

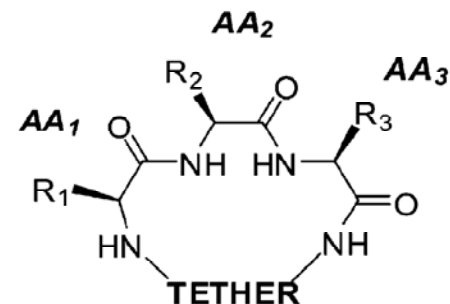
TZP-201: A potent *h*MOT-r antagonist

□ Based on Macrocyclic Template Chemistry (MaTCh™)

- MW 587.1 g/mol

□ Pharmacodynamics

- Receptor binding (*h*MOT-r): $K_i = 1.2$ nM
- Cell-based signaling (*h*MOT-r): $IC_{50} = 0.12$
- Rabbit antral strips: $pA_2 = 8.35$ nM



□ PK/ADME Profile

- Plasma half-life ($t_{1/2}$) = 24 min (rat), Cl 45 mL/min/kg, F 16%
- CYP inhibition (IC_{50})
 - 1A2, 2A6, 2B6, 2C8, 2C19, 2E1: > 100 μ M
 - 2C9: 63.4 μ M
 - 3A4 (BFC): 12.6 μ M

□ Well tolerated in rats up to 400 mg/kg p.o.

TZP-201: Potential Target Indications

- ❑ Gastrointestinal hypermotility disorders
 - Irritable Bowel Syndrome, diarrhea type (IBS-D)
 - Stress induced diarrhea
 - GvHD induced diarrhea
 - Bacterial diarrhea diseases
 - Radiation/radiotherapy induced diarrhea
 - Chemotherapy induced diarrhea (CID)
- ❑ Short Bowel Syndrome (SBS)
- ❑ Functional dyspepsia

Simrén *et al. Neurogastroenter. Motil.* **2005**, *17*, 51-57

Kamerling *et al. Dig. Dis. Sci.* **2002**, *47*, 1732-1736

TZP-201: CID as PoC Indication

- ❑ High-hurdle indication for PoC
 - Clearly defined clinical endpoint
 - Easy to achieve
- ❑ High medical need – Commercial viability
 - Frequent event upon cytotoxic chemotherapy
 - >60,000 Patients affected annually worldwide
 - 5-FU, irinotecan, epothilones, and combinations
 - Particularly in colorectal cancer
- ❑ Limited treatment/management options
 - Loperamide for low-grade diarrhea
 - Octreotide for severe diarrhea
- ❑ Mainly secretory type diarrhea

For a review, see Yang *et al. Curr. Med. Chem.* **2005**, *12*, 1343-1358

Intestinal secretagogue activity described for 13-norleucin motilin by Kachel *et al. Gastroenterology* **1984**, *87*(3) 550-556

TZP-201: Dog CID Study Design

Group and Designation	Treatment					
	Irinotecan			TZP-201		
	Dose (mg/kg/day)	Days	Route	Dose (mg/kg/day)	Days	Route
1 (Positive Control)	4 4 (8) 6	1-5 15-18 (19) 25-29	IV infusion IV infusion IV bolus	0	0	0
2 (TZP-201 LD)	6 6	1-5 15-19	IV bolus	5 (2x2.5)	4-28	IV infusion (45 min)
3 (TZP-201 HD)	6 6	1-5 15-19	IV bolus	15 (2x7.5)	4-28	IV infusion (45 min)
4 (TZP-201 PT-LD)	6	5-9	IV bolus	5 (2x2.5)	1-18	IV infusion (45 min)
5 (Vehicle Control)	0	1-5	IV bolus	0	0	IV infusion (45 min)
6 (Octreotide)	6	1-5	IV bolus	0.021 (3x0.007)	4-29	Subcutaneous
7 (Loperamide)	6 6	1-5 23-25	IV bolus	0.18 (3x0.06)	4-29	Oral

TZP-201: Dog CID Model Results

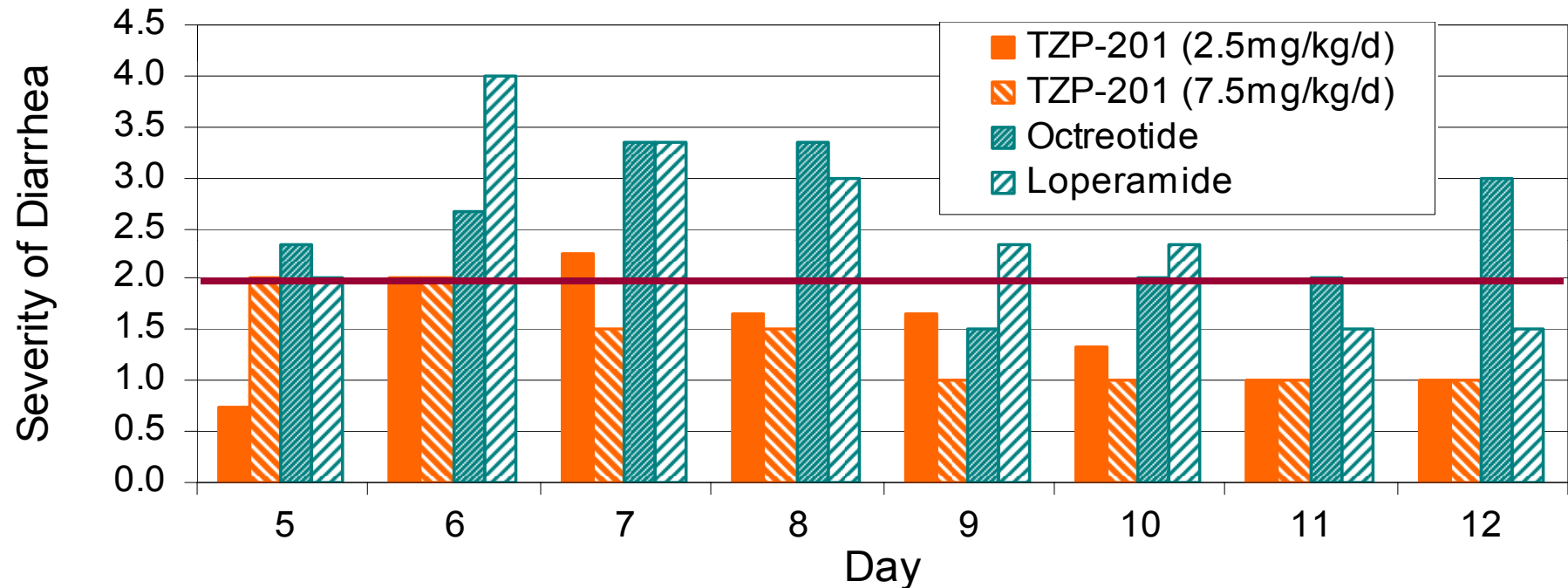
Model outline and 2-cycle diarrhea data

Animal ID	Treatment/ Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28	Day 29			
		Irionotecan Treatment													Irionotecan Treatment (Groups 2, 3)																		
2001B		1	1	3	0	0	0	2	2	1	1	1	1	1	2	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
2002B	TZP-201	1	1	2	2	2	3	2	2	2	2	1	1	1	1	1	2	3	1	2	2	2	1	2	2	2	2	2	1				
2003B	(2x2.5	1	1	1	2	1	1	1	1	2	1	1	1	1	1	1	1	1	0	3	2	3	3	1	2	1	1	1	1				
2004I	mg/kg/d)	1	1	1	4	0	4	4	Animal †																								
3001C	TZP-201	1	1	1	3	4	4	Animal †																									
3002C	(2x7.5	2	3	2	2	1	1	1	1	1	1	1	1	1	2	1	2	2	1	2	1	1	1	1	1	1	1	1	1	1			
3003C	mg/kg/d)	1	1	1	1	1	1	2	2	1	1	1	1	1	1	1	0	2	2	1	1	1	1	1	1	1	1	1	1	1			
6001F	Octreotide	2	1	1	1	3	3	3	3	1	2	2	4	1	2	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1			
6002F	(3x0.07	1	1	1	4	3	4	4	4	Animal †																							
6003F	mg/kg/d)	1	1	1	2	1	1	3	3	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
7001G	loperamid	1	2	1	1	4	4	4	4	4	4	Animal †																					
7002G	e (3x0.06	1	1	1	4	1	4	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	1	1				
7003G	mg/kg/d)	1	1	1	1	1	4	4	4	2	2	2	2	2	2	1	1	1	2	1	1	1	1	1	1	3	1	3	3				

↑ Start of treatment with TZP-201, octreotide or loperamide

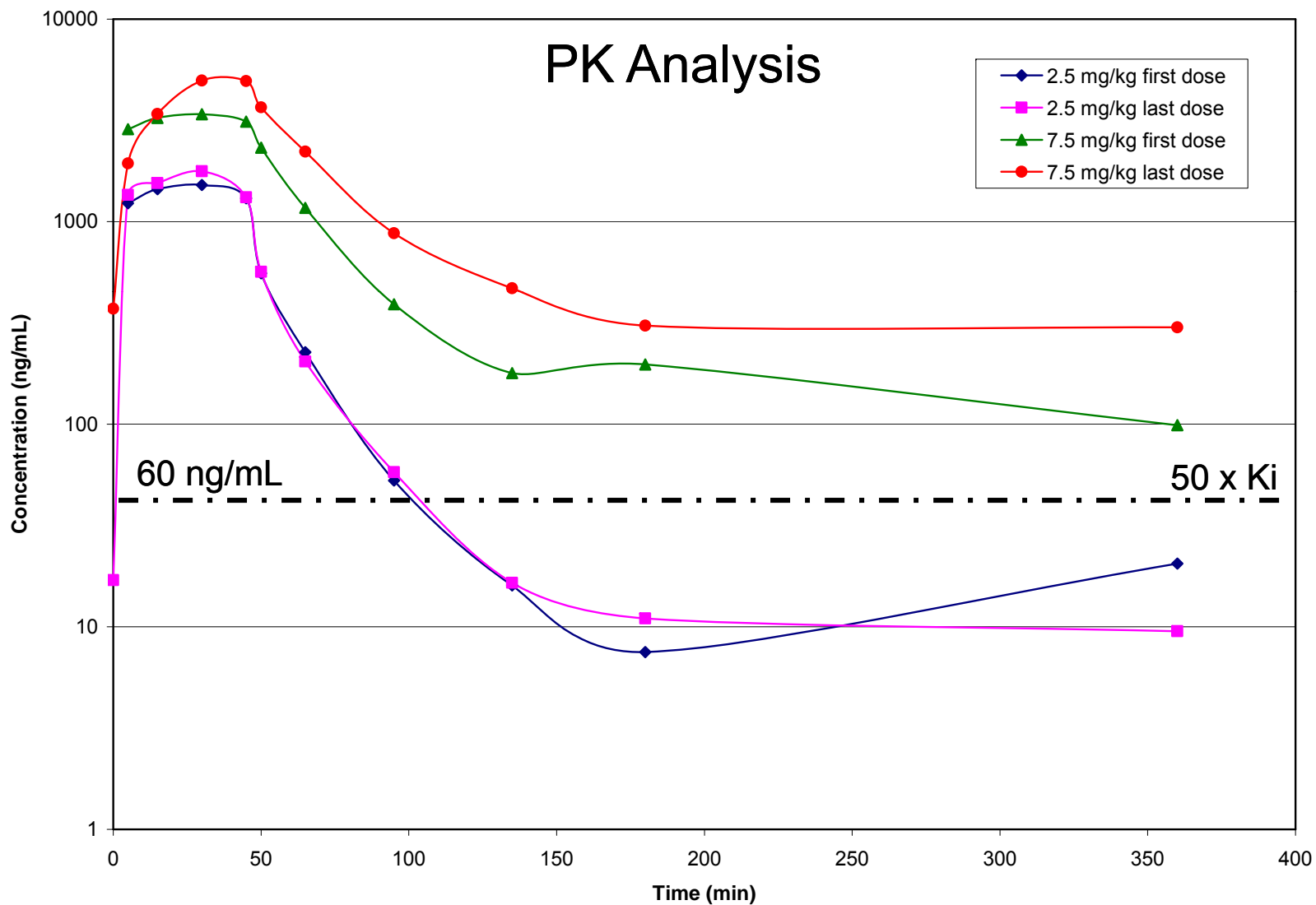
- 0 No feces
- 1 Normal feces
- 2 Soft feces
- 3 Diarrhea
- 4 Severe diarrhea containing blood

TZP-201: Dog CID Model Results



- ❑ Severity scale: 1- normal, 2- soft stool, 3- diarrhea, 4- severe, bloody diarrhea
- ❑ Irinotecan treatment for 5 days; TZP-201 drug treatment begins day 4
- ❑ All animals alive on the day of scoring are included in the score
- ❑ No significant histopathological differences across groups

TZP-201: Dog CID Model Results



TZP-201: Conclusions

TZP-201 is a potent and selective motilin antagonist that

- ❑ Shows superior efficacy in the treatment of irinotecan induced CID in dogs vs standard of care
 - More effective
 - Quicker onset and longer duration of action
 - Likely through anti-secretory and anti-motility activity in the lower GI tract
- ❑ Appears to be an attractive drug candidate for the treatment of CID in cancer patients
- ❑ Appears to have potential for the treatment of
 - GI hypermotility disorders (diarrheas of various origin, IBS-d)
 - Conditions with intended hypomotility (SBS and obesity)

Acknowledgements

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