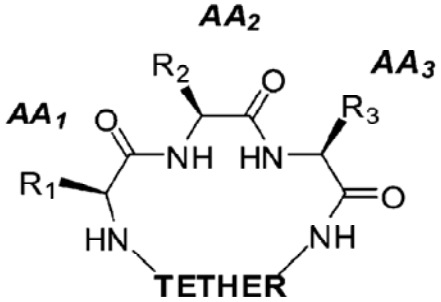
TZP-201: A potent *h*MOT-r antagonist

- 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 µM
    - 2C9: 63.4 µM
    - 3A4 (BFC): 12.6 µM
- Well tolerated in rats up to 400 mg/kg p.o.

Marsault *et al. J. Med. Chem*. **2006**, *49*, 7190-7197

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

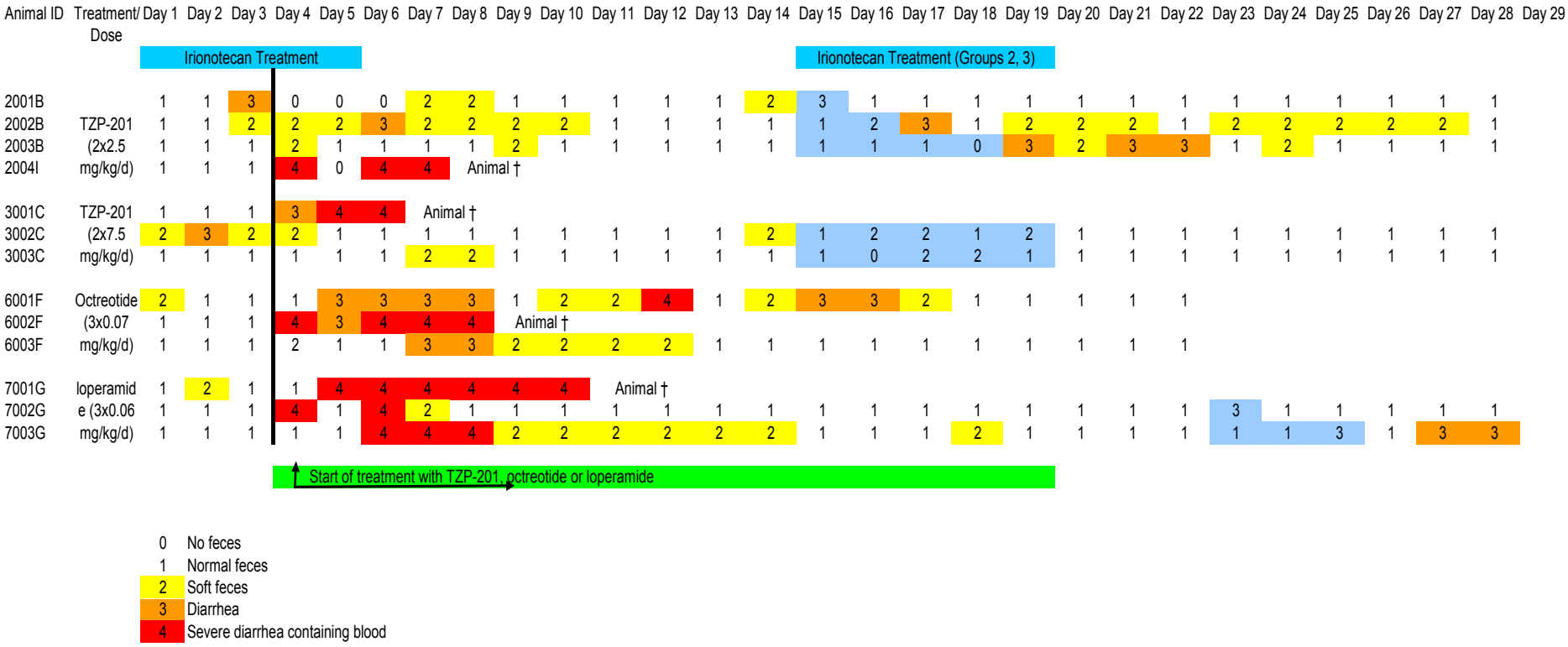
Intestinal secretagogue activity described for 13-norleucin motilin by Kachel *et al. Gastroenterology* **1984**, *87(3)* 550-556

TZP-201: Dog CID Study Design

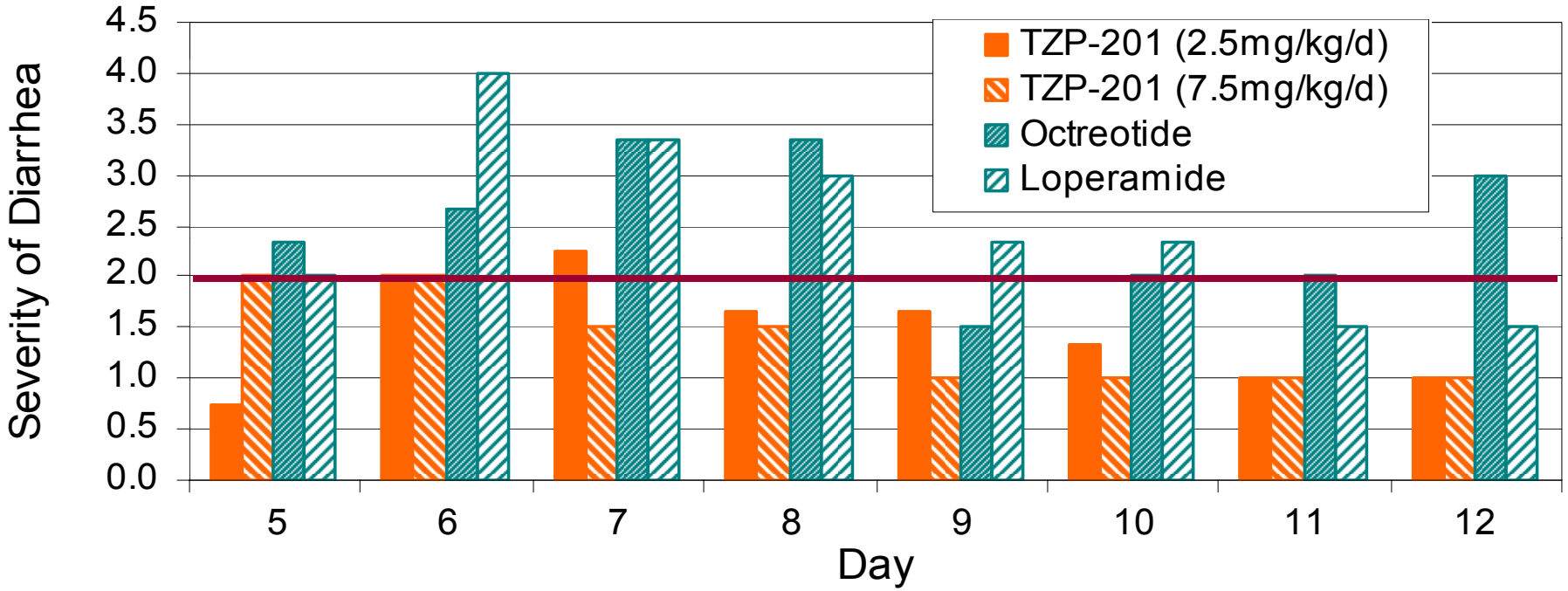
Group and Designation	Treatment					
	Irinotecan			TZP-201		
	Dose (mg/kg/day)	Days	Route	Dose (mg/kg/day)	Days	Route
1 (Positive Control)	4 4 (8) 6	1-5 15-18 (19) 25-29	IV infusion IV infusion IV bolus	0	0	0
2 (TZP-201 LD)	6 6	1-5 15-19	IV bolus	5 (2x2.5)	4-28	IV infusion (45 min)
3 (TZP-201 HD)	6 6	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

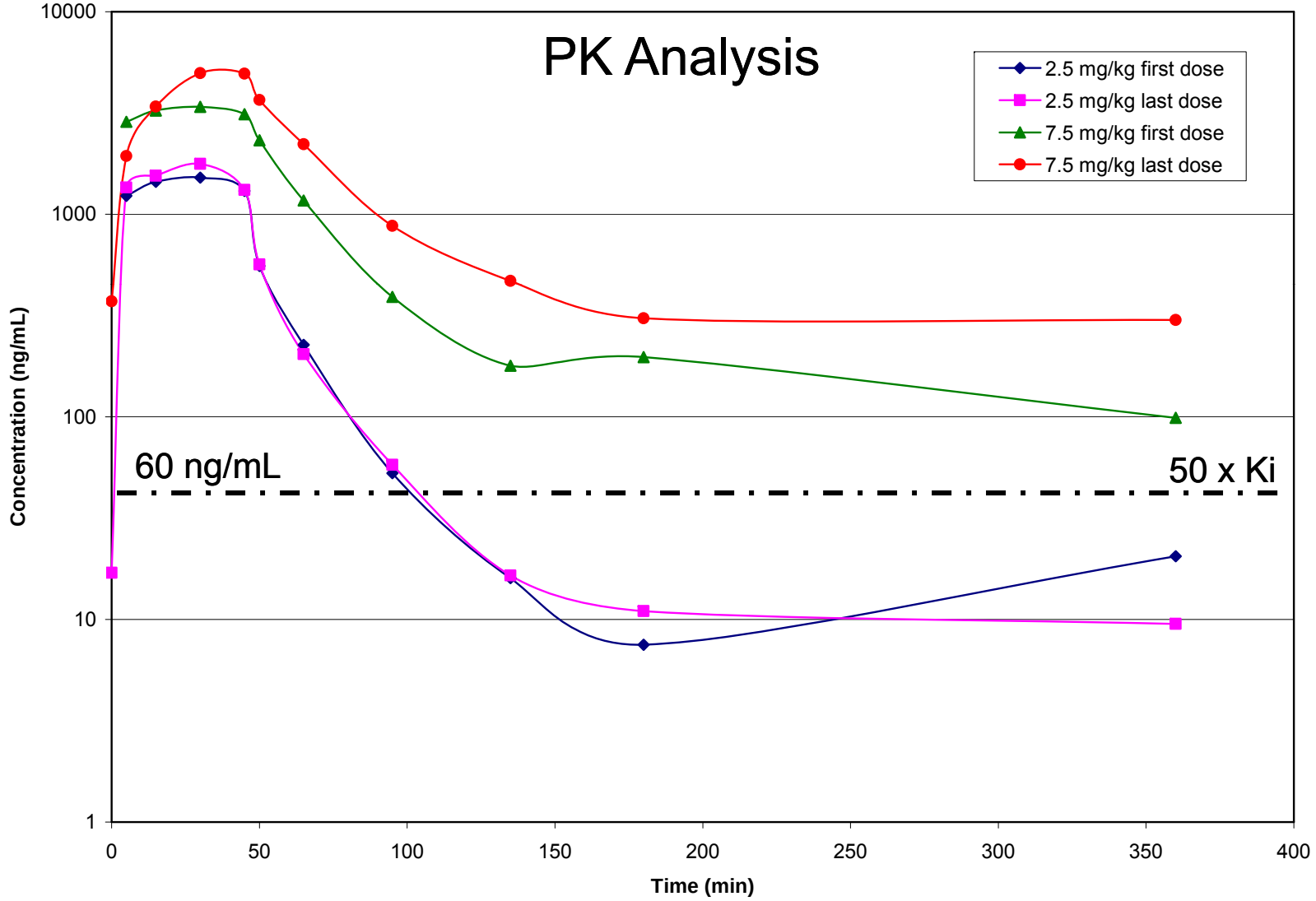


TZP-201: Dog CID Model Results



- 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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