

Gastrointestinal Drugs Advisory Committee

Preclinical Properties of Velusetrag and TD-8954,
Selective 5-HT₄ Receptor Agonists

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Functional Gastrointestinal Disorders

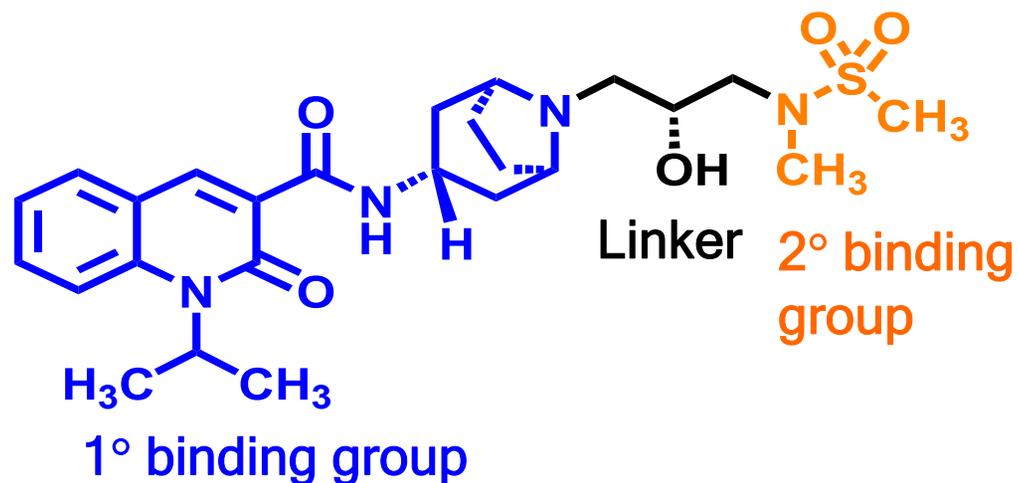
- Significant impact on quality of life
- Patients with severe GI dysfunction may not respond to existing treatment options
- Additional therapeutic options needed
- Early generation 5-HT receptor modulators, cisapride and tegaserod: clinical efficacy but cardiovascular safety concerns
- New class of selective 5-HT₄ agonists: potential to address unmet medical need safely

New Generation, Highly Selective 5-HT₄ Receptor Agonists

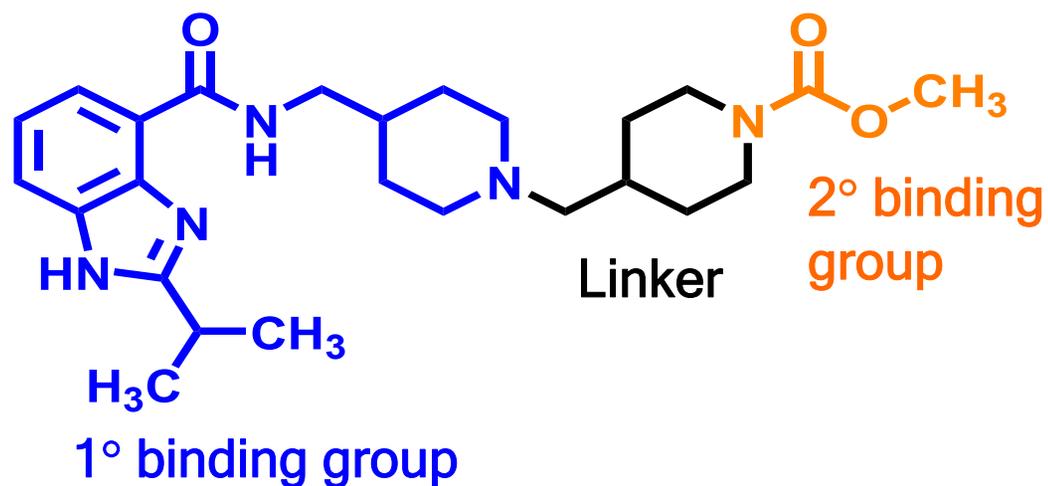
- Velusetrag (TD-5108): completed Phase 2 study in chronic idiopathic constipation
- TD-8954: completed Phase 1 single and multiple ascending dose studies in healthy subjects
- New class of selective 5-HT₄ agonists differentiated from early generation agents, cisapride and tegaserod
 - ◆ Potential to increase clinical efficacy and safety

Velusetrag and TD-8954: Multivalent Design

Velusetrag



TD-8954

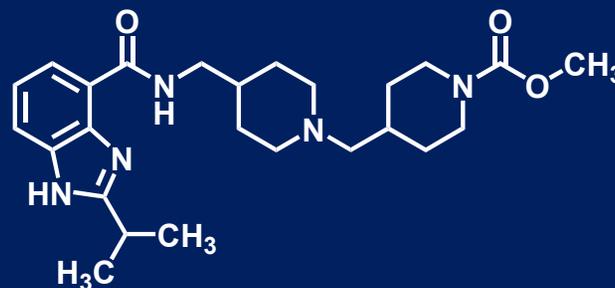


5-HT Receptor Agonists: Structural Diversity



Velusetrag

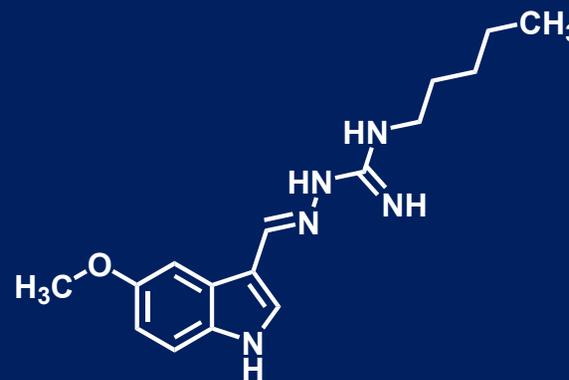
(major metabolite: THRX-830449)



TD-8954



Cisapride



Tegaserod

Ratio of Affinities at 5-HT₄ and non-5-HT₄ Serotonergic Receptors

Human 5-HT Receptor	Cisapride	Tegaserod	Velusetrag	THRX-830449 (velusetrag metabolite)	TD-8954
1A	6	3	>500	>400	>2,500
1B	NT [†]	8	400	>400	>2,500
1D (bovine)	79	16	>500	>400	>2,500
2A	0.05	8	>500	>400	>2,500
2B	0.3	0.5	>500	>400	>2,500
2C	6	25	>500	>400	>2,500
3A	17	400	3,000	300	>2,500
5A	>5	20	>500	>400	>2,500
6	80	5	>500	>400	>2,500
7	8	16	>500	>400	>2,500

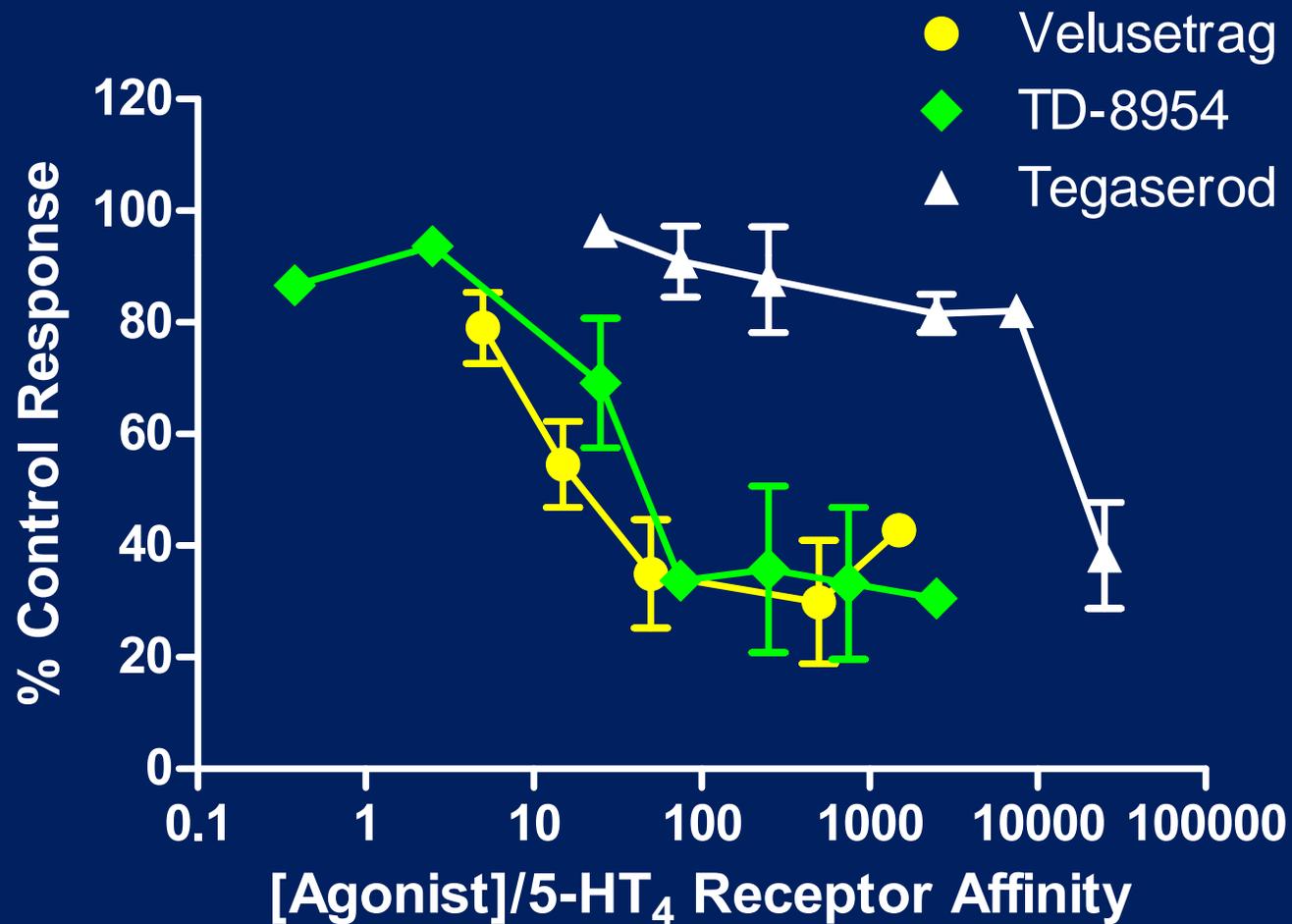
[†] Not tested

Ratio of Affinities at 5-HT₄ and non-5-HT₄ Serotonergic Receptors: GI-related

Human 5-HT Receptor	Cisapride	Tegaserod	Velusetrag	THRX-830449 (velusetrag metabolite)	TD-8954
1A	6	3	>500	>400	>2,500
1B	NT†	8	400	>400	>2,500
1D (bovine)	79	16	>500	>400	>2,500
2A	0.05	8	>500	>400	>2,500
2B	0.3	0.5	>500	>400	>2,500
2C	6	25	>500	>400	>2,500
3A	17	400	3,000	300	>2,500
5A	>5	20	>500	>400	>2,500
6	80	5	>500	>400	>2,500
7	8	16	>500	>400	>2,500

† Not tested

Influence of Non-5-HT₄ Receptors on 5-HT₄ Agonist Potency

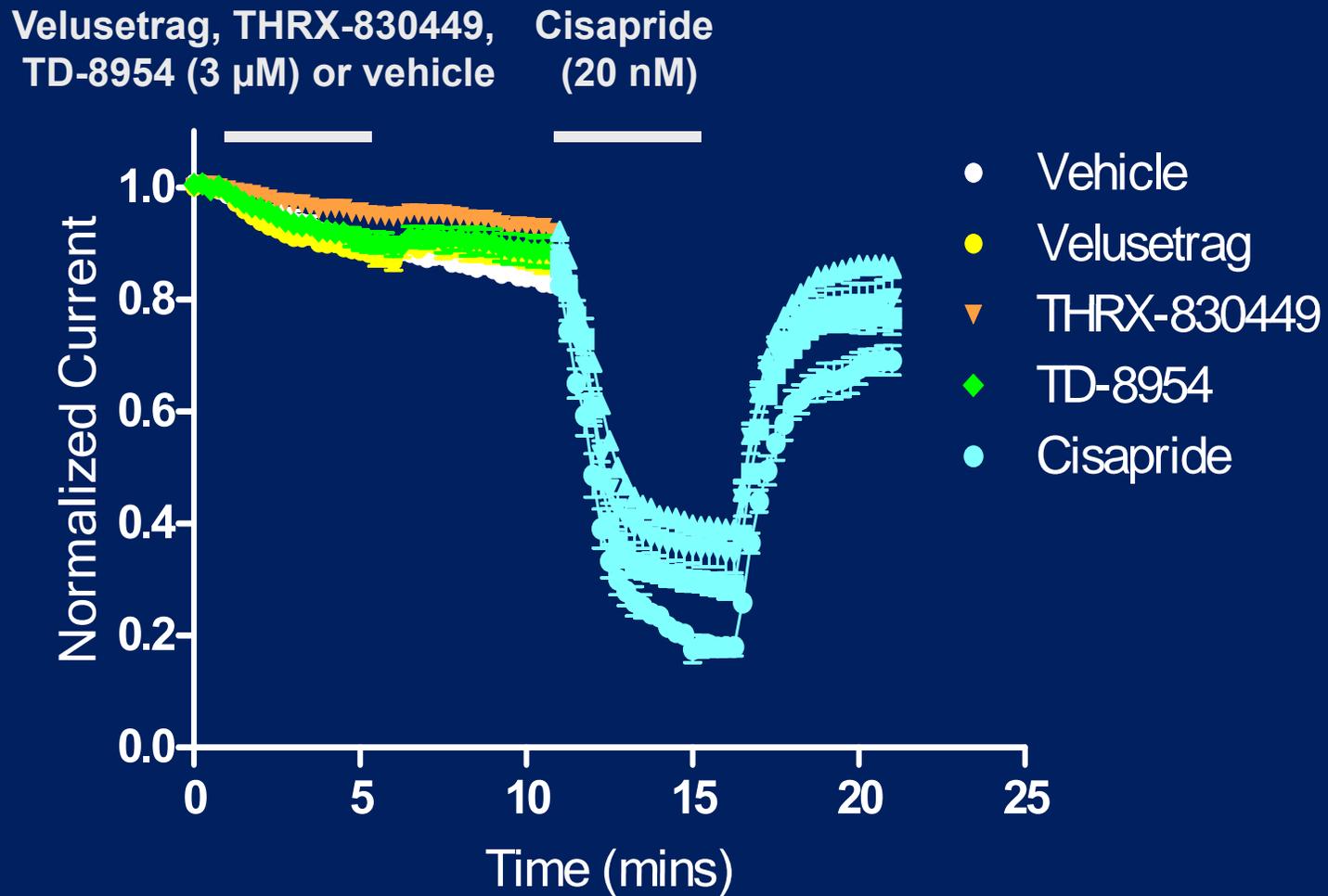


Ratio of Affinities at 5-HT₄ and non-5-HT₄ Serotonergic Receptors: CV-related

Human 5-HT Receptor	Cisapride	Tegaserod	Velusetrag	THRX-830449 (velusetrag metabolite)	TD-8954
1A	6	3	>500	>400	>2,500
1B	NT†	8	400	>400	>2,500
1D (bovine)	79	16	>500	>400	>2,500
2A	0.05	8	>500	>400	>2,500
2B	0.3	0.5	>500	>400	>2,500
2C	6	25	>500	>400	>2,500
3A	17	400	3,000	300	>2,500
5A	>5	20	>500	>400	>2,500
6	80	5	>500	>400	>2,500
7	8	16	>500	>400	>2,500

† Not tested

Interaction with the hERG Potassium Channel



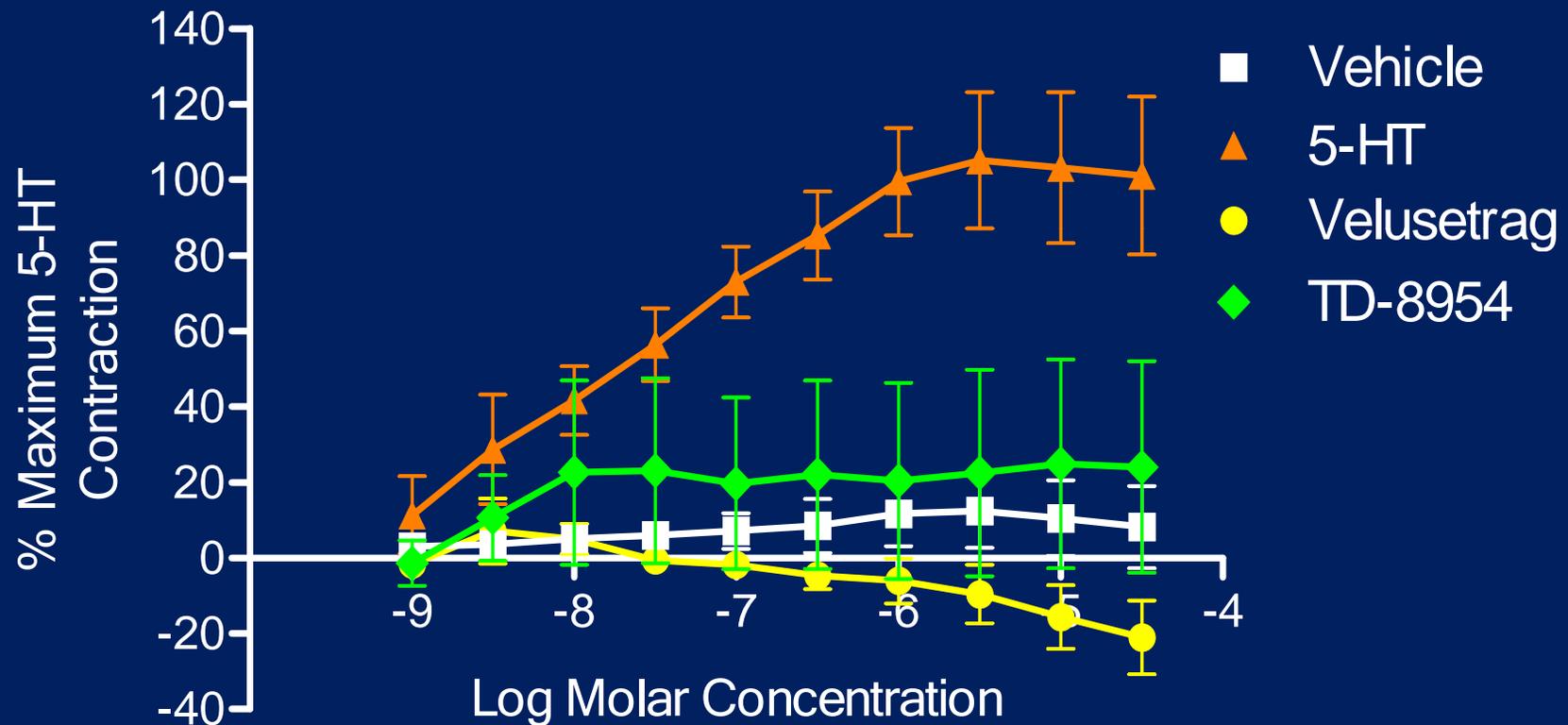
Interaction with the hERG Potassium Channel

Compound	hERG IC ₅₀ (nM)	5-HT ₄ EC ₅₀ (nM)	hERG IC ₅₀ / 5-HT ₄ EC ₅₀ Ratio
Velusetrag	5,200	5.0	1,040
THRX-830449	1,400	6.3	222
TD-8954	6,200	0.5	12,400
Cisapride	18	80	0.2
Tegaserod	1,100 [†]	2.5	400

[†] Lynah et al (2010). Society of Toxicology

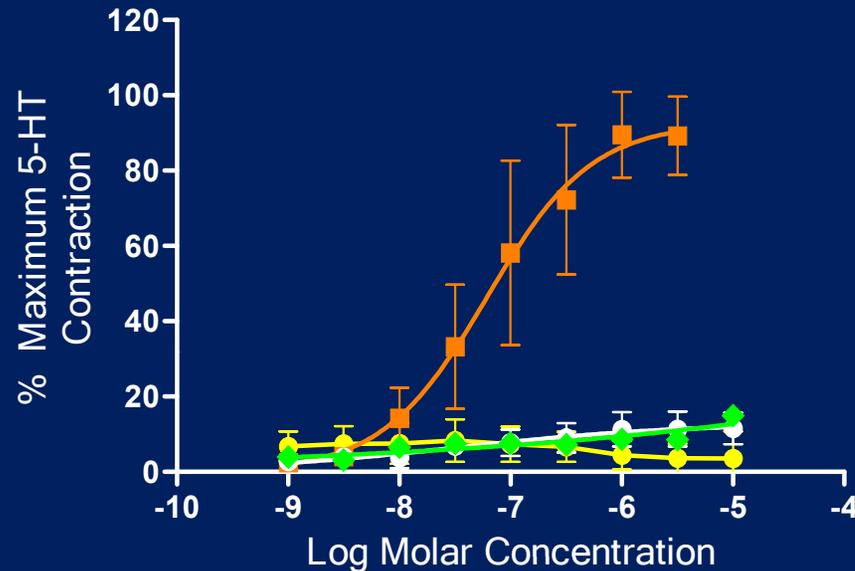
Velusetrag and TD-8954: Preclinical Cardiovascular Findings

Constrictor Activity in Human Isolated Coronary Arteries



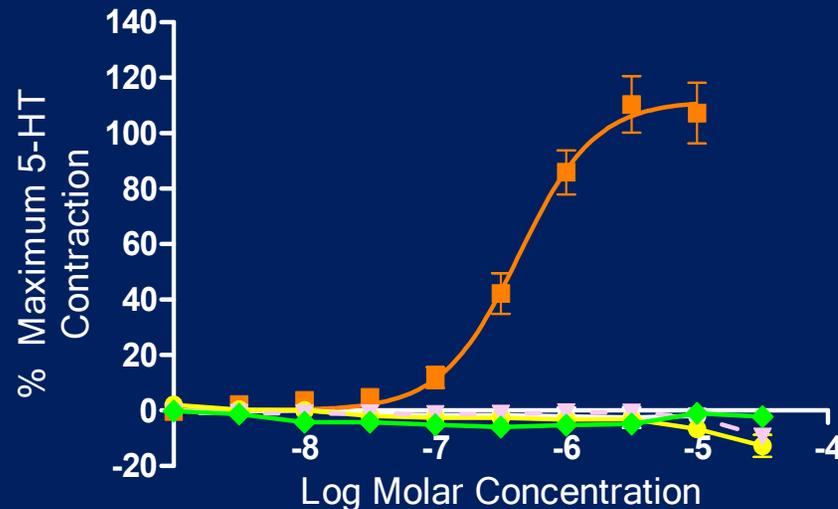
Constrictor Activity in Canine and Porcine Isolated Coronary Arteries

Canine

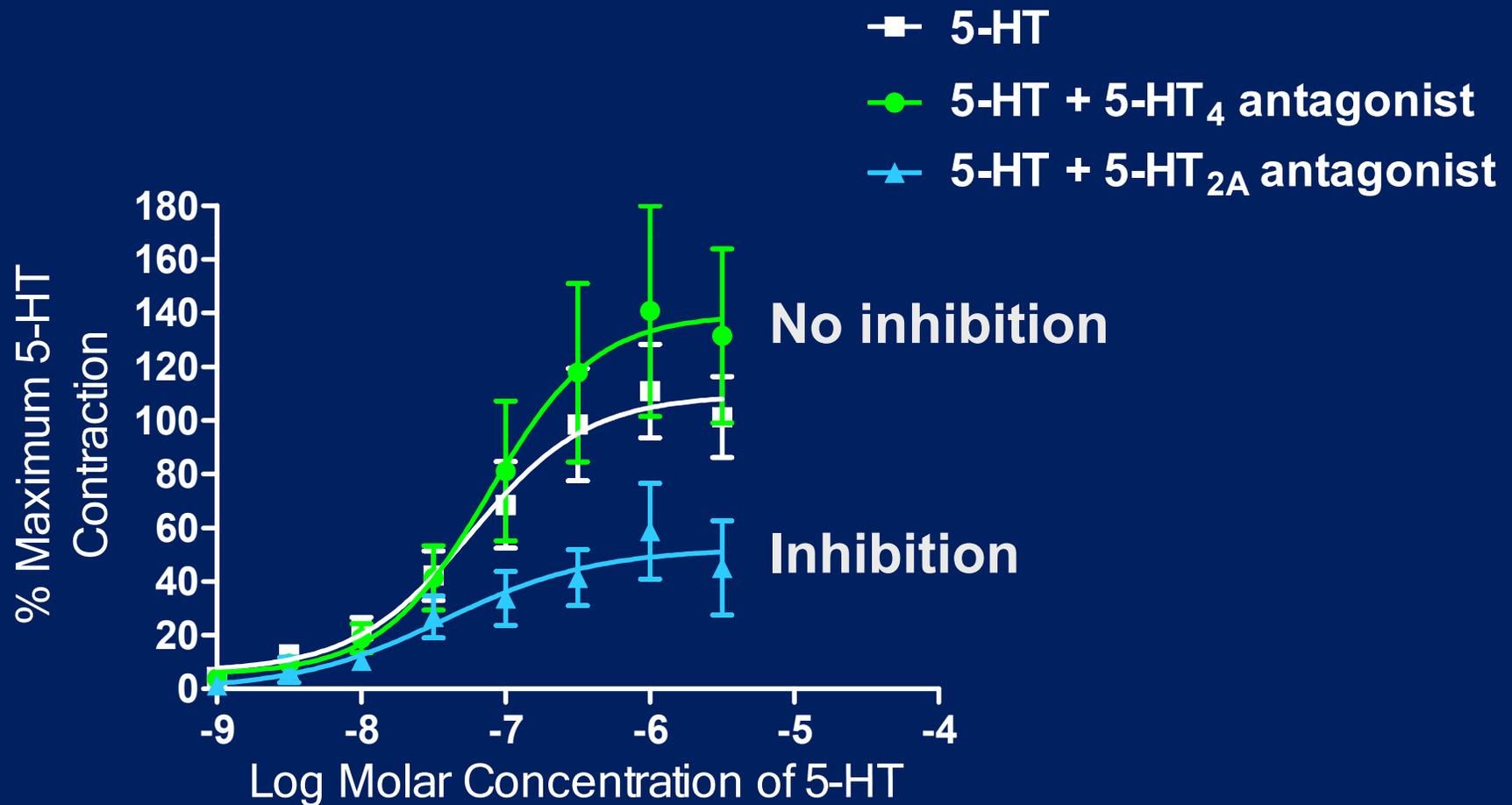


- Vehicle
- 5-HT
- Velusetrag
- ◆ TD-8954
- ▼ THR-830449

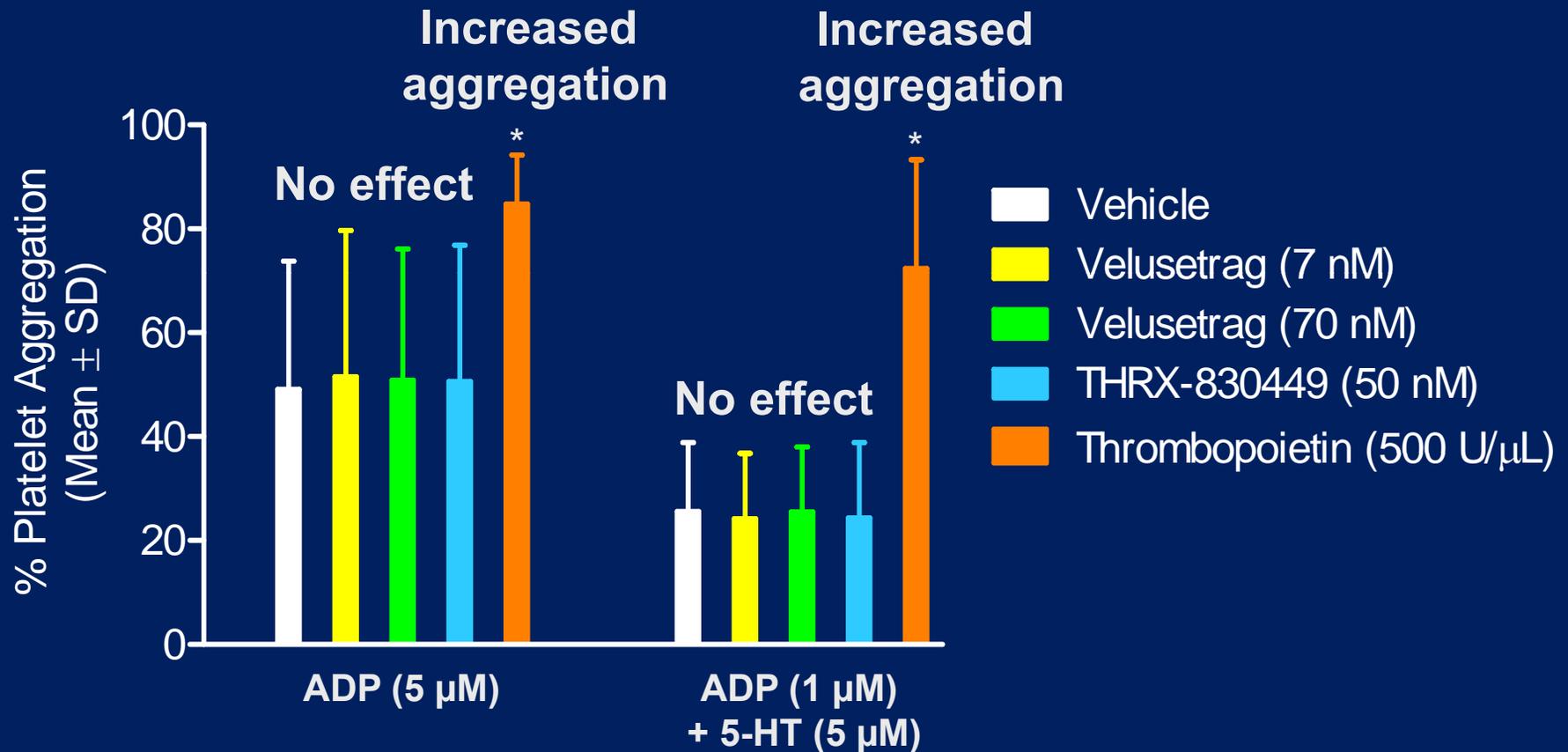
Porcine



Antagonism of 5-HT-induced Coronary Artery Constriction in Canine Isolated Tissue



Influence on Human Platelet Aggregation



Summary of Mechanistic Studies

- Velusetrag and TD-8954 are highly selective 5-HT₄ receptor agonists
 - ◆ No significant affinity for non-5-HT₄ serotonergic receptors
 - ◆ No effects in coronary arteries
 - ◆ No influence on platelet aggregation
 - ◆ No significant hERG affinity
- Cisapride and tegaserod have affinity for non-5-HT₄ serotonergic receptors
- Cisapride is a potent hERG blocker

Velusetrag and TD-8954: Cardiovascular-related Nonclinical Safety Studies Conducted

Study	Velusetrag	TD-8954
hERG	✓	✓
Canine Purkinje fiber	✓	✓
Cardiovascular safety in dogs	✓	✓
4- and 13-week oral dosing in dogs	✓	✓
39-week oral dosing in dogs	✓	Not conducted

Velusetrag and THRX-830449: Cardiovascular Margins

Observation	Result	Fold Margin at Clinically Active Dose (15 mg \approx 0.2 mg/kg)
hERG inhibition	Velusetrag IC ₅₀ : 5.2 μ M	690X
	THRX-830449 IC ₅₀ : 1.4 μ M	380X
Increased action potential duration in canine Purkinje fibers	NOEL 0.3 μ M	40X
Increased heart rate in dogs	NOAEL = 25 mg/kg	
	Velusetrag C _{max}	280X
	THRX-830449 C _{max}	4,180X

TD-8954: Cardiovascular Margins

Observation	Result	Fold Margin at Clinically Active Dose (0.2 mg \approx 0.003 mg/kg)
hERG inhibition	IC ₅₀ : 6.2 μ M	2,400X
Increased action potential duration in dog Purkinje fibers	NOEL 3 μ M	1,100X
Increased heart rate and blood pressure in dogs	NOAEL = 30 mg/kg C _{max}	5,100X

Summary

- Pharmacology of velusetrag, THRX-830449 and TD-8954 differentiated from cisapride and tegaserod
 - ◆ No affinity for non-5-HT₄ serotonergic receptors
 - ◆ No significant effect on hERG potassium channels
- No effect on human coronary artery or platelet aggregation responses
- No cardiovascular findings in dogs at clinically relevant exposures

Conclusions

- Velusetrag and TD-8954
 - ◆ New class of highly selective 5-HT₄ agonists
 - ◆ Potential to treat serious GI motility disorders
- No clinically relevant preclinical cardiovascular findings
- High 5-HT₄ receptor selectivity
 - ◆ Differentiated from earlier products
 - ◆ Should translate into greater efficacy and safety