



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

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

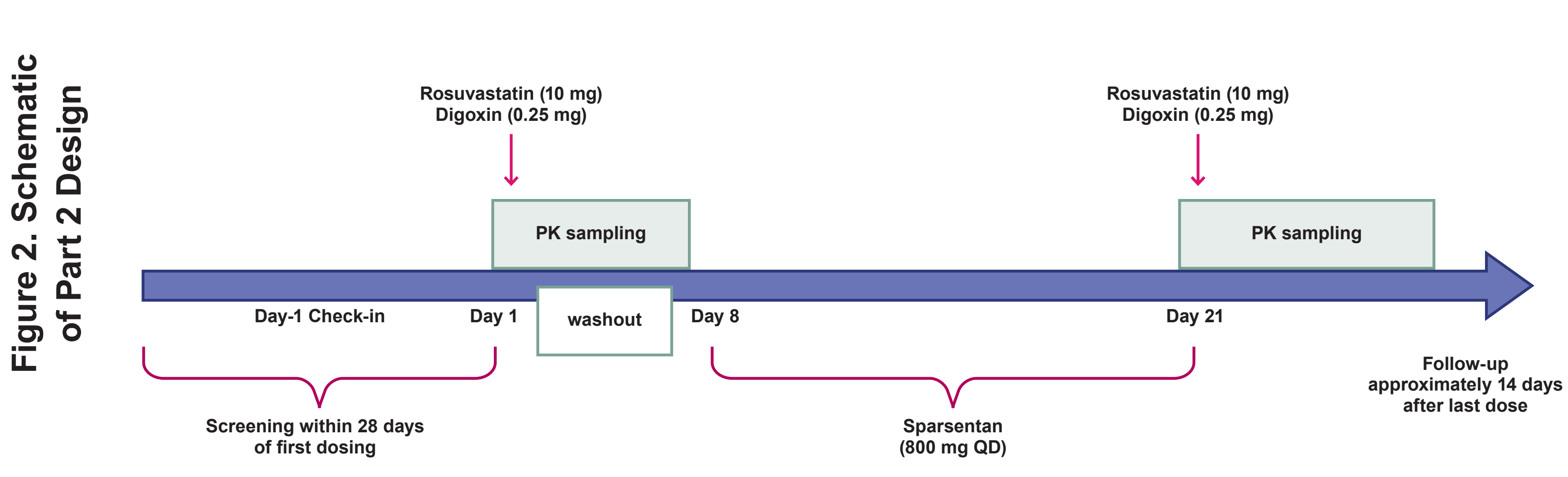
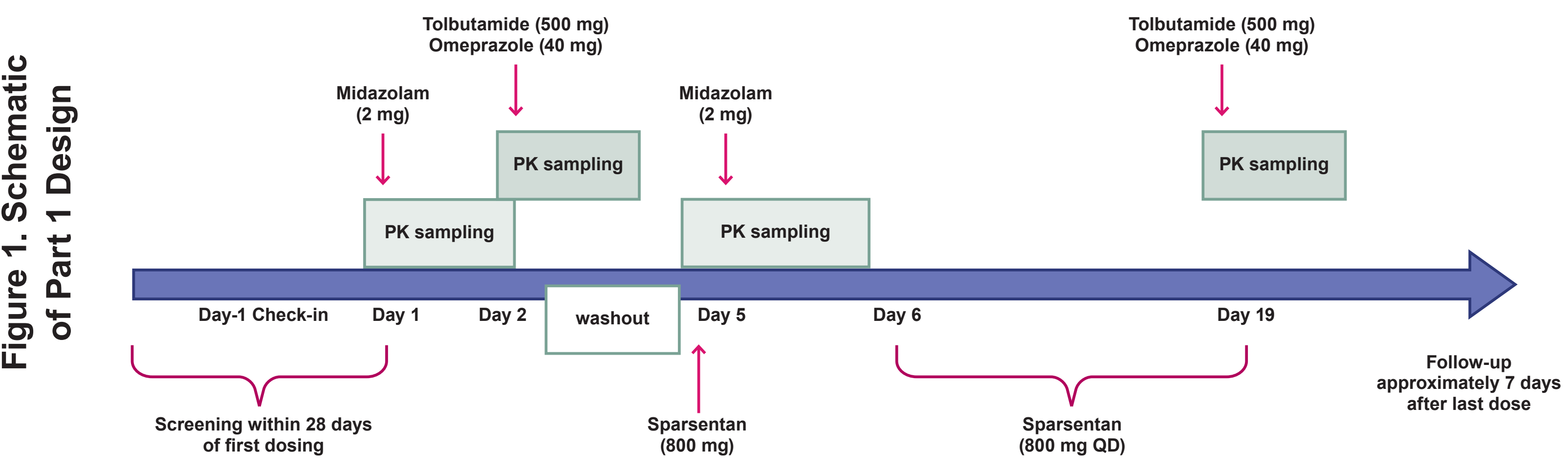


BACKGROUND

- 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 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

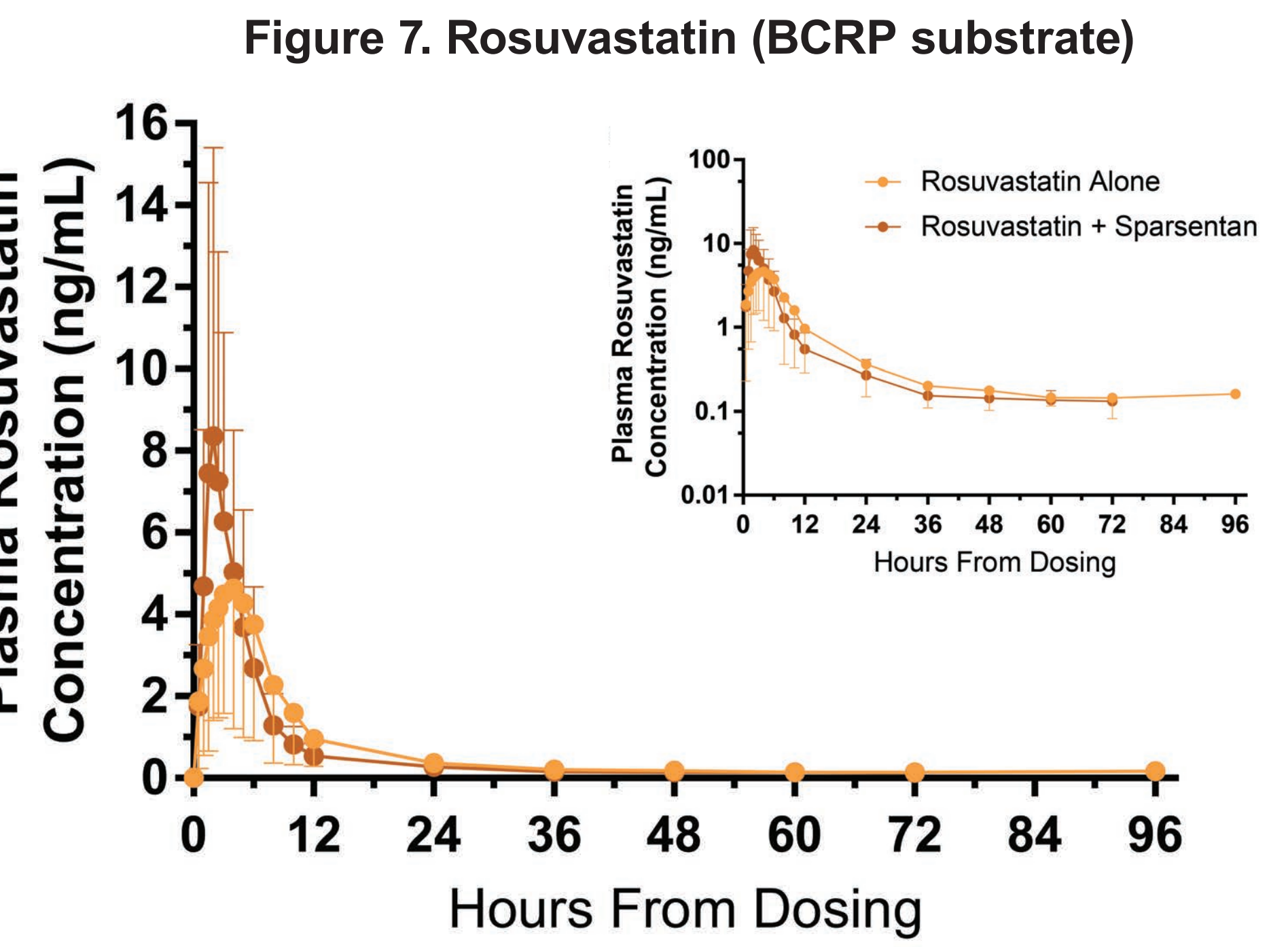
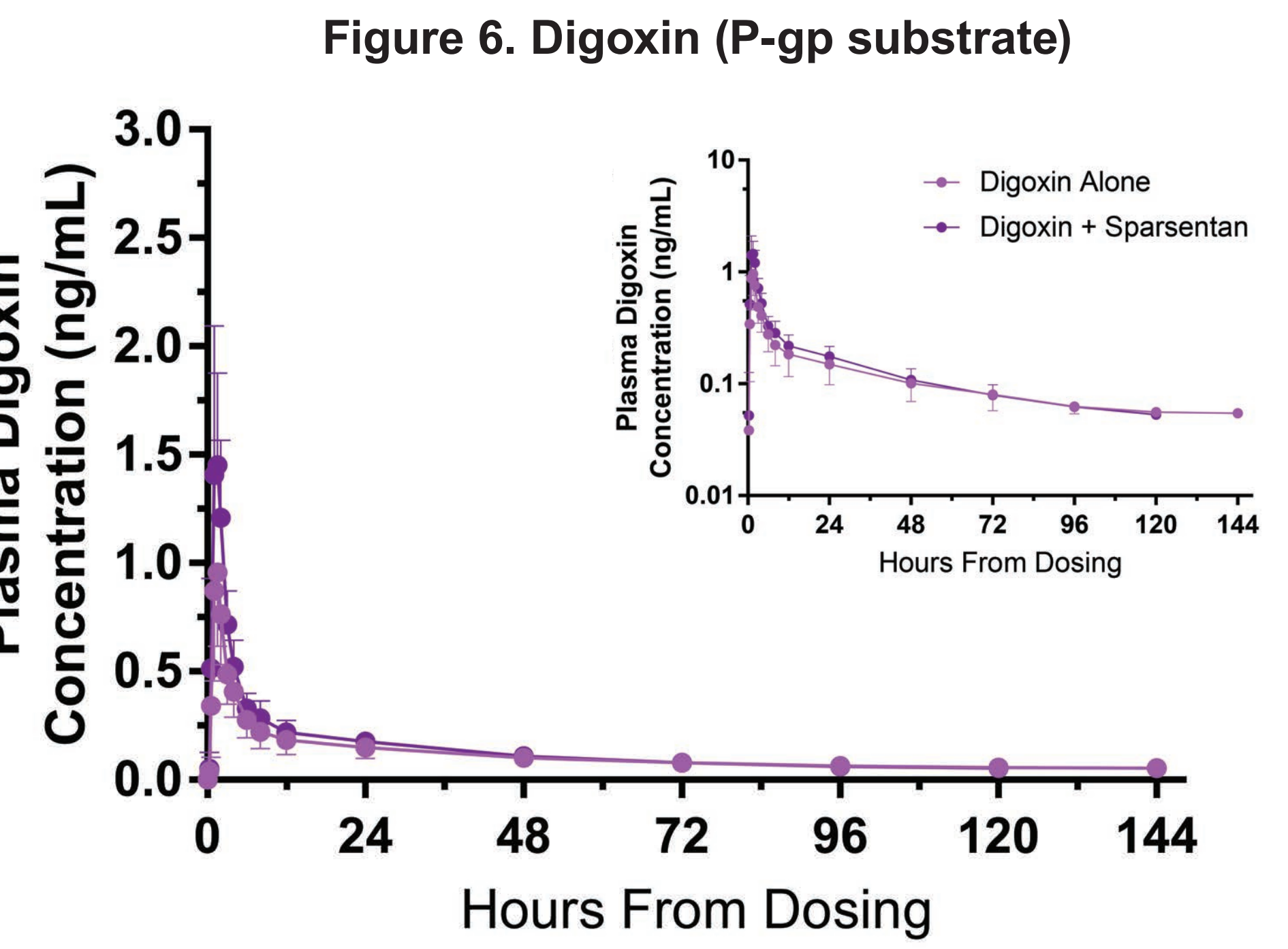
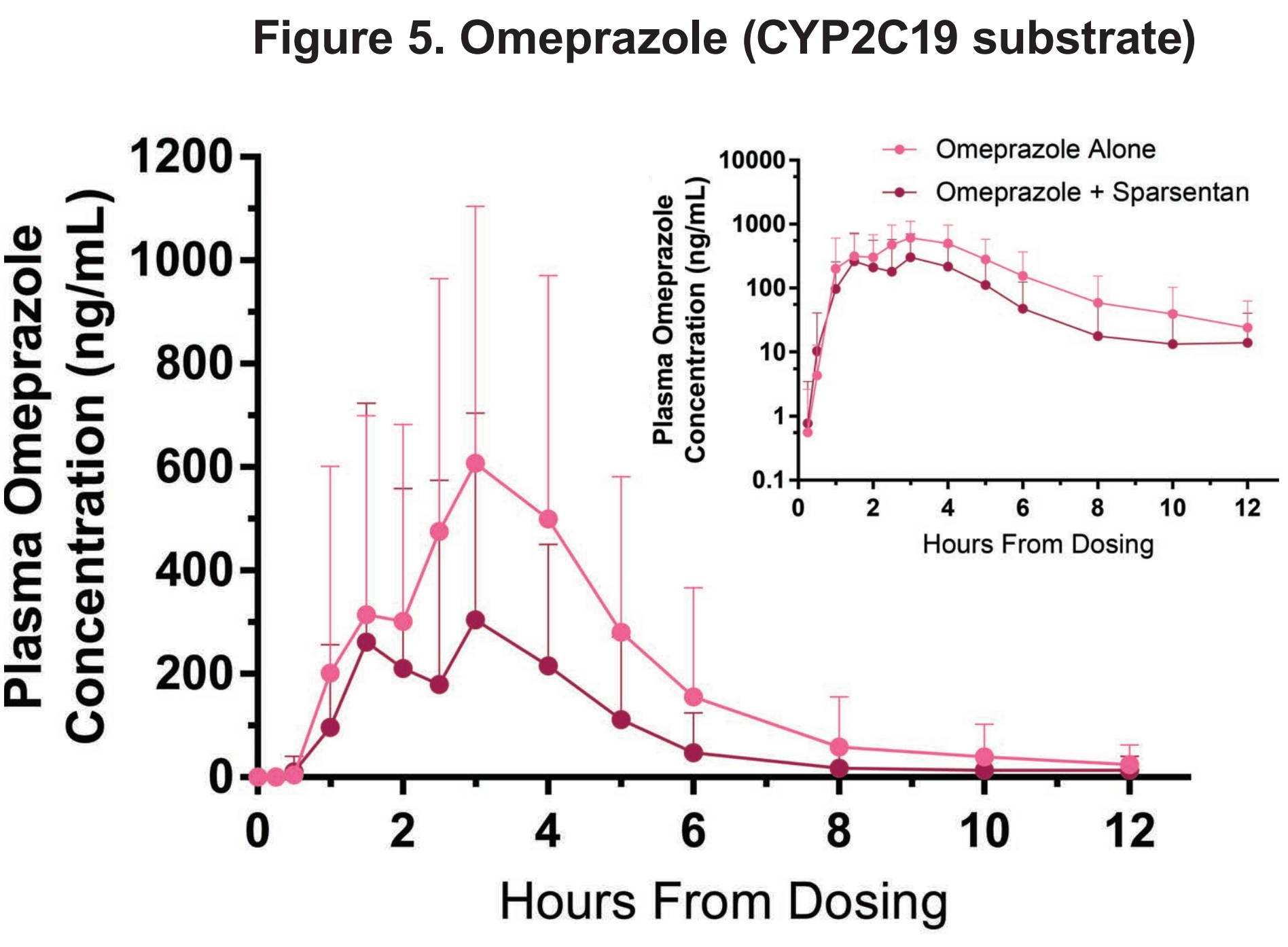
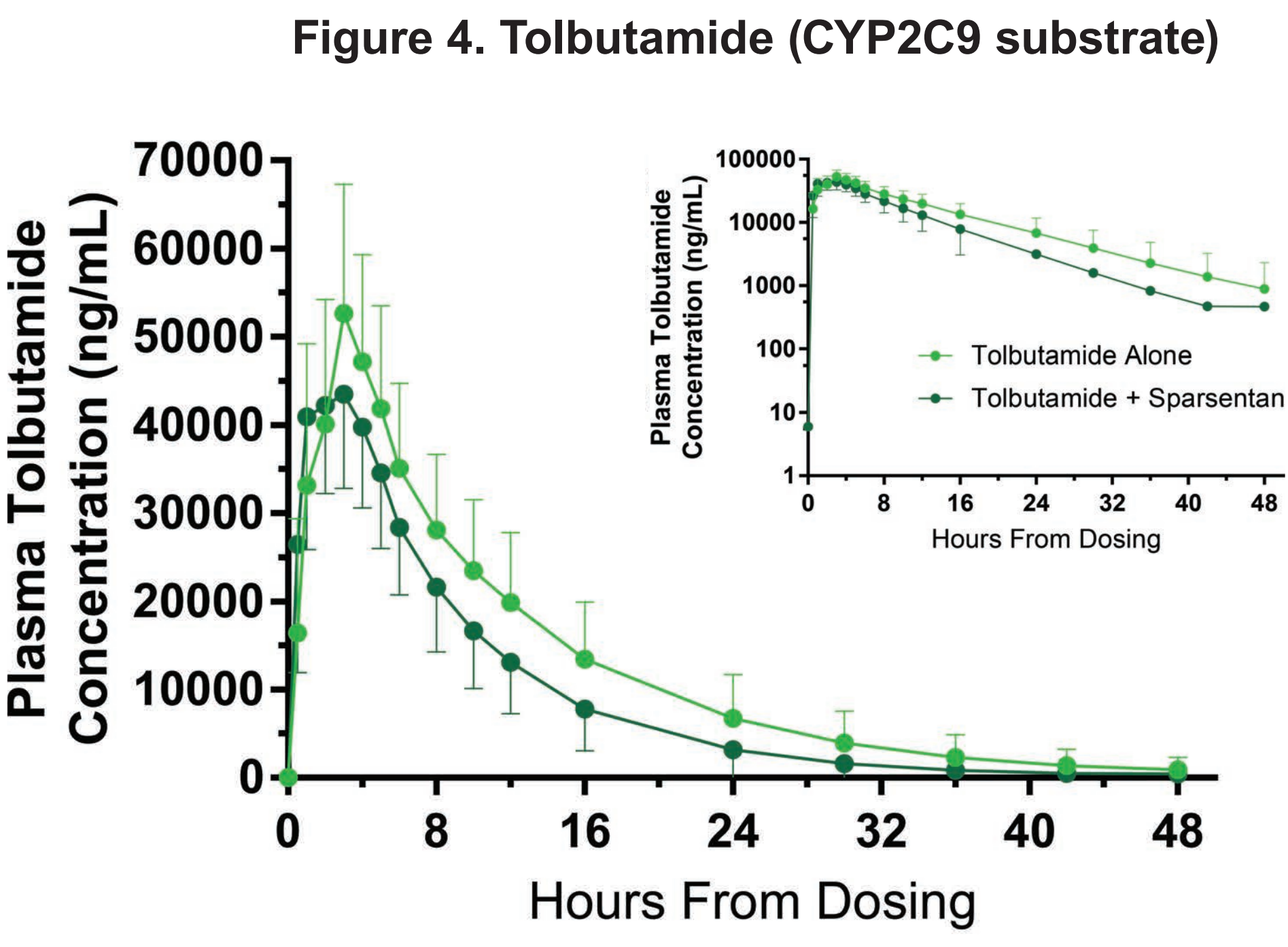
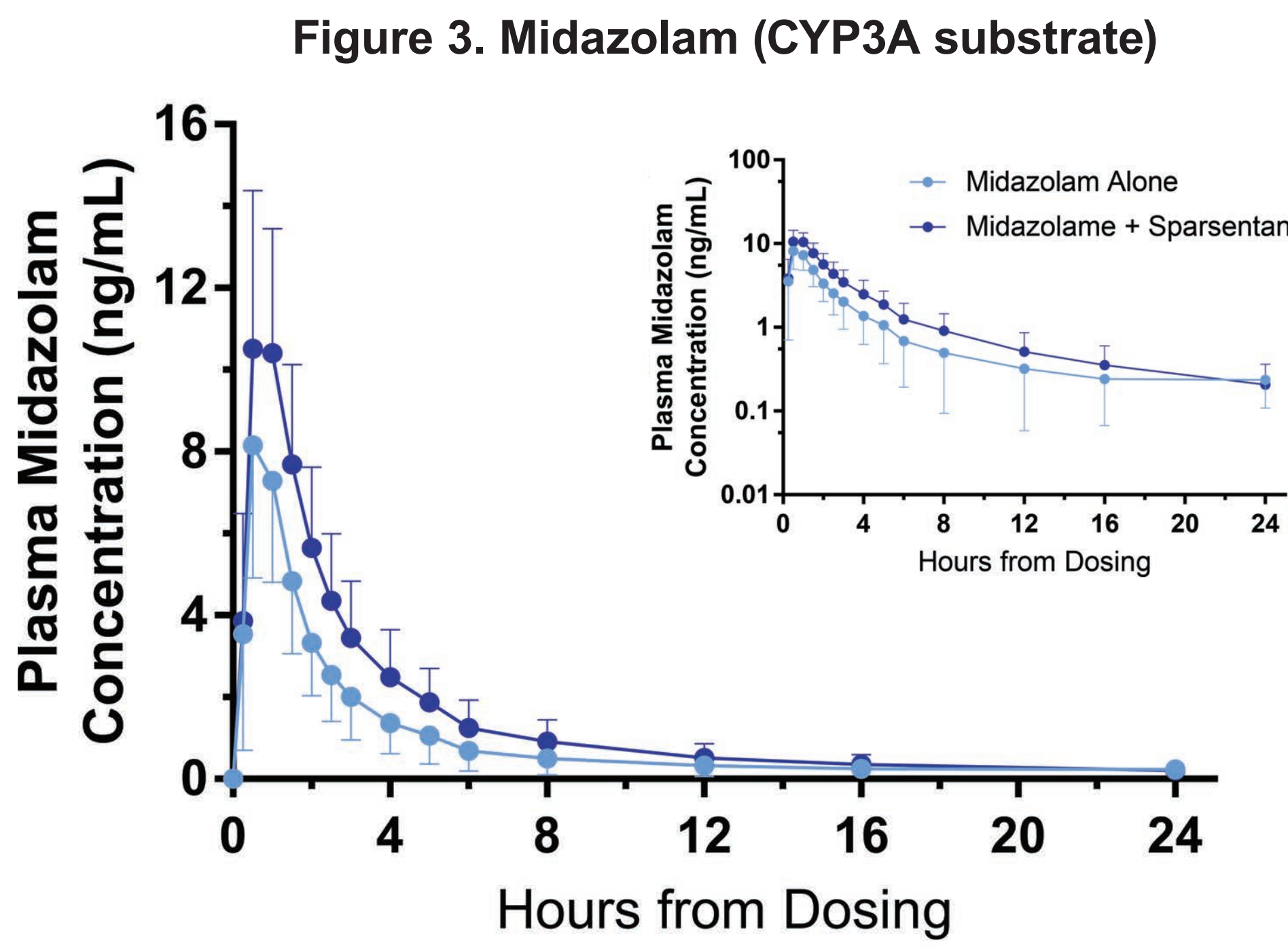
METHODS

- 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-inf and Cmax, and treatment GMRs of LSMs with 90% CIs were assessed
- A 90% CI outside the 80–125% range was considered an interaction



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



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 t1/2 (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

