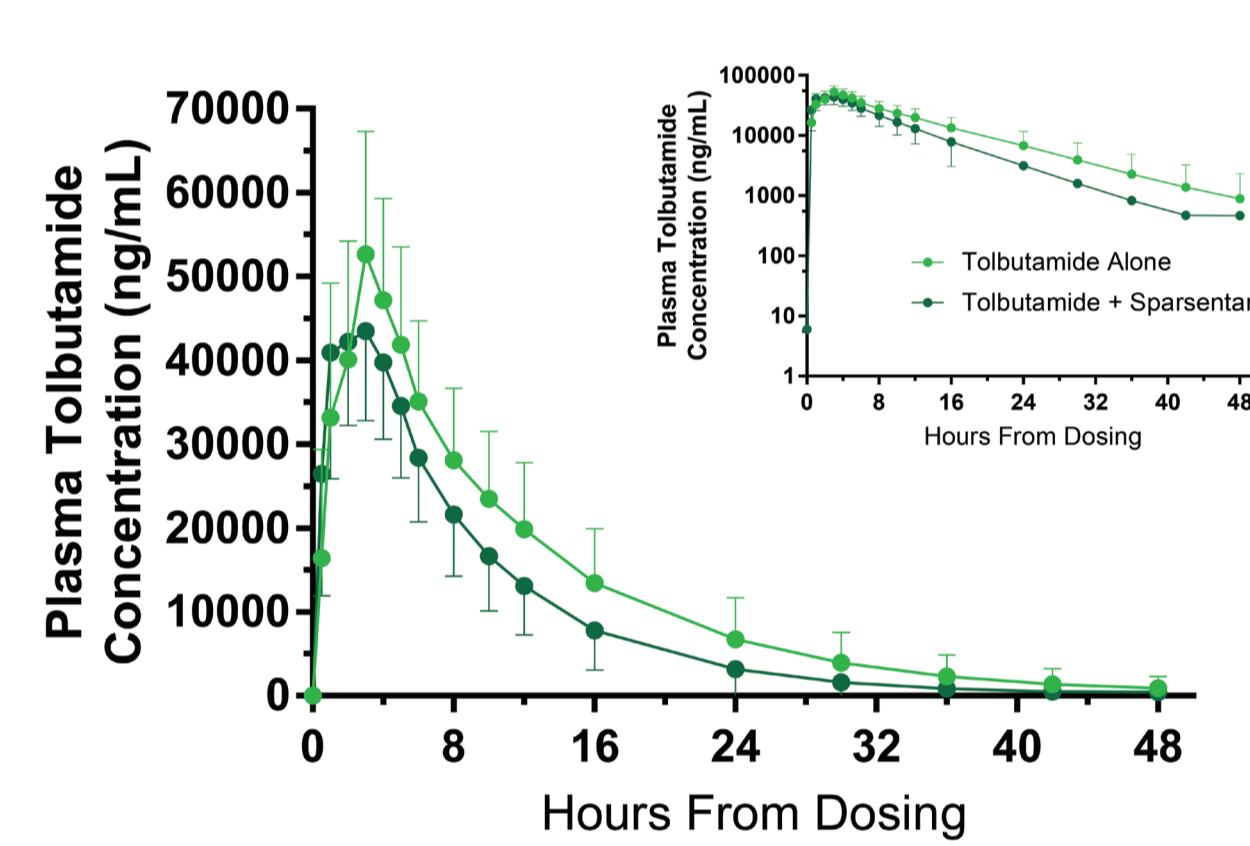


Figure 4. Tolbutamide (CYP2C9 substrate)

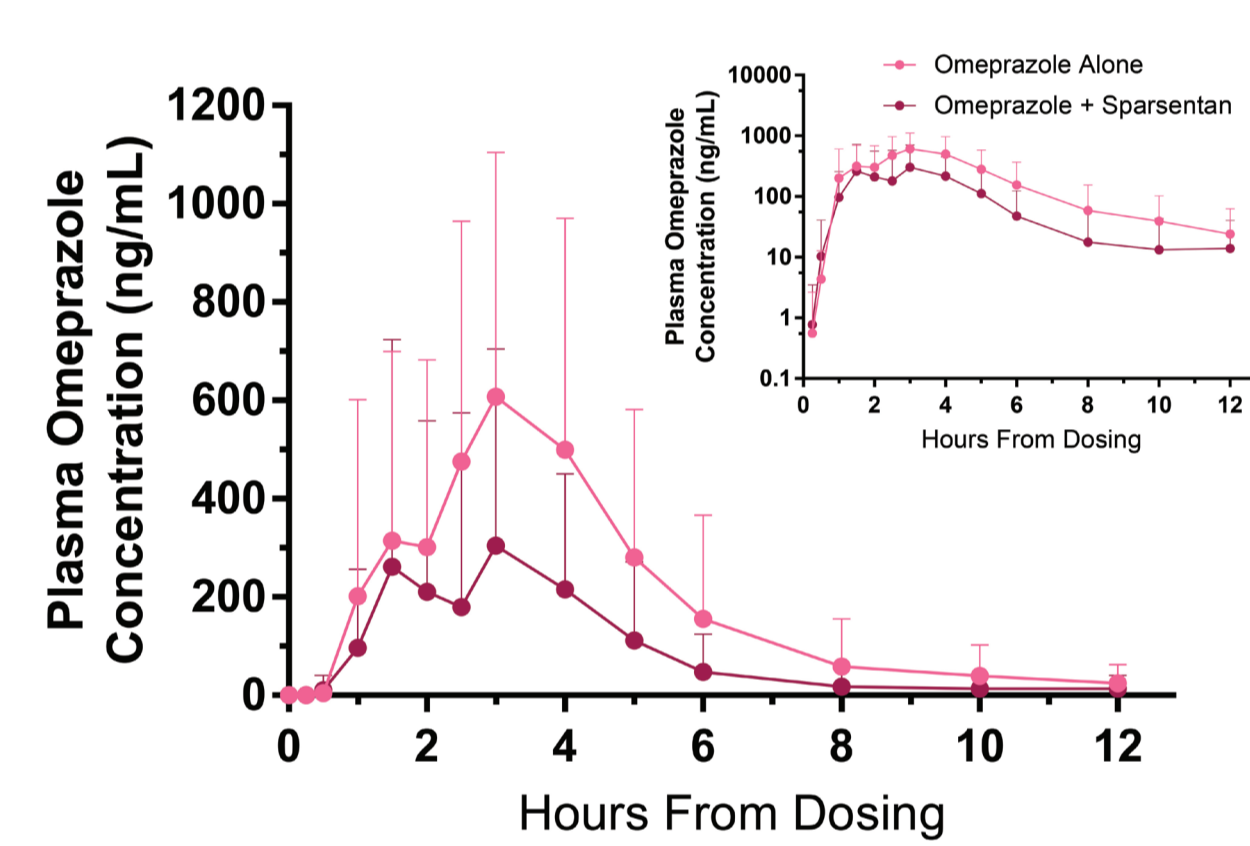


Figure 5. Omeprazole (CYP2C19 substrate)

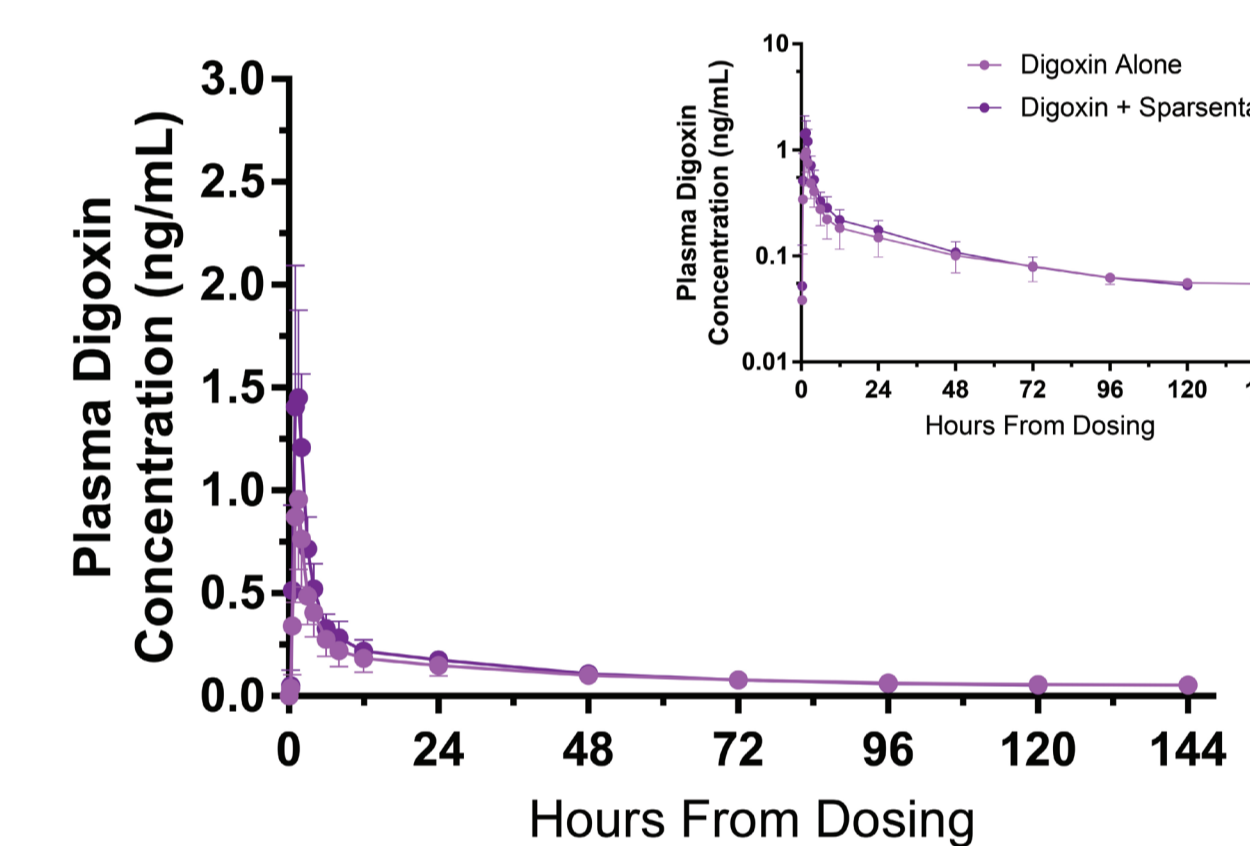


Figure 6. Digoxin (P-gp substrate)

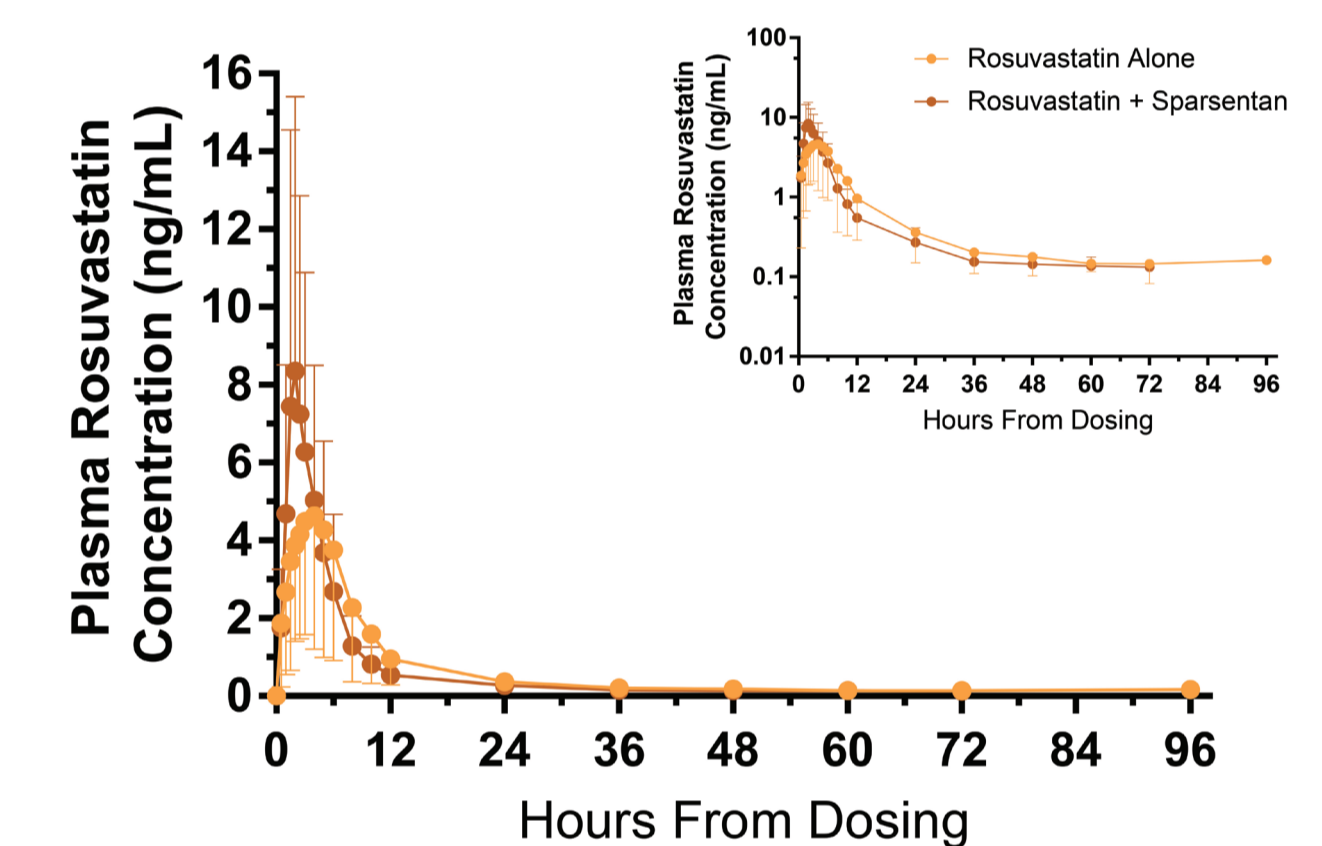


Figure 7. Rosuvastatin (BCRP substrate)

Table 1: Summary of statistical comparison of plasma PK parameters for specific substrate + sparsentan and substrate alone

Substrate	Geometric LSM AUC _{0-t} values (ng*hr/mL)		GMR (%) (90% CI)	Geometric LSM AUC _{0-inf} values (ng*hr/mL)		GMR (%) (90% CI)	Geometric LSM C _{max} (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

- PK versus time profiles of individual substrates are, with and without coadministration of sparsentan, depicted in Figures 3–7 (Arithmetic mean & Stddev)
- A statistical comparison of plasma PK is shown in Table 1
- After a SD of sparsentan:
 - Midazolam AUC_{0-t} and C_{max} 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 C_{max} by 9% and 49%, respectively
 - AUC_{0-t}, AUC_{0-inf} and C_{max} of digoxin were increased by 34%, 18% and 61%, respectively.
 - Rosuvastatin C_{max} 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

Abbreviations:

- AUC_{0-inf}: Area under the concentration-time curve from time 0 to infinity
- AUC_{0-t}: Area under the concentration-time curve from time 0 to last measurable concentration
- BCRP: Breast cancer resistance protein
- CI: Confidence interval
- C_{max}: 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
- SD: Single dose
- Stddev: Standard deviation

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 SD sparsentan 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

Table 2: Summary of plasma PK parameters for substrate metabolites alone or with sparsentan

Metabolite	Mean AUC _{0-t} (Stddev)		Mean AUC _{0-inf} (Stddev) (ng*hr/mL)		Mean C _{max} (Stddev) (ng/mL)		Mean t _{1/2} (Stddev) (hr)		MR AUC _{0-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)	6.107 (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)

