EP4 Receptor Antagonist for Chronic Inflammatory Pain

Worldwide Partnering Opportunity

ASKAT

2026, AskAt Inc.

Non-confidential Information

1. Executive Summary: AAT-007 (grapiprant)

- Background Information
  - Galliprant® (grapiprant tablet) has been marketed by Elanco as a veterinary medicine worldwide for the treatment of osteoarthritis (OA) pain and inflammation in dogs
  - Back up compound of different chemical structure, AAT-008, in the pre-clinical stage
- Non-Clinical
  - Potent and selective PGE_2 EP4 receptor antagonist
  - Analgesic and anti-inflammatory efficacy in animal models of acute and chronic pain and inflammation
  - Safety profiles confirmed in GLP toxicology studies
  - Renal safety is superior to NSAIDs in an animal model
- Clinical
  - Human PK profiles consistent with QD or BID dosing
  - Robust analgesic efficacy in two Phase 2 OA pain studies
  - CV safety profiles are equivalent or superior to naproxen
  - GI safety is superior to naproxen (An endoscopy study)

1. Executive Summary

- Unmet Medical Need
  - Chronic pain conditions, i.e., osteoarthritis (OA), rheumatoid arthritis (RA), and back pain, continue to represent significant unmet medical needs

- Product Concept
  - A safe and effective orally available drug with rapid and sustained analgesic effect in OA, RA, and other inflammatory pain conditions
  - A new analgesic drug that will replace NSAIDs/COX-2 inhibitors

2. Table of Contents

3. Medical Needs

- NSAIDs and COXIBs are commonly used for long-term treatment of chronic painful musculoskeletal conditions (e.g., OA, RA, and back pain).

- There is a significant need for more efficacious and safer treatment (e.g., less GI, renal, and CV side effects) over the existing therapies.

4. Market Opportunity

- Arthritis Pain
  - Over 32.5 million adults in the US were suffering from OA in 2024[1].
  - The global arthritic pain management drugs market was valued at $7,665.21 million in 2019 and is projected to reach $9,937.93 million by 2027*
  - Pain relief enhances quality of life for arthritis patients

- An EP4 antagonist has potential to replace NSAIDs/COXIBs
  - The global NSAIDs market was valued at $16,181.46 million in 2019, and is projected to reach $21,483.78 million by 2027*
  - The global pain management drugs market was valued at $71,431.85 million in 2019, and is projected to reach $91,649.16 million by 2027*

1) Centers for Disease Control and Prevention (CDC) in the US, https://www.cdc.gov/arthritis/types/osteoarthritis.htm
2) PAIN MANAGEMENT DRUGS MARKET, Global Opportunity Analysis and Industry Forecast, 2020-2027 (Allied Market Research, 2020)

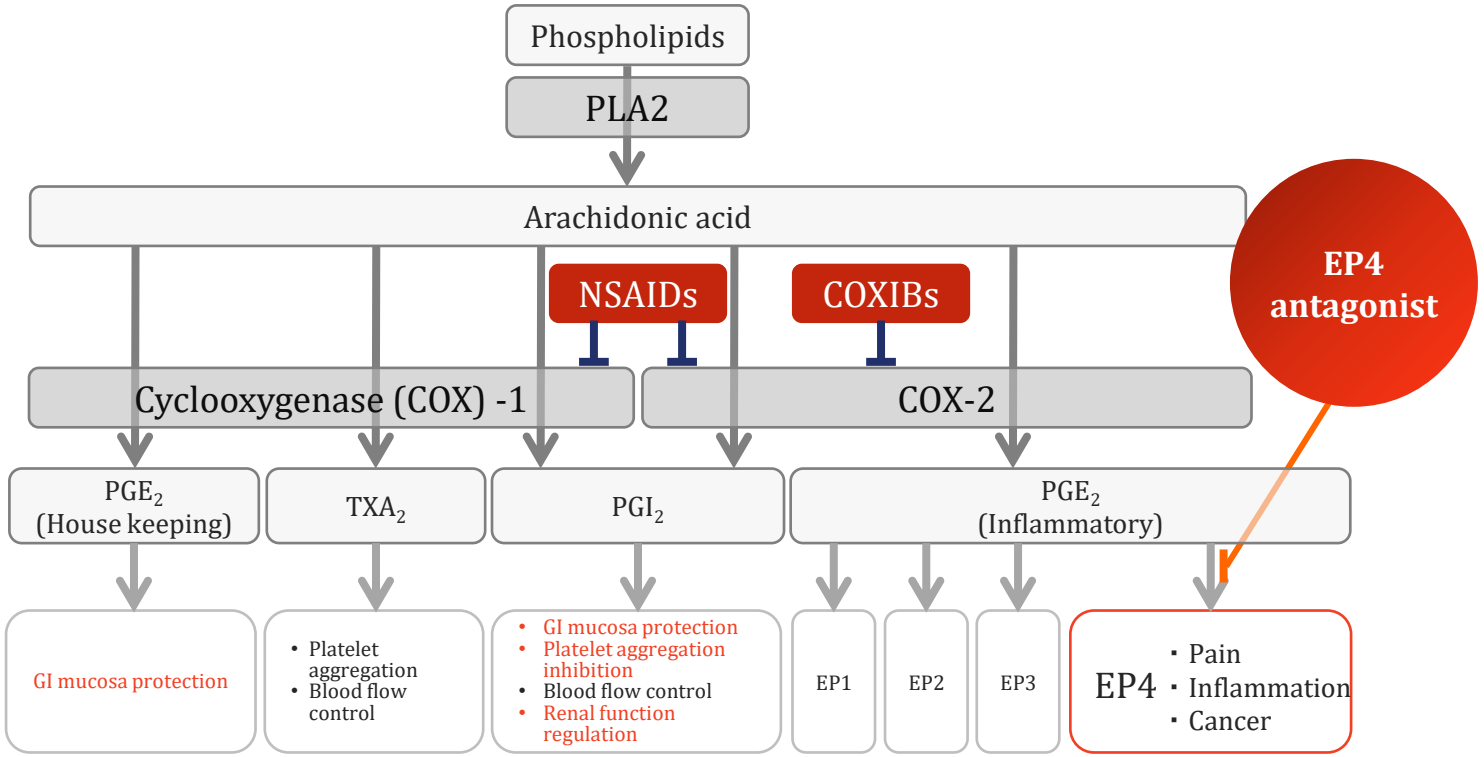
5. EP4 Antagonist: Improved Pain Management

- NSAIDs/COXIBs provide anti-inflammatory and analgesic effects by inhibiting PGE_2 production
- The inhibition of other prostanoids (e.g., PGI_2) syntheses may leads to associated adverse events
- EP4 receptor-mediated PGE_2 action plays a key role in inflammation and pain

A potent and selective EP4 antagonist represents a new treatment option for the management of inflammation and pain

6. Potential for Improved Safety and Efficacy Profile vs. NSAIDs/COXIBs

- Selective EP4 antagonists block the action mediated by PGE_2 without any effect on the prostanoids biosynthesis
- In contrast, NSAIDs/COXIBs inhibit biosynthesis of prostanoids including PGE_2



Selective EP4 antagonists have no direct effect on the prostaglandin biosynthesis

7. Compound Attributes of AAT-007

7.1. Compound Information
7.2. Pivotal field study of GALLIPRANT® in client-owned dogs with OA-pain
7.3. Non-Clinical Pharmacology
7.4. Non-Clinical Safety Pharmacology
7.5. Non-Clinical Safety Pharmacology Studies
7.6. Non-Clinical Pharmacokinetic Studies
7.7. Non-Clinical Toxicology Studies
7.8. Clinical Studies
7.9 Phase 1 Profile
7.10. Phase 2 Profile
7.11. Clinical Studies Summary

7.1. Compound Information of AAT-007

- Compound Code
  - AAT-007 (grapiprant)
- IP status (as of January 28, 2026)
  - Crystal forms (WO 2006/095268) filed on March 1, 2006
    - Granted: BR, CA, CN, EP (FR, DE, GB, IE, IT, ES, TR, GR, PL, NL, BE), IN, JP, KR, MX, RU, US
    - Five-year patent term extension for Galliprant: GB, FR, DE, IE, IT, ES, GR, PL, NL, BE, JP, US
  - Use for Cartilage Disease (WO 2014/148053) filed on March 19, 2014
    - Granted: CA, CN, EP (FR, DE, GB, IT, ES), HK, JP, KR, MX, RU, US
- Chemistry, Manufacturing and Control (CMC)
  - Active Pharmaceutical Ingredient:
    No major issue in the bulk campaign to provide ca. 80 kg
    Stability testing at room temperature up to 43 months
  - Drug Product:
    Biopharmaceutics Classification System: Class 3 (high solubility / low permeability)
    Immediate release tablets for phase studies

7.2. Pivotal field study of Galliprant® (grapiprant) in client-owned dogs with OA-pain[1)]

Client–owned OA-pain dogs were enrolled and randomized assigned two group (N=131 per group).
Each dogs was treated once daily with either placebo or grapiprant at a dosage of 2 mg/kg using 20, 60 , and 100 mg whole or half tablets.
Placebo tablets were matched to grapiprant tablets.

1) J Vet Intern Med 2016; 30: 756-763

Table 2. Percentage of dogs treated with either grapiprant or placebo classified as treatment success comparing CBPI scores on Day 0 to scores on Days 7, 14, and 21.

	Treatment Success		
Timepoint	Grapiprant N (%)	Placebo N (%)	*P* value
Day 7	40 (30.5)	21 (16.0)	.0154
Day 14	54 (41.2)	37 (28.2)	.0442
Day 21	61 (46.6)	43 (32.8)	.0443

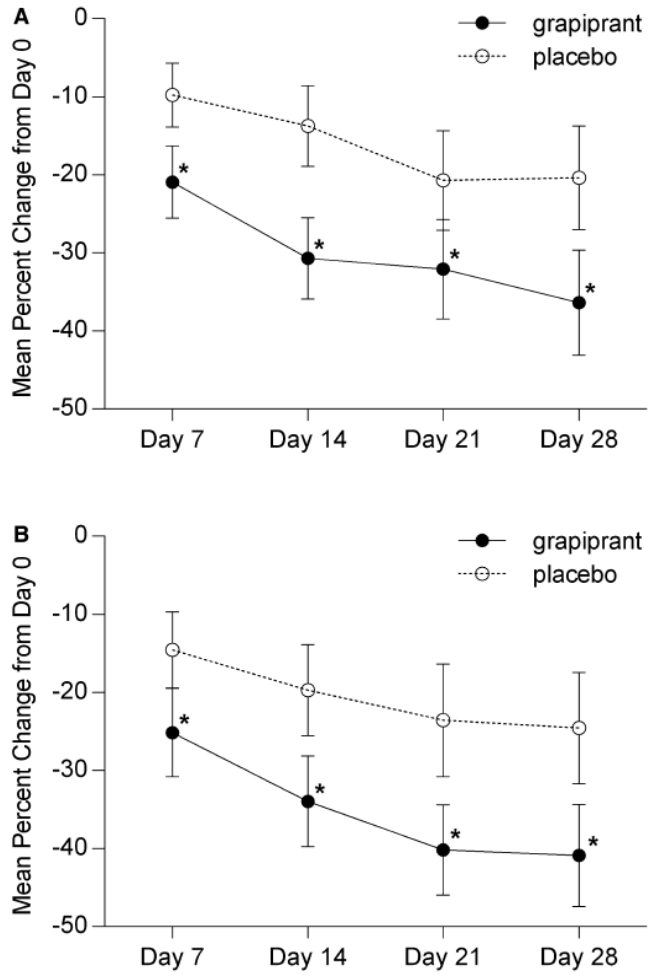


Fig 2. Mean percentage change (with 95% confidence intervals) in (**A**) pain severity score and (**B**) pain interference score scores from Day 0 to Days 7, 14, 21, and 28 in dogs treated with grapiprant (n = 131) or placebo (n = 131). *Denotes statistical significance ($P < .05$).

Grapiprant at 2 mg/kg is an effective treatment for alleviation of pain in dogs with OA

7.3. Non-Clinical Pharmacology of AAT-007

Binding affinities

Receptor	Ligand	Binding Ki (nM)
hEP1	[^{3}H]-PGE_2	>5000
hEP2	[^{3}H]-PGE_2	>5000
hEP3	[^{3}H]-PGE_2	>5000
hEP4	[^{3}H]-PGE_2	13
hDP	[^{3}H]-PGD_2	2926
hFP	[^{3}H]-$PGF_{2\alpha}$	>5000
hIP	[^{3}H]-iloprost	>5000
hTP	[^{3}H]-SQ29548	19% inh. @20 µM

Over 200-fold selectivity against other prostanoid receptors was observed

7.3. Non-Clinical Pharmacology of AAT-007

Functional activities

Inhibition of PGE_2-induced cAMP elevation

Recombinant human EP4	$pA_2 = 8.32$
Recombinant rat EP4	$pA_2 = 8.19$
Rat DRG primary culture	$IC_{50} = 41$ nM

Inhibition of PGE_2 and Concanavalin A-induced IL-6 production

Human PBMC[a]	$IC_{50} = 75$ nM

[a] Peripheral blood mononuclear cells

Potent antagonistic activities on the EP4 receptors in human and rat cells were demonstrated

7.3. Non-Clinical Pharmacology of AAT-007

Analgesic activities in rats

	MED[a] (mg/kg, PO)
PGE_2-induced thermal hyperalgesia	29
Carrageenan-induced mechanical hyperalgesia	30
CFA-induced weight bearing deficit	19

[a] Minimum effective dose.

Anti-inflammatory activities in rats

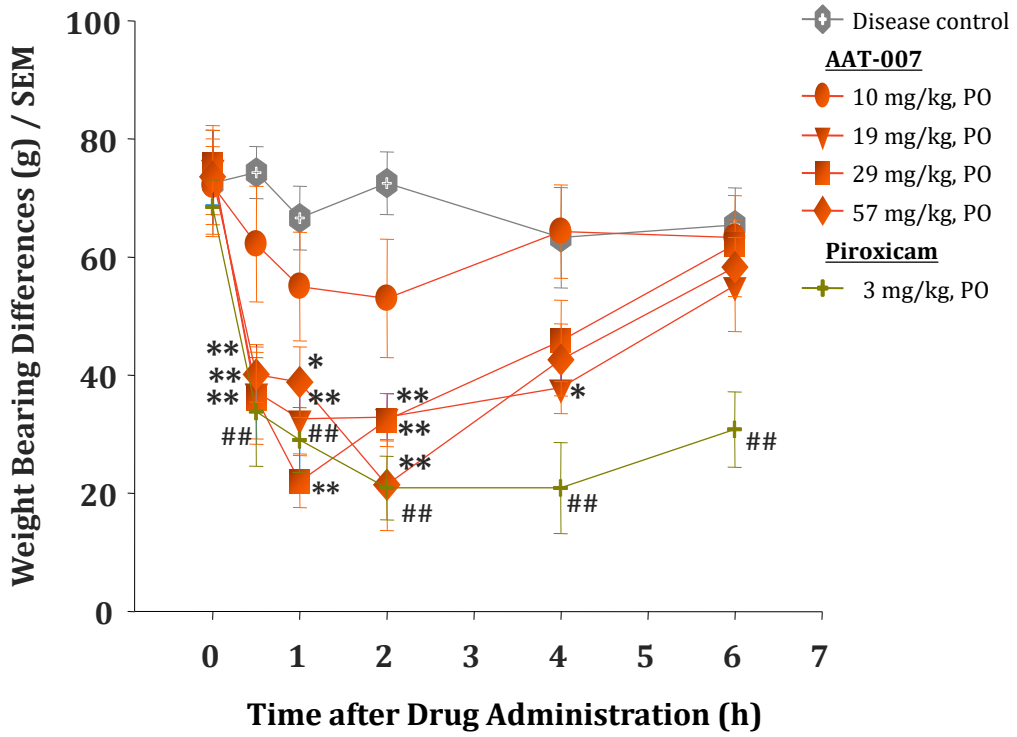
	MED (mg/kg, PO)
Carrageenan-induced foot edema	100
Adjuvant-induced arthritis for swelling	ED_{70} = 57 mg/kg[b]

[b] BID dosing for 21 days.

Analgesic and anti-inflammatory effects in rats were demonstrated

7.3. Non-Clinical Pharmacology of AAT-007

Effect of AAT-007 on CFA-induced hyperalgesia in rats



Method

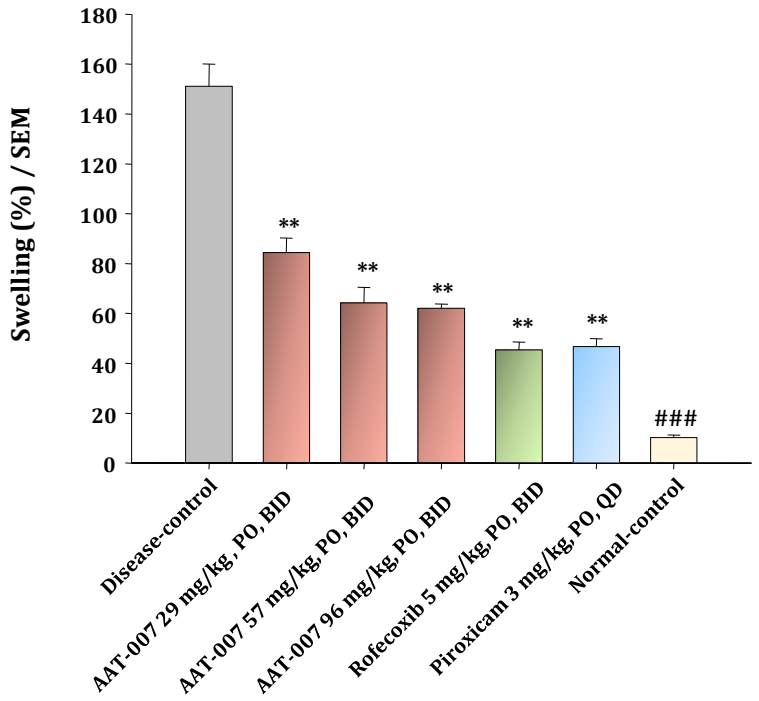
CFA was injected into the right foot pad in male SD rats. On two days after CFA injection, changes in hind paw weight distribution between the right (inflamed) and the left (contralateral) limbs were measured as an index of pain by Linton Incapacitance tester.

*: $p < 0.05$, **: $p < 0.01$ by One-way ANOVA, Dunnett post test, ##: $p < 0.01$ by *t*-test.

Maximum efficacy of AAT-007 was comparable to piroxicam on CFA-induced weight bearing deficit in rats

7.3. Non-Clinical Pharmacology of AAT-007

Anti-inflammatory effect of AAT-007 in adjuvant arthritis rats on Day 21



Method

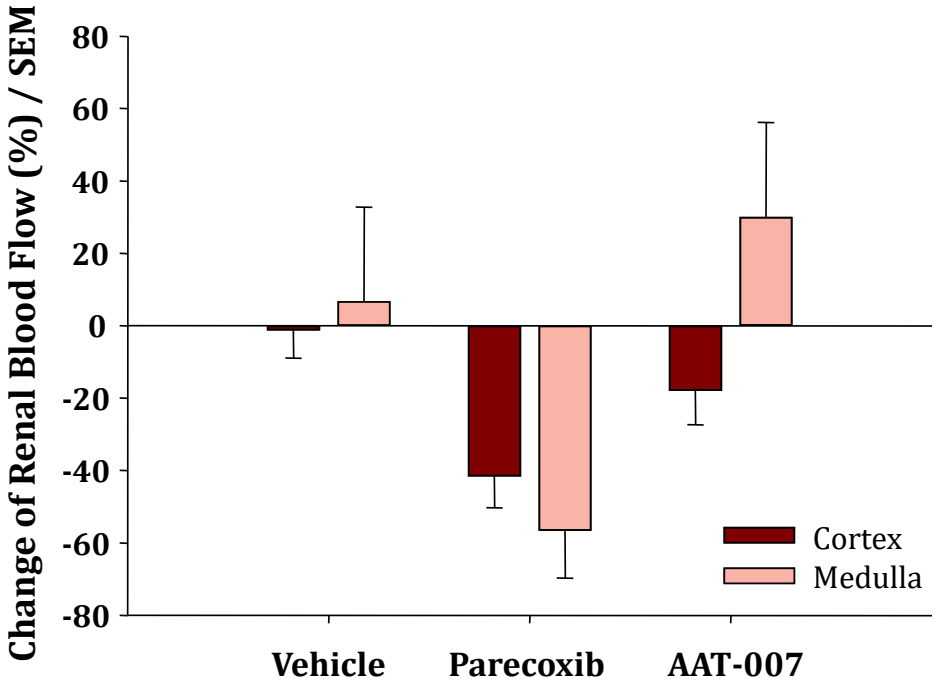
CFA was injected into the right foot pad in male Lewis rats. On 21 days after CFA injection, changes in left (contralateral) hind paw volume were measured using a plethysmometer. Drug or vehicle administration was started on day 0 and continued until on day 21.

**: $p < 0.01$ by One-way ANOVA, Dunnett post test, ###: $p < 0.001$ by *t*-test.

AAT-007 exhibited an anti-inflammatory efficacy comparable to rofecoxib and piroxicam in the rat adjuvant arthritis model

7.4. Non-Clinical Safety Pharmacology of AAT-007

Effects of AAT-007 and parecoxib on cortical and medullary renal blood flow in anesthetized volume-depleted rats



Method

Furosemide-treated SD rat was anesthetized with urethane and received intravenous injection of AAT-007 or parecoxib. Renal blood flow was measured using MRI.

*: $p < 0.05$ compared to vehicle (furosemide-treated) group by *t*-test.

X = fold the estimated anti-inflammatory exposure at the $ED_{70 \text{ or } 80}$ in the rat adjuvant arthritis model.

AAT-007 demonstrated no significant effect on cortical and medullary renal blood flow in frosemide-treated volume-depleted rats, although parecoxib reduced

7.5. Non-Clinical Safety Pharmacology Studies of AAT-007

Study Type			Route of Administration	Species
Core Battery	CNS		PO	Rat
	CVS		PO	Dog
	Respiratory System		PO	Rat
	CVS	HERG Assay	-	Human
Follow-Up	CVS	Purkinje Fiber	-	Dog
Supplemental	Renal and Urinary System	Renal and PK	PO	Rat
		Renal Blood Flow	IV Bolus and Infusion	Rat
		Plasma Renin Activity	PO	Rat
	Broad Ligand Assay		-	Human

7.6. Non-Clinical Pharmacokinetic Studies of AAT-007

Study Type and Duration		Route of Administration	Species / Cell Line
Absorption	Single Dose	IV and PO	Rat, Dog, Monkey
	Multiple Dose (10-Day)	PO	Rat, Dog
Distribution	Tissue Distribution	PO	Rat
	Serum Protein Binding	-	Mouse, Rat, Rabbit, Dog, Monkey, Human
	RBC Partitioning (Blood / Plasma Ratio)	-	Rat, Dog, Human
	Brain Penetration	PO	Mouse, Rat
Metabolism	*In vivo* Metabolism	PO	Rat, Dog
	In vitro Metabolism	-	Rat / Human Liver Microsome, Rat / Human Hepatocyte
	Inhibition of Drug Metabolizing Enzymes (DDI)	-	Human
Excretion	Excretion into Urine	IV	Rat, Dog, Monkey
	Biliary Secretion	IV	Rat
Others	Cell Permeability Assay	-	Caco-2
	Transporter Assay	-	MDCK / MDR1

7.7. Non-Clinical Toxicology Studies of AAT-007

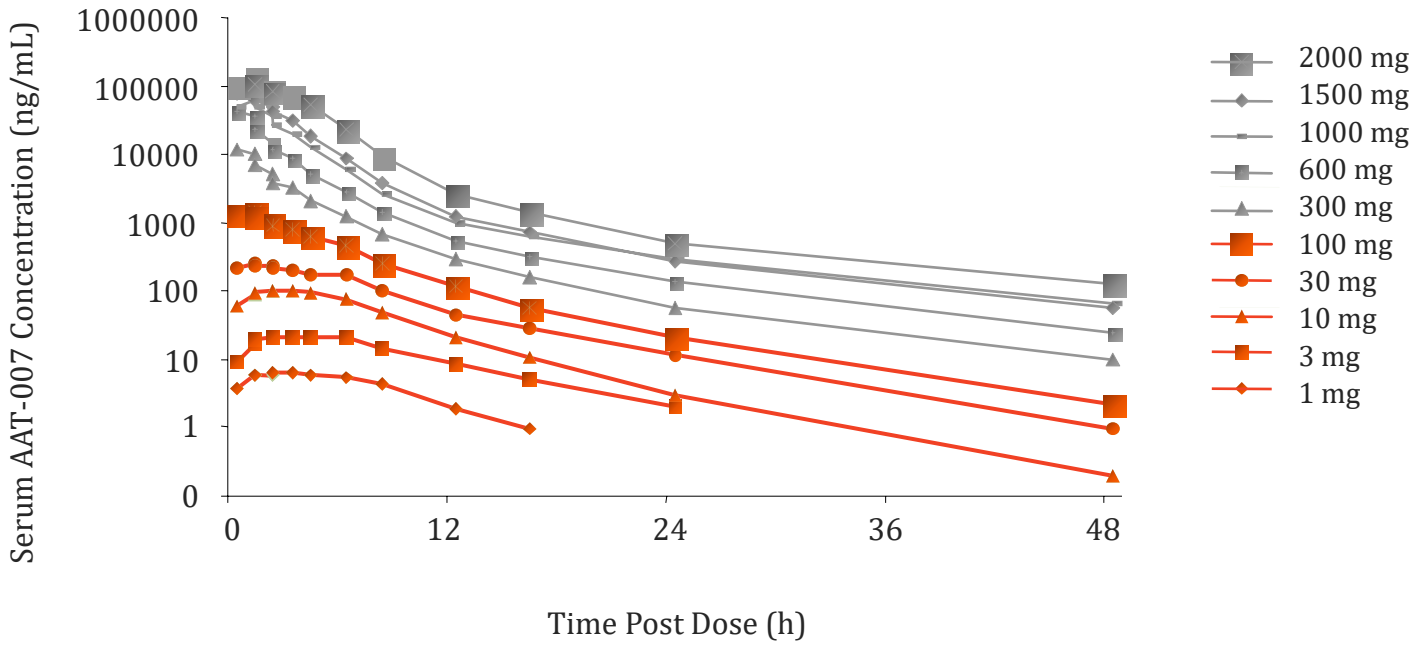
Study Type and Duration		Route of Administration	Species
Single-Dose Toxicity		PO	Rat, Dog
Repeated-Dose Toxicity	10-Day Range-Finding	PO	Rat, Dog
	1-Month	PO	Rat, Dog
	3-Month	PO	Rat
	9-Month	PO	Dog
Genotoxicity	Mutagenicity Assay (Ames)	-	Bacteria
	Clastogenicity Assay (Human Lymphocyte)	-	Human
	In vivo Micronucleus Assay	PO	Rat
	Other Genetic Toxicology Assay	*In vivo* and *In vitro*	Rat
Carcinogenicity	2-Week	PO	Mouse
	2- to 4-Week Range-Finding	PO	Mouse
	1-Month Range-Finding	PO	Mouse

7.8. Clinical Studies of AAT-007

Stage	Study	Subjects (N)
Phase 1	Single Dose Tolerance and PK	Healthy Volunteers (78)
	Food Effect	Healthy Volunteers (12)
	Multiple Dose Tolerance and PK	Healthy Volunteers (36) Elderly Volunteers (21)
	Gastroduodenal Endoscopy	Healthy Volunteers (193) Elderly Volunteers (165)
Phase 2	OA Pain (2-week)	Subjects with OA Pain (201)
	OA Pain (4-week)	Subjects with OA Pain (739)

7.9. Phase 1 Profile of AAT-007

- Single-dose study in healthy subjects
  - Well-tolerated up to 1000 mg
  - Exposure increases with dose in an approximately dose proportional manner between 1 - 100 mg, and between 600 - 2000 mg
  - The average terminal elimination half-life was ～ 9 hours, with a fast distribution phase
  - Systemic exposure parameters decrease slightly with food



7.9. Phase 1 Profile of AAT-007

- 14-day multiple-dose study
  - Well-tolerated 300 mg BID in healthy subjects
  - Well-tolerated 250 mg BID in elderly subjects with mild renal impairment
- Endoscopic GI safety study
  - No significant difference in incidence of GI ulcer compared to placebo after 7 days treatment at 75 mg BID
  - Significantly lower incidence of GI ulcer compared to Naproxen at 500 mg BID in elderly subjects after 7 days treatment

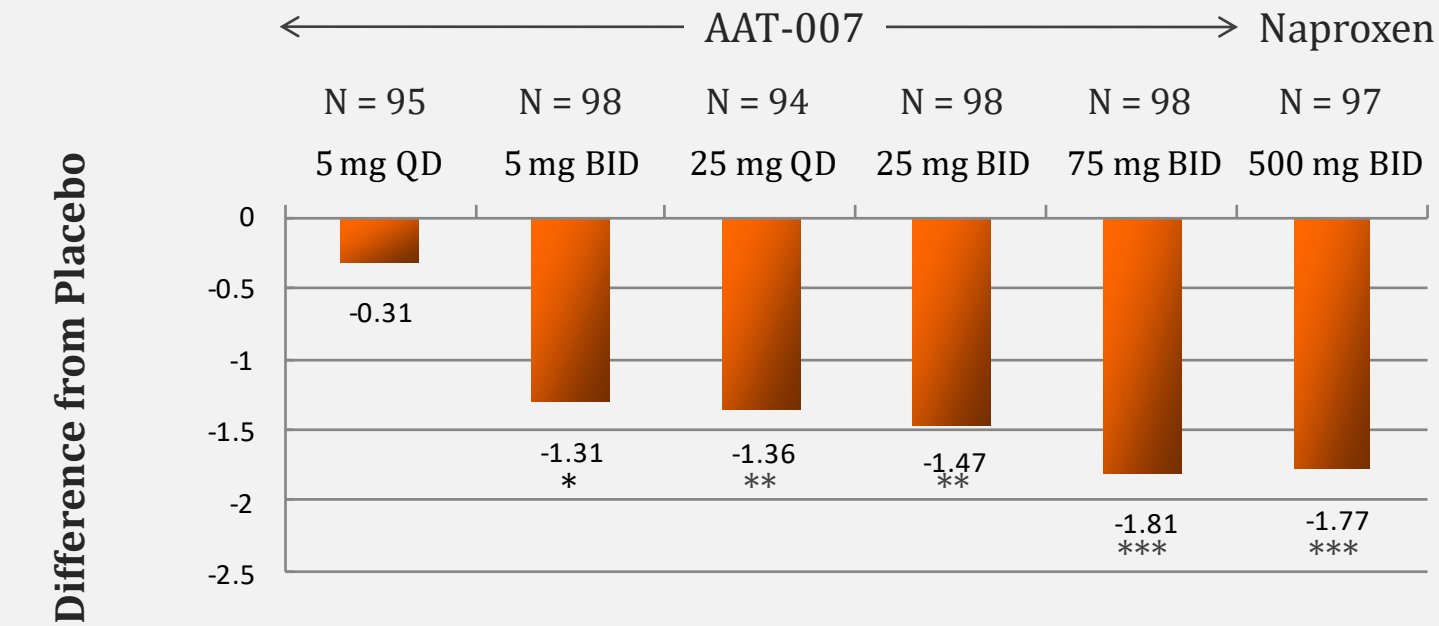
Treatment Group (Elderly)	Number of Ulcer * Subject (Incidence %)
AAT-007 (N = 63)	3 (5%)
Naproxen (N = 63)	11 (18%)
Placebo (N = 39)	1 (3%)

Comparison	P-value
AAT-007 vs Naproxen	0.018
AAT-007 vs Placebo	0.619
Naproxen vs Placebo	0.020

*: Any break in the mucosa >3 mm in diameter with unequivocal depth

7.10. Phase 2 Profile of AAT-007

- 4 weeks study of OA pain
  - AAT-007 was efficacious in relief of signs and symptoms in the 4 weeks treatment of OA pain on once- or twice-a-day dosing



Two-sided p-value vs. placebo (N = 99) * < 0.05, ** < 0.01, *** < 0.001
Overall two-sided p-value ≤ 0.0001 for linear contrast test of overall dose-related trend

Mean change from baseline in WOMAC pain scores compared to placebo
(Week 4, ITT, Mixed model with repeated measures)

7.11. Clinical Studies Summary of AAT-007

- Phase 1 Studies
  - Well-tolerated in single dose and 14 days multiple dose studies
  - Systemic exposure increased in an approximate dose-proportional manner after single and multiple dose
  - No significant difference in incidence of GI ulcer compared to placebo
  - Significantly lower incidence of GI ulcer compared to Naproxen in elderly

- Phase 2 Studies
  - Two Phase 2 studies were conducted in the US
  - AAT-007 was efficacious in relief of signs and symptoms in the 4 weeks treatment of OA pain on once- or twice-a-day dosing
    - Estimated total daily dose of 96 mg achieve the same efficacy as Naproxen 1000 mg per day
    - Minimum efficacious dose range estimated (19.5 to 32.0 mg/day)
  - Efficacious dose without safety issue was identified

8. References

8.1. Publication List of AAT-007

8.2. Other Publications

8.1. Publication List of AAT-007

1. Nakao K, Murase A, Ohshiro H, Okumura T, Taniguchi K, Murata Y, Masuda M, Kato T, Okumura Y, and Takada J (2007) CJ-023,423, a novel, potent and selective prostaglandin EP_4 receptor antagonist with antihyperalgesic properties. *J Pharmacol Exp Ther* **322**:686-694.

2. Okumura T, Murata Y, Taniguchi K, Murase A, and Nii A (2008) Effects of the selective EP_4 antagonist, CJ-023,423 on chronic inflammation and bone destruction in rat adjuvant-induced arthritis. *J Pharm Pharmacol* **60**:723-730.

3. Murase A, Nakao K, and Takada J (2008) Characterization of binding affinity of CJ-023,423 for human prostanoid EP_4 receptor. *Pharmacology* **82**:10-14.

8.2. Other Publications

4. Murase A, Taniguchi Y, Tonai-Kachi H, Nakao K, and Takada J (2008) In vitro pharmacological characterization of CJ-042794, a novel, potent, and selective prostaglandin EP_4 receptor antagonist. *Life Sci* **82**:226-232.

5. Murase A, Okumura T, Sakakibara A, Tonai-Kachi H, Nakao K, and Takada J (2008) Effect of prostanoid EP_4 receptor antagonist, CJ-042,794, in rat models of pain and inflammation. *Eur J Pharmacol* **580**:116-121.

6. Takeuchi K, Tanaka A, Kato S, Aihara E, and Amagase K (2007) Effect of (*S*)-4-(1-(5-chloro-2-(4-fluorophenyoxy) benzamido)ethyl)benzoic acid (CJ-42794), a selective antagonist of prostaglandin E receptor subtype 4, on ulcerogenic and healing responses in rat gastrointestinal mucosa. *J Pharmacol Exp Ther* **322**:903-912.

7. Hatazawa R, Tanaka A, Tanigami M, Amagase K, Kato S, Ashida Y, and Takeuchi K (2007) Cyclooxygenase-2/prostaglandin E_2 accelerates the healing of gastric ulcers via EP_4 receptors. *Am J Physiol Gastrointest Liver Physiol* **293**:G788-G797.