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

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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)

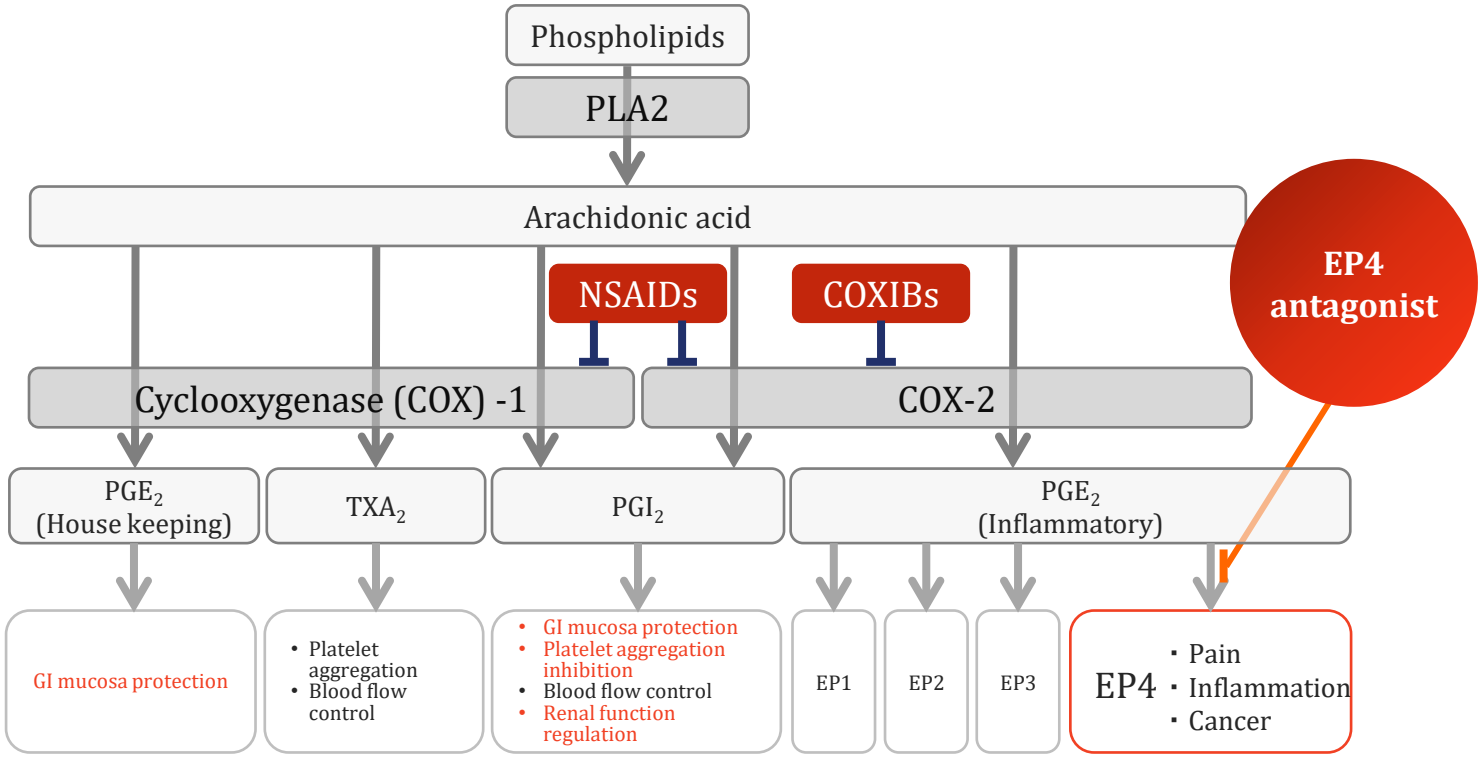
5. EP4 Antagonist: Improved Pain Management

- 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

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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

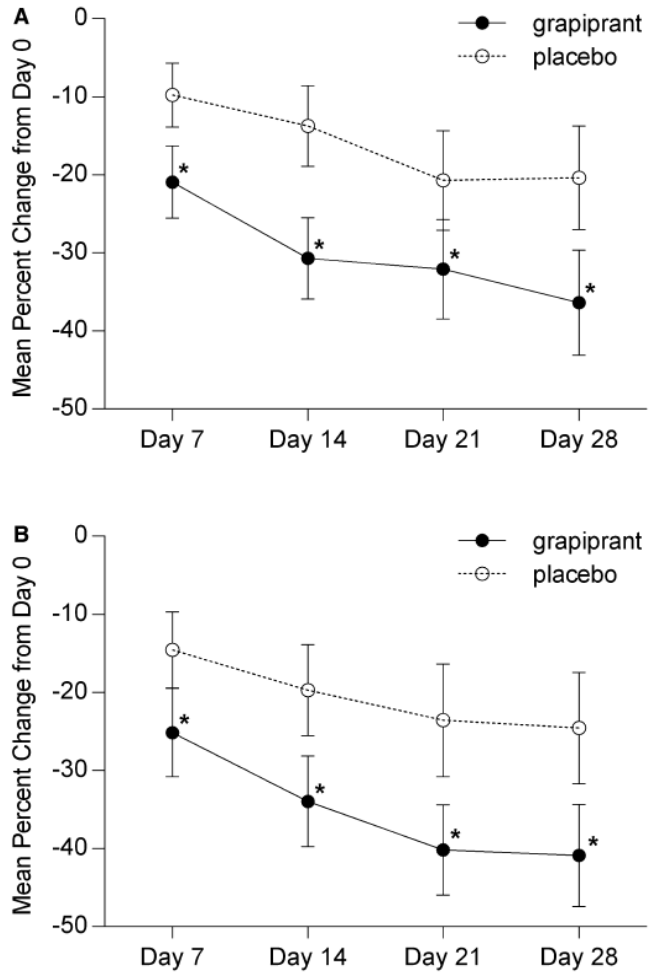


Fig 2. Mean percentage change (with 95% confidence intervals) in (**A**) pain severity score and (**B**) pain interference score scores from Day 0 to Days 7, 14, 21, and 28 in dogs treated with grapiprant (n = 131) or placebo (n = 131). *Denotes statistical significance ($P < .05$).

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

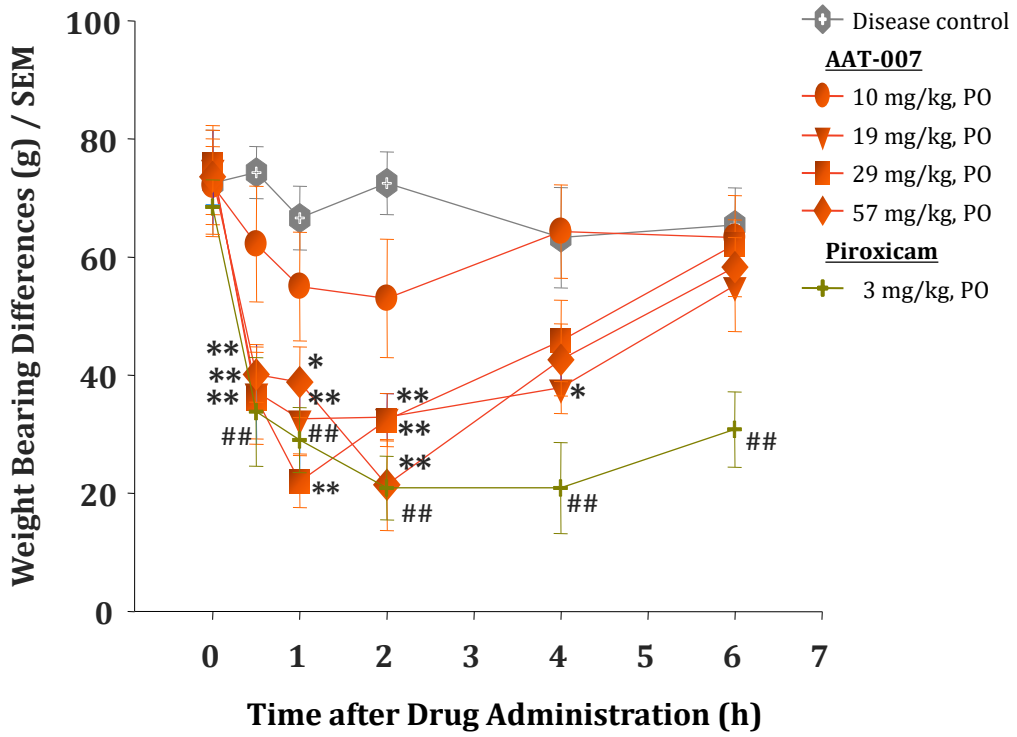
	MED (mg/kg, PO)
Carrageenan-induced foot edema	100
Adjuvant-induced arthritis for swelling	ED_{70} = 57 mg/kg[b]

[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

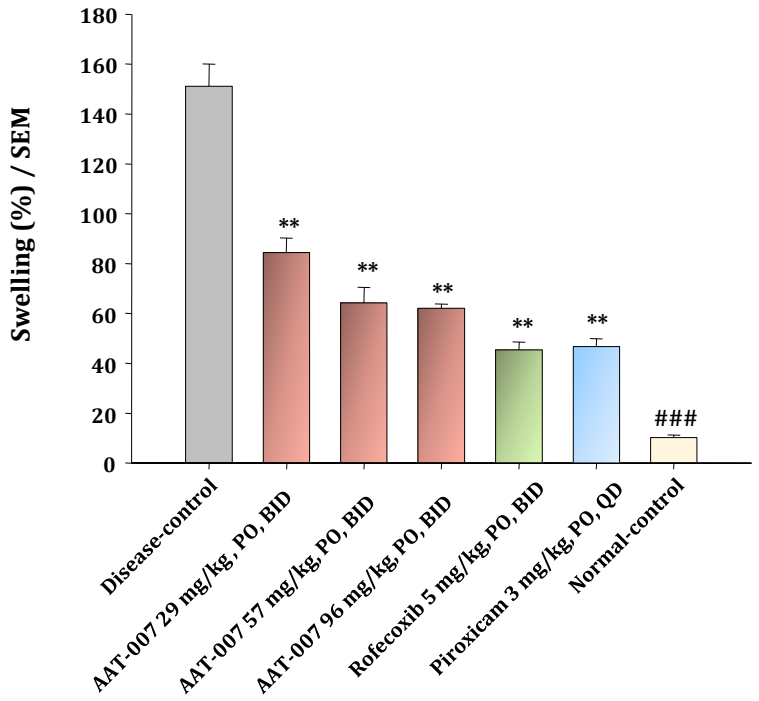
CFA was injected into the right foot pad in male SD rats. On two days after CFA injection, changes in hind paw weight distribution between the right (inflamed) and the left (contralateral) limbs were measured as an index of pain by Linton Incapacitance tester.

*: $p < 0.05$, **: $p < 0.01$ 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

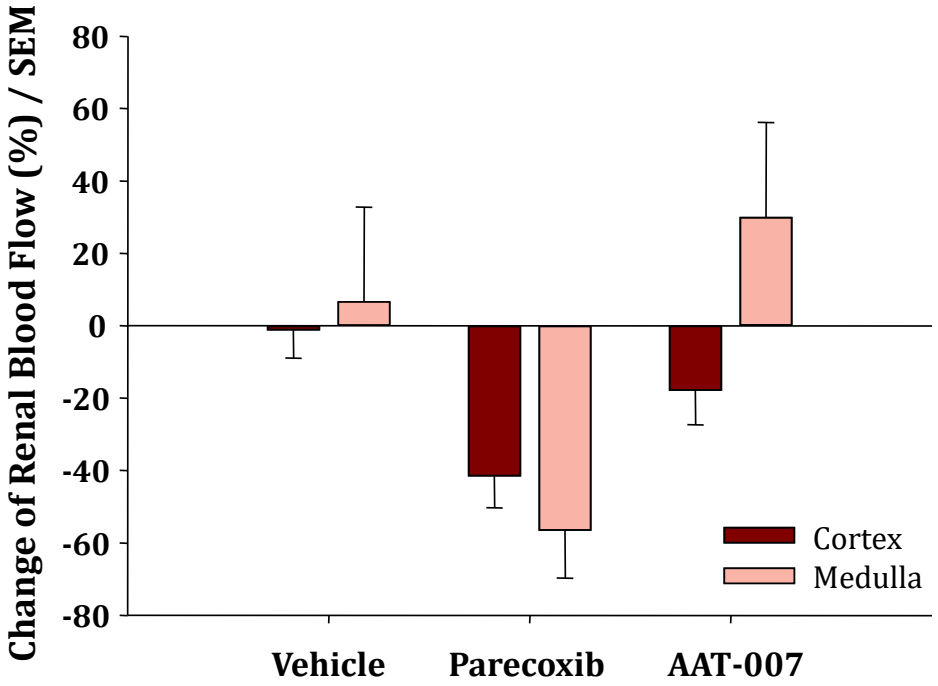
CFA was injected into the right foot pad in male Lewis rats. On 21 days after CFA injection, changes in left (contralateral) hind paw volume were measured using a plethysmometer. Drug or vehicle administration was started on day 0 and continued until on day 21.

**: $p < 0.01$ 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

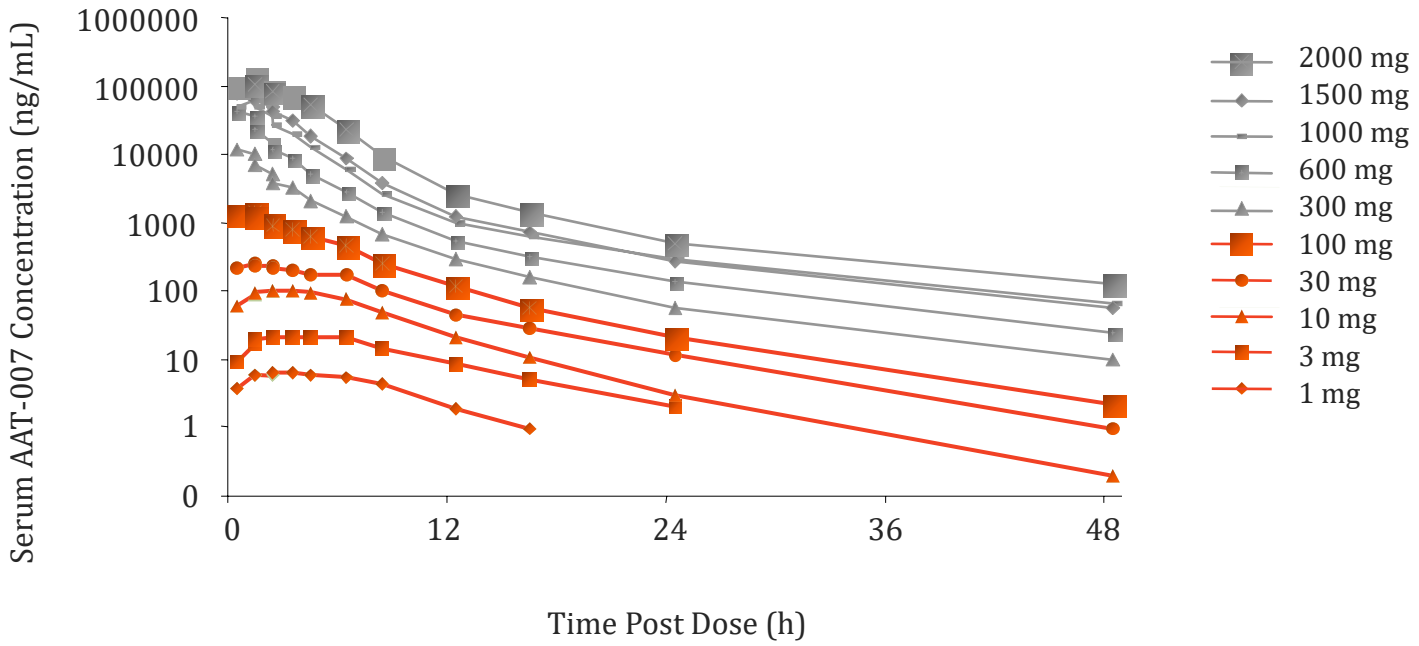
Study Type and Duration		Route of Administration	Species
Single-Dose Toxicity		PO	Rat, Dog
Repeated-Dose Toxicity	10-Day Range-Finding	PO	Rat, Dog
	1-Month	PO	Rat, Dog
	3-Month	PO	Rat
	9-Month	PO	Dog
Genotoxicity	Mutagenicity Assay (Ames)	-	Bacteria
	Clastogenicity Assay (Human Lymphocyte)	-	Human
	In 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

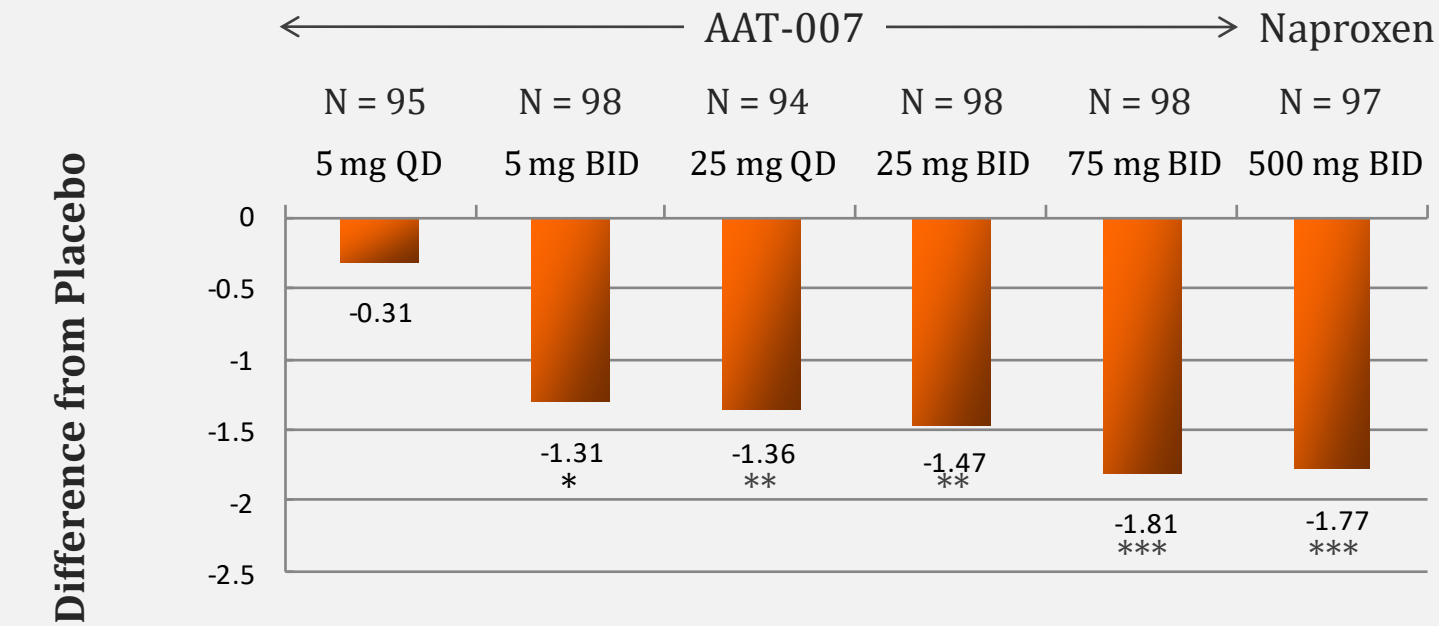
Treatment Group (Elderly)	Number of Ulcer * Subject (Incidence %)
AAT-007 (N = 63)	3 (5%)
Naproxen (N = 63)	11 (18%)
Placebo (N = 39)	1 (3%)

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.

EP4 Receptor Antagonist for Autoimmune Diseases and Allergy

Worldwide Partnering Opportunity

ASKAT

Non-confidential Information

1. Executive Summary

- Unmet Medical Need
  - Autoimmune diseases such as rheumatoid arthritis (RA), psoriasis, Crohn's disease, and multiple sclerosis (MS) represent a significant unmet medical need

- Product Concept
  - A new disease-modifying agent for the autoimmune conditions driven by cytokines such as IL-23, IL-17 and IL-6, and macrophages, dendritic cells and Th17 cells
  - A novel, orally available, and safe small molecule drug with inhibitory activity of IL-23, IL-17, and IL-6 production has the potential to displace steroids and expensive biologics
  - A stand alone and/or combination treatment with other agents such as steroid, immunosuppressants, and biologics

1. Executive Summary

- Compound Information
  - AAT-007 (grapiprant)
    - » Proof of concept in osteoarthritis (OA) pain in two Phase 2a studies
    - » Marketed worldwide as a veterinary medicine for dog OA-pain
  - AAT-008
    - » Completed non-clinical profiling, i.e., safety pharmacology, DMPK, and toxicology studies, for Phase 1 studies

- Pharmacological Profile
  - Inhibit PGE_2-induced IL-23 production in dendritic cells and PGE_2-induced IL-6 production in PBMC *in vitro*
  - Exhibit efficacy in animal models of inflammatory bowel disease (IBD), allergic contact dermatitis, and arthritis

2. Table of Contents

3. PGE_2-EP4 Signaling: Immune Activation and Autoimmune Diseases / Type IV Allergic Diseases

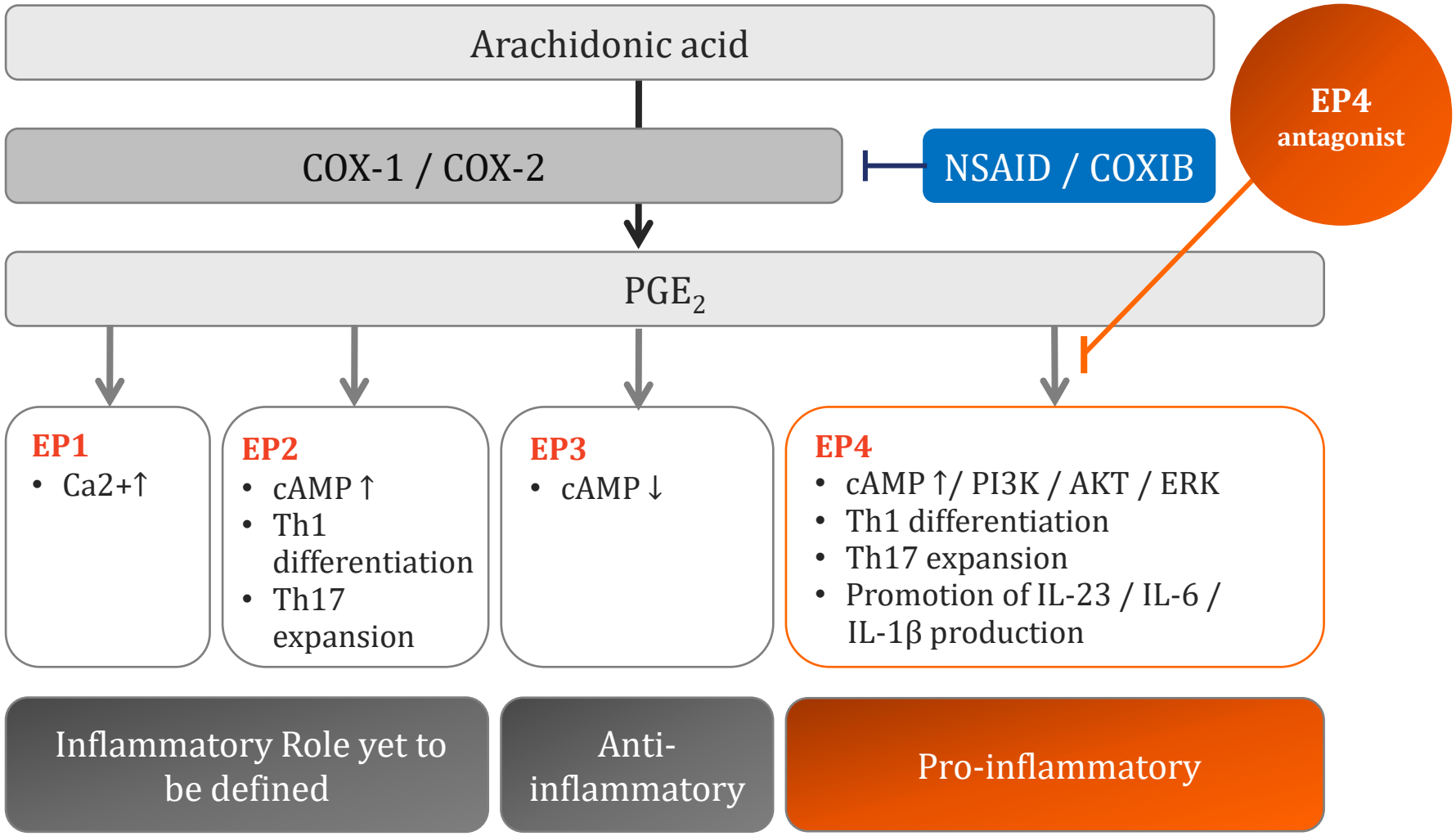
- PGE_2-EP4 signaling
  - Promotes Th1 differentiation and Th17 expansion (Ref. 1)
  - Induces IL-23 production, which promotes Th17 expansion and inhibits Treg differentiation (Ref. 1-2)
  - Induces IL-6 production in T cell (Ref. 3)

- In mice
  - EP4 antagonists exhibited efficacy in MS, allergic contact dermatitis and arthritis models (Ref. 1, 4 and 17)
    - » Oral administration of EP4 antagonist suppressed Th1 and Th17 cytokine production
  - Homozygous deletion of the EP1, EP2, or EP3 receptor did not affect the development of arthritis, whereas EP4 -/- mice showed decreased incidence and severity of disease (Ref. 5)
    - » Joint histopathology of EP4 -/- animals revealed reduced bone destruction, proteoglycan loss, and type II collagen breakdown in cartilage
    - » EP4 -/- animals showed reduced inflammation as assessed by circulating IL-6 and serum amyloid A levels
    - » Liver and macrophages isolated from EP4 -/- animals produced significantly less IL-1β and IL-6

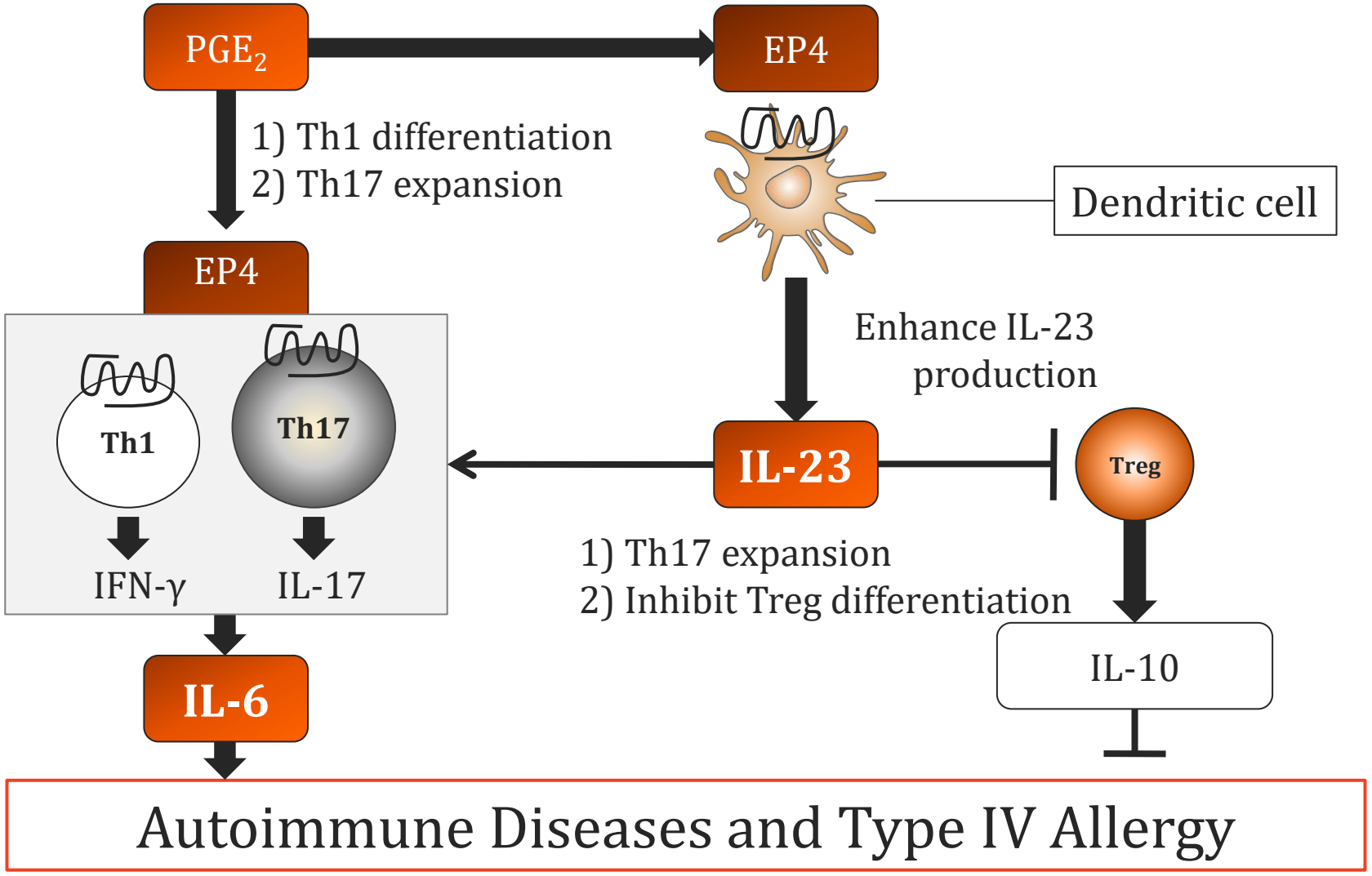
4. Down Stream to PGE_2-EP4 Signaling

- In human
  - Increased producton of IL-23 and IL-17 is reportedly associated with RA, psoriasis, and allergic contact dermatitis (Ref. 6-10)
  - Anti-IL-17A antibody or anti-p40 antibody that neutralizes IL-12 and IL-23 demonstrated clinical efficacy in patients with psoriasis, psoriatic arthritis and IBD (Ref. 11-13)
  - Dosing with antibody to IL-6 receptor led to a significant clinical efficacy in RA patients (Ref. 14)

5. Pro-Inflammatory Signaling via PGE_2-EP4 Receptor



6. PGE_2-EP4 Signaling and Immune Activation



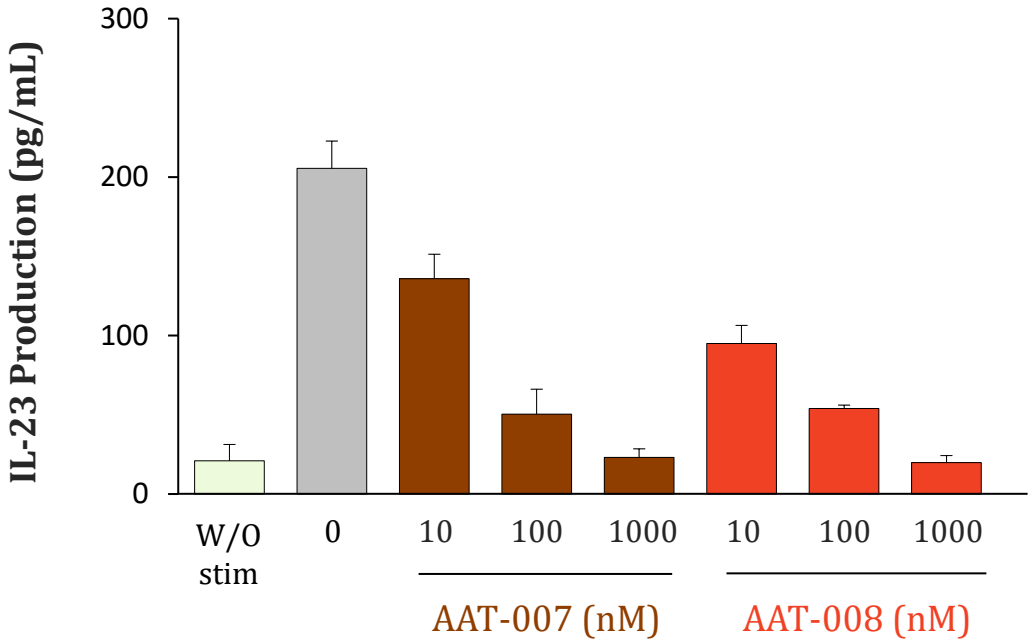
7. Non-Clinical Pharmacology

7.1. *In vitro* Pharmacology Summary

- AAT-007
  - Human EP4 binding K_i — 13 nM
  - Human functional pA_2* — 8.3
  - Mouse IL-23 production (IC_{50}) — 16 nM
  - Human IL-23 production (IC_{50}) — 2.4 nM
  - Human IL-6 production (IC_{50}) — 75 nM
  - Selectivity — >200-fold against over 100 enzymes and receptors
- AAT-008
  - Human EP4 binding K_i — 0.97 nM
  - Human functional pA_2* — 9.0
  - Mouse IL-23 production (IC_{50}) — <10 nM
  - Human IL-23 production (IC_{50}) — 8.7 nM
  - Selectivity — >1000-fold against over 100 enzymes and receptors

* Inhibition of PGE_2-induced cAMP elevation

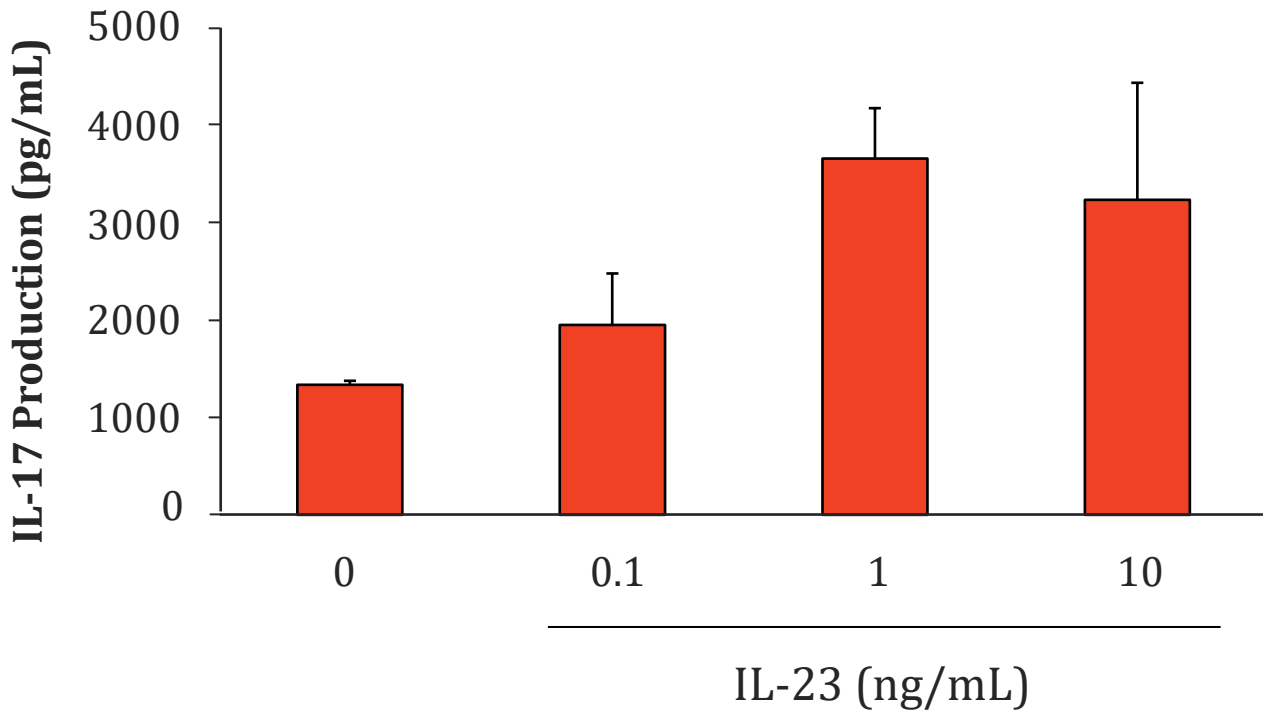
7.2. IL-23 Production in Mouse CD11c (+) Cells



Mouse splenic CD11c (+) cells were incubated with 100 nM PGE_2 and 10 µg/mL anti-CD40 for 36 hrs. The supernatant was subjected to IL-23 ELISA. Data represent mean + SD (N = 3).

AAT-007 & AAT-008 inhibited IL-23 production in mouse CD11c (+) cells.

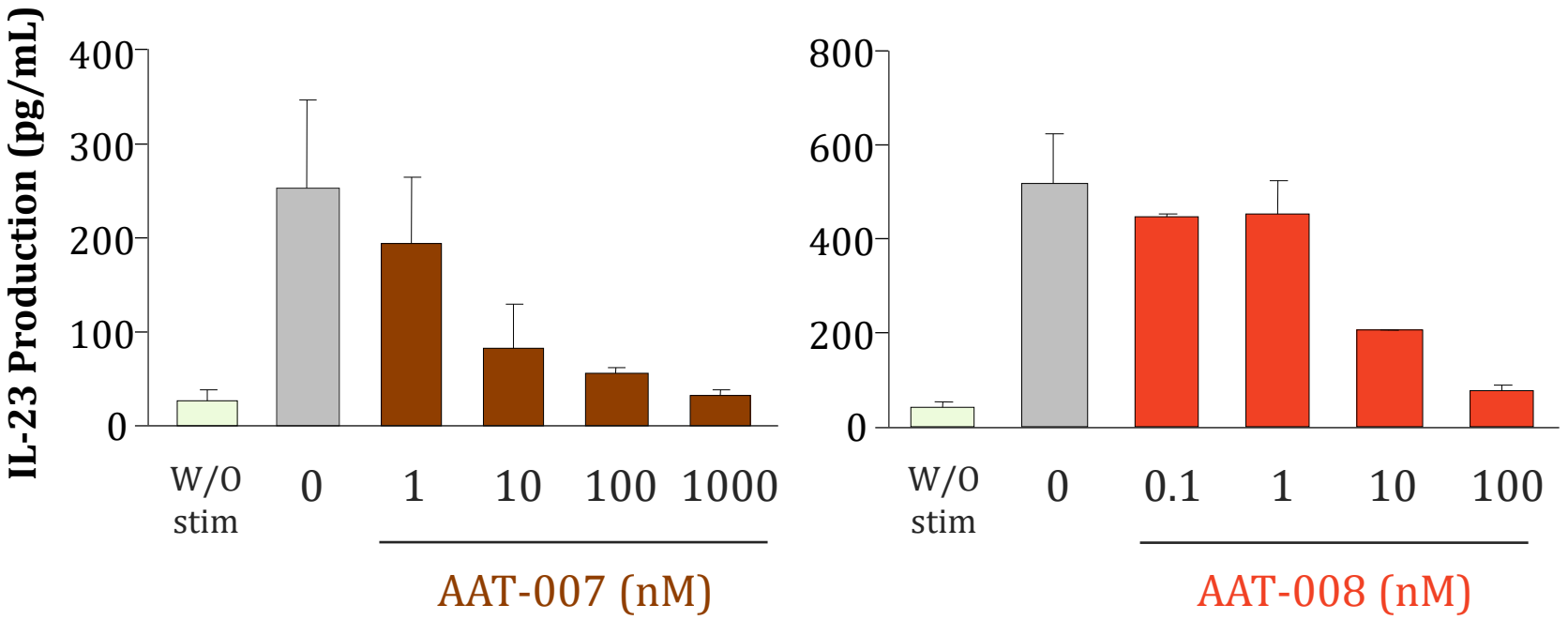
7.3. IL-17 Production in Mouse IL-17 (+) cells



Mouse splenic naïve T cells were incubated with IL-23, 1 ng/mL TGF-β, 50 ng/mL IL-6, and 5 μg/mL anti-IL-4 antibody for 96 hrs. The supernatant was subjected to IL-17 ELISA. Data represent mean + SD (N = 3).

IL-23 enhanced IL-17 production in mouse IL-17 (+) T cells.

7.4. IL-23 Production in Human Dendritic Cells

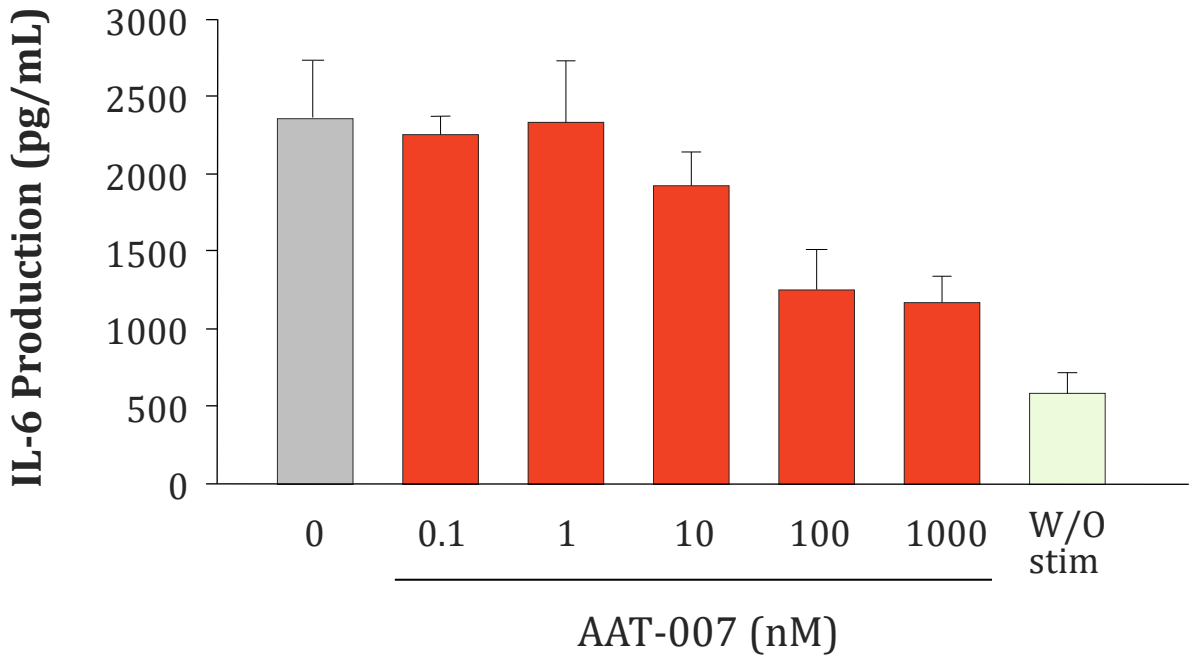


Dendritic cells from Human peripheral blood mononuclear cells (PBMCs) were incubated with 100 nM PGE1-OH, 10 ng/mL LPS, and 2.5 µg/mL R-848 for 24 hrs.

The supernatant was subjected to human IL-23 ELISA. Data represent mean + SD (N = 2-3).

AAT-007 & AAT-008 dose-dependently inhibited IL-23 production in human dendritic cells.

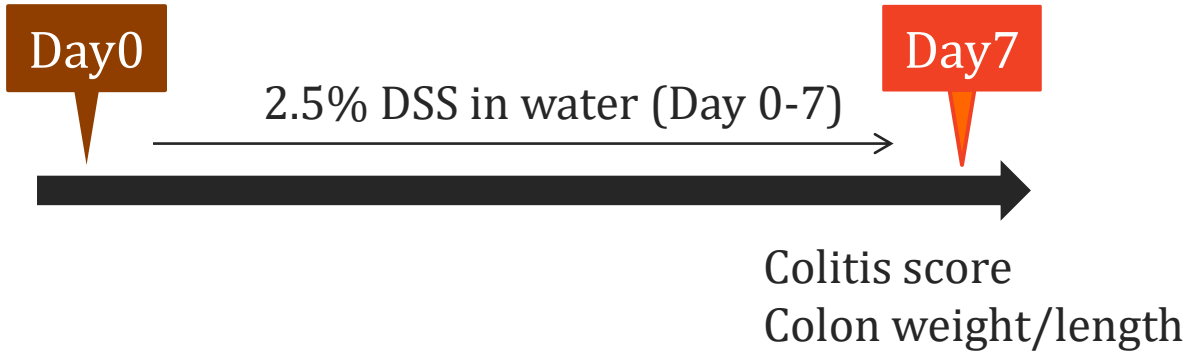
7.5. IL-6 Production in Human PBMC



PBMCs were incubated with 100 nM PGE_2 and 5 µg/mL Concanavalin A (ConA) for 24 hrs. The supernatant was subjected to IL-6 ELISA. Data represent mean + SD (N = 3).

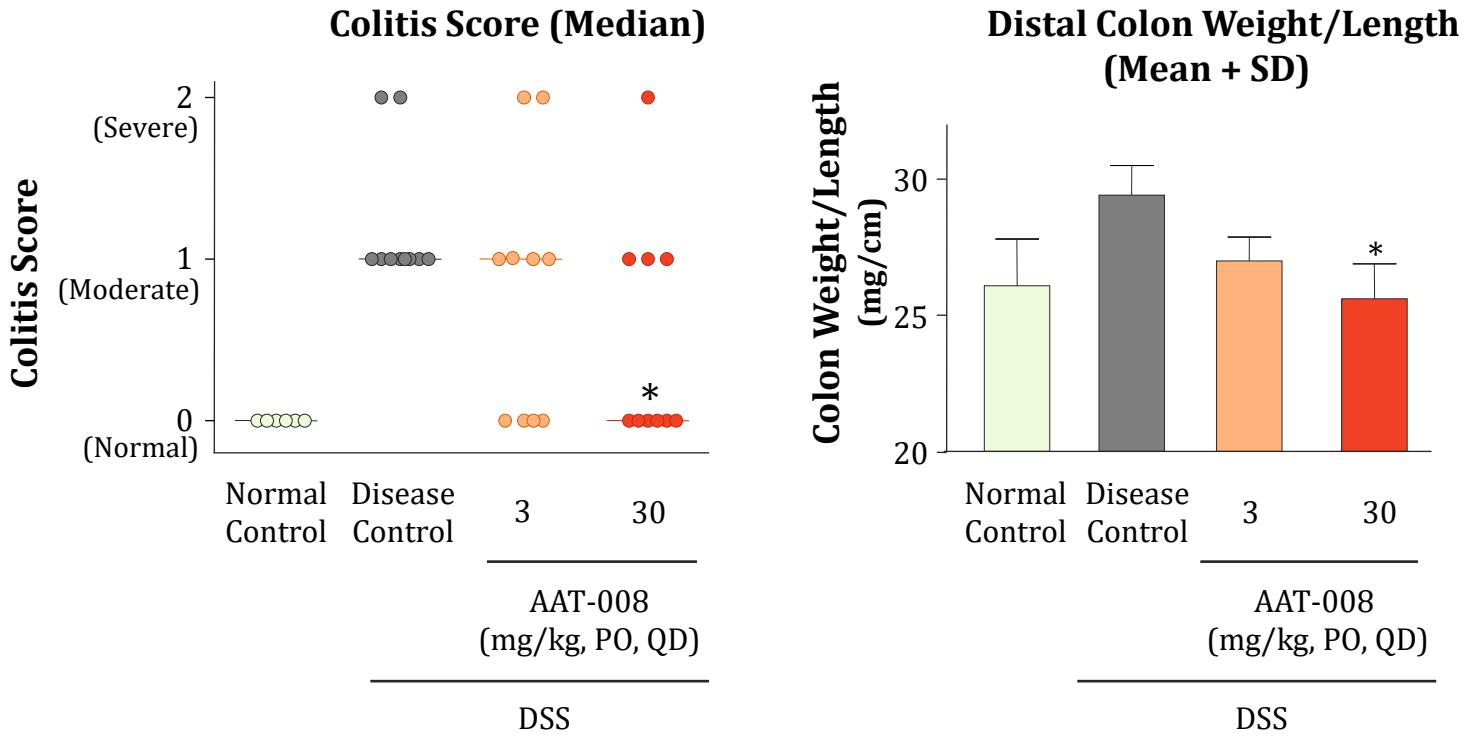
AAT-007dose-dependently inhibited IL-6 production in human PBMC

7.6. Dextran Sulfate Sodium (DSS)-Induced Colitis Model in Mice



Model	A well-characterized, non-clinical model of IBD
Dose (Duration)	AAT-008: 3, 30 mg/kg, PO, QD (Day 0-6)
Endpoint	Colitis score, colon weight/length
Aggravation of symptoms	Indomethacin (Ref. 15)

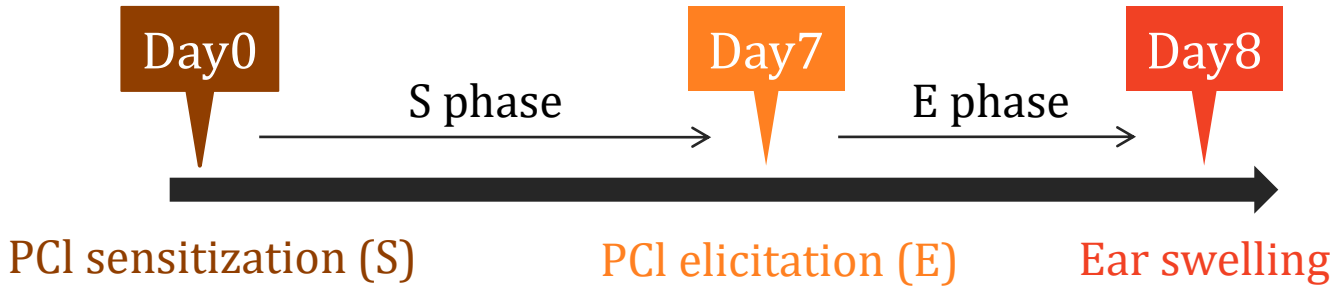
7.6. DSS-Induced Colitis in Mice



* p <0.05 versus disease control by Mann-Whitney test (N = 6-10)

AAT-008 at 30 mg/kg significantly decreased colitis score and colon weight/length.

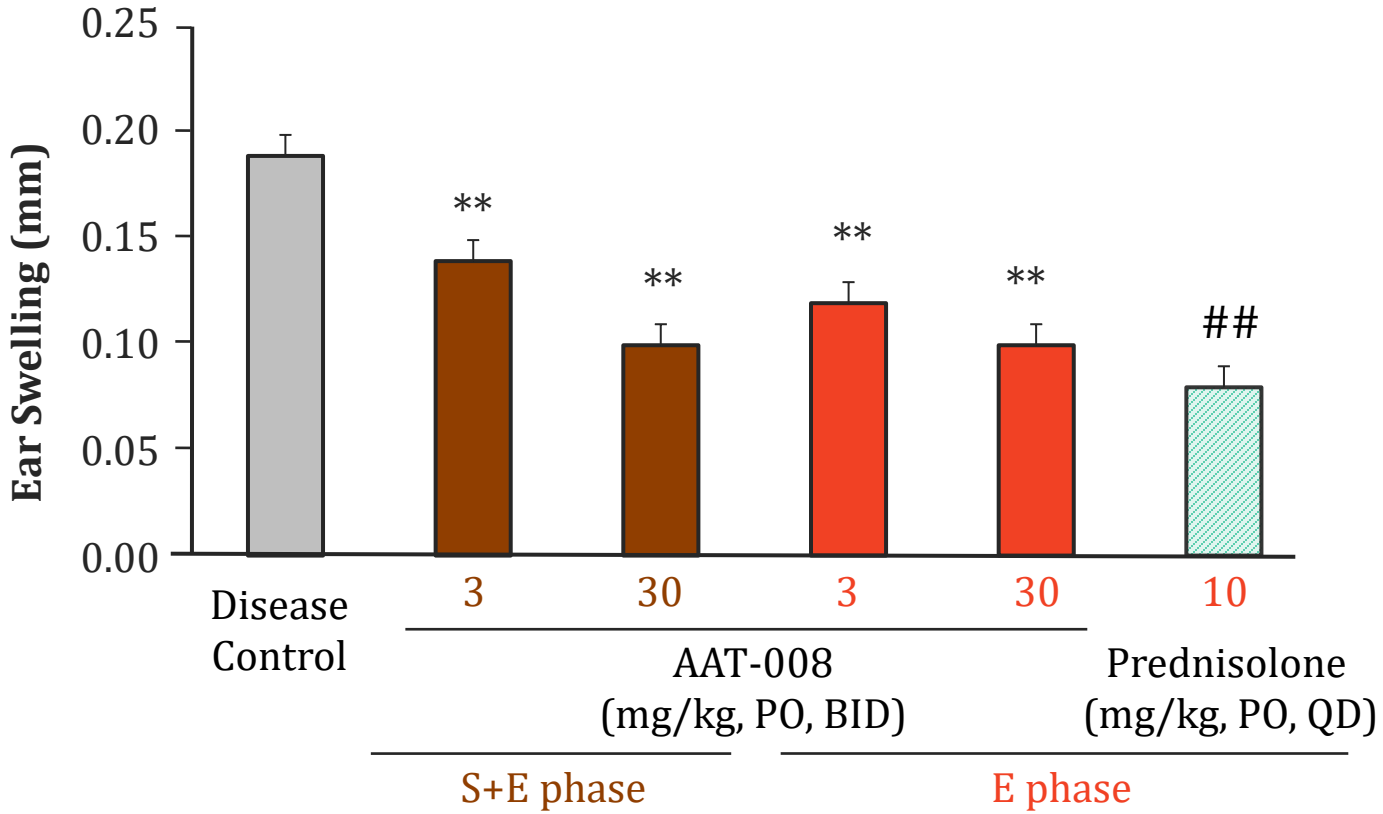
7.7. Picryl Chloride (PCl)-Induced Contact Hypersensitivity (CHS) Model in Mice



S phase: Promotion of Th1 differentiation
E phase: Induction of Th1 immune response = psoriasis-like model

Model	A well-characterized allergic contact dermatitis model, which is also utilized as non-clinical model of psoriasis
Dose (Duration)	AAT-008: 3, 30 mg/kg, PO, BID (S+E: day0-8, E: day7-8) Prednisolone: 10 mg/kg, PO, QD (E: day7)
Endpoint	Ear swelling (24 hrs after elicitation)
Aggravation of symptoms	Indomethacin, EP3 -/- mice (Ref. 16)

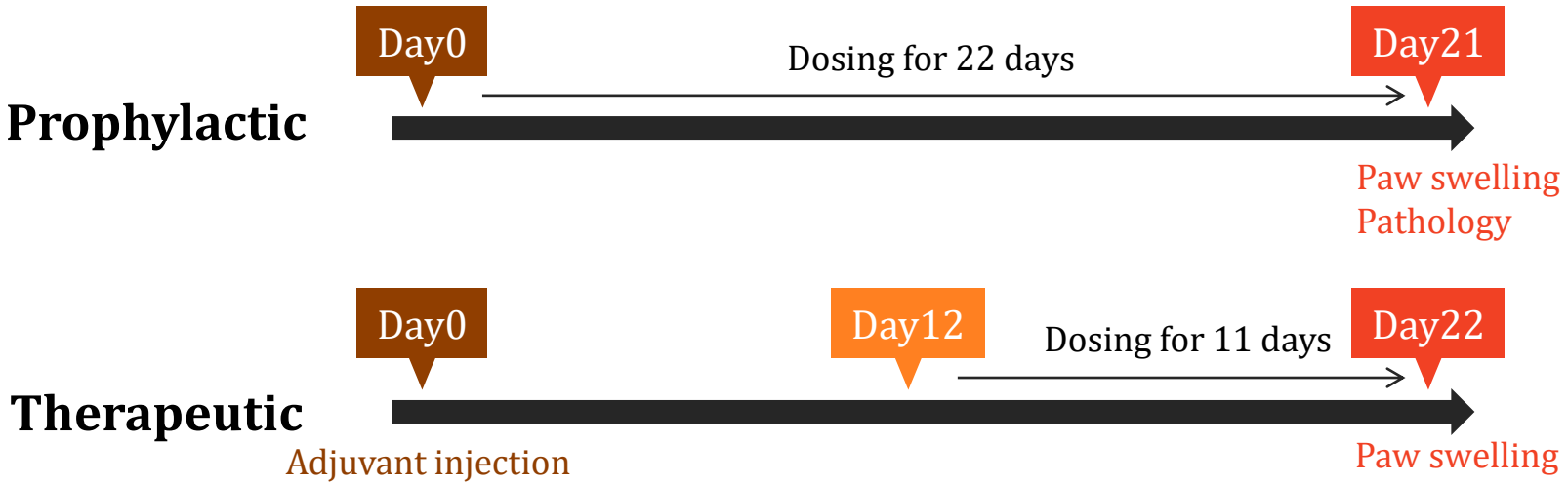
7.7. PCl-Induced CHS in Mice



Data represent mean + SE (N = 10)
** p <0.01 versus disease control by Dunnett's test
p <0.01 versus disease control by t-test

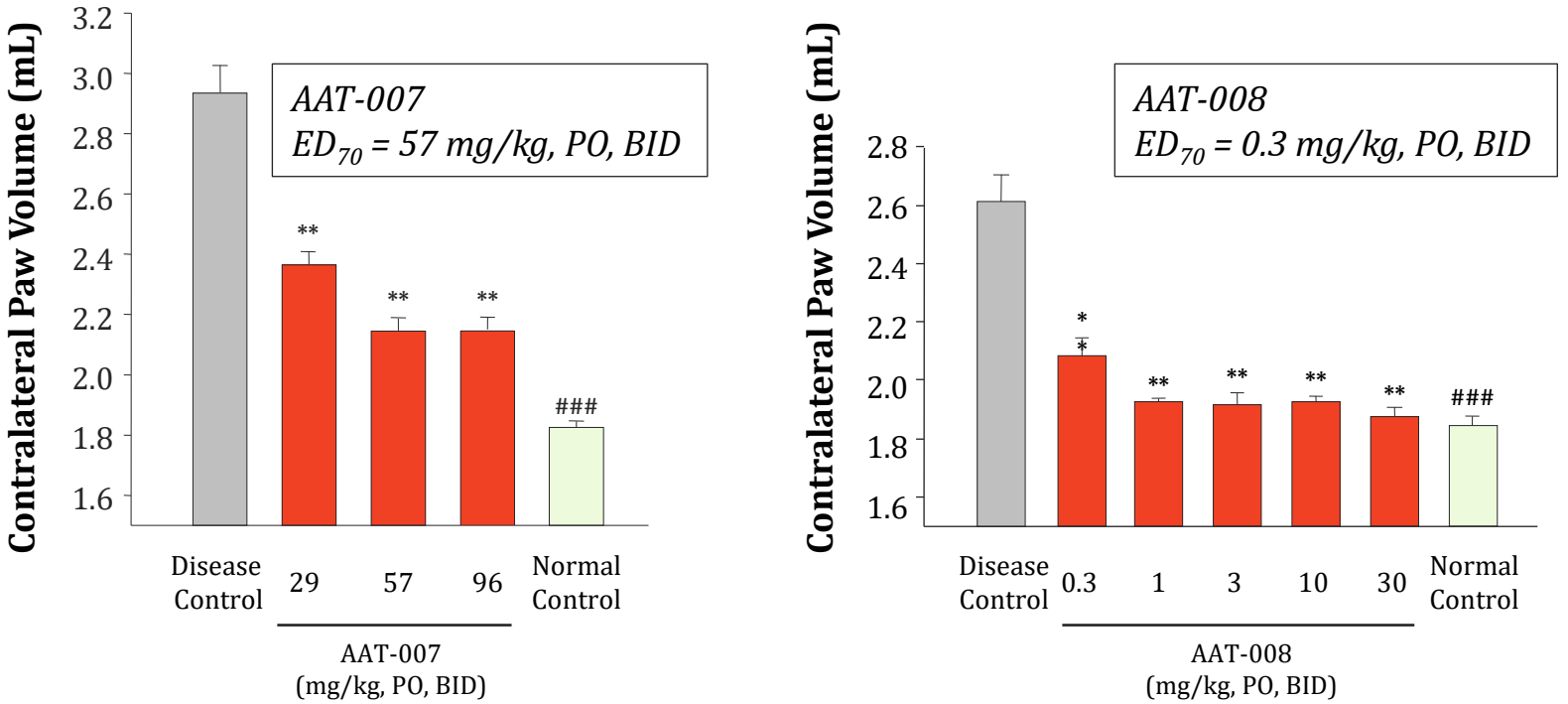
AAT-008 at both doses significantly decreased ear swelling.
The maximum efficacy of AAT-008 at 30 mg/kg was equal to that of prednisolone.

7.8. Adjuvant-Induced Arthritis Model in Rats



Model	A well-characterized rat poly-arthritis model, which is also utilized as non-clinical model of rheumatoid arthritis
Dose (Duration)	Prophylactic (for 22 days) treatment AAT-007: 29, 57, 96 mg/kg, PO, BID Prophylactic (for 22 days) or therapeutic (for 11 days) treatment AAT-008: 0.3, 1, 3, 10, 30 mg/kg, PO, BID
Endpoint	Paw swelling, Pathology (Prophylactic treatment)

7.8. Paw Swelling in Rats with Adjuvant-Induced Arthritis - Prophylactic Treatment -

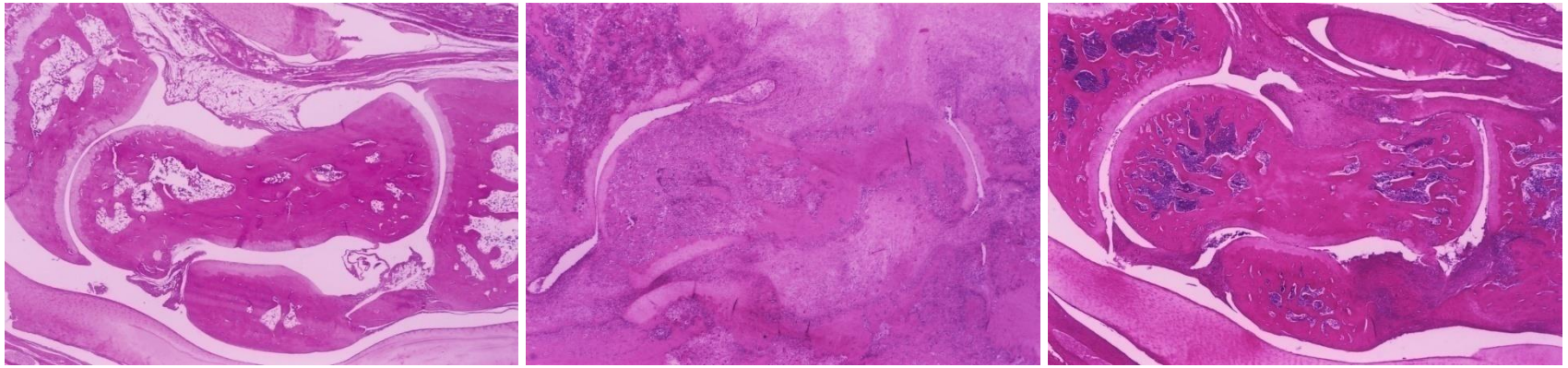


Data represent mean + SE (N = 8)
** p <0.01 versus disease control by One-way ANOVA, Dunnett post test
p <0.001 versus disease control by t-test

AAT-007 and AAT-008 suppressed paw swelling in the rat adjuvant-induced arthritis with ED_{70} of 57 and 0.3 mg/kg, PO, respectively.

7.8. Histopathology of Foot of Rats with Adjuvant-Induced Arthritis - Prophylactic Treatment -

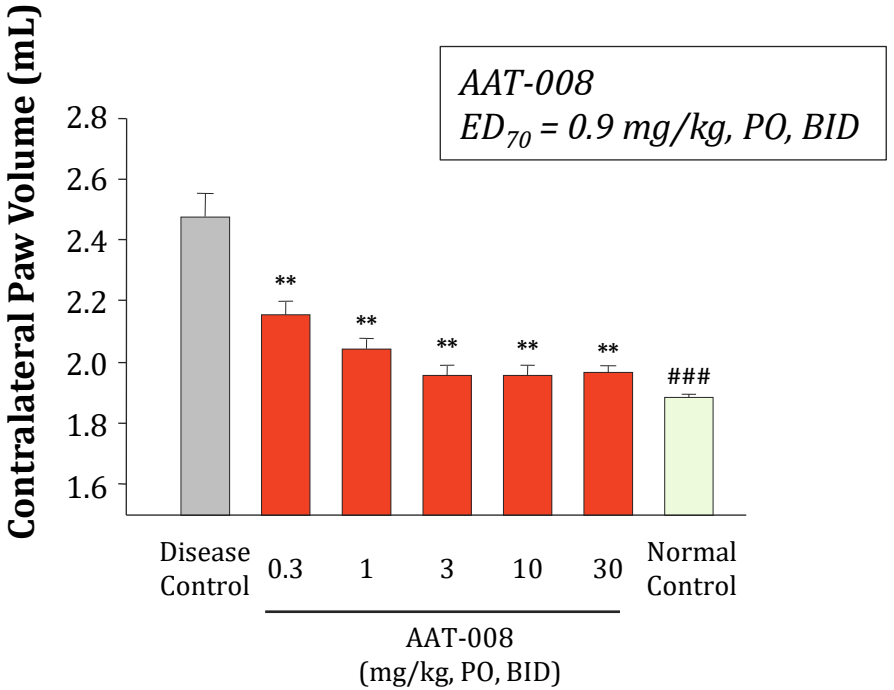
Normal control	Disease control	AAT-008 30 mg/kg, PO, BID



Photomicrographs of representative tarsal joint sections from contralateral foot stained with H&E (x 20)

AAT-008 inhibited bone erosion and synovial inflammation in the rat adjuvant-induced arthritis.

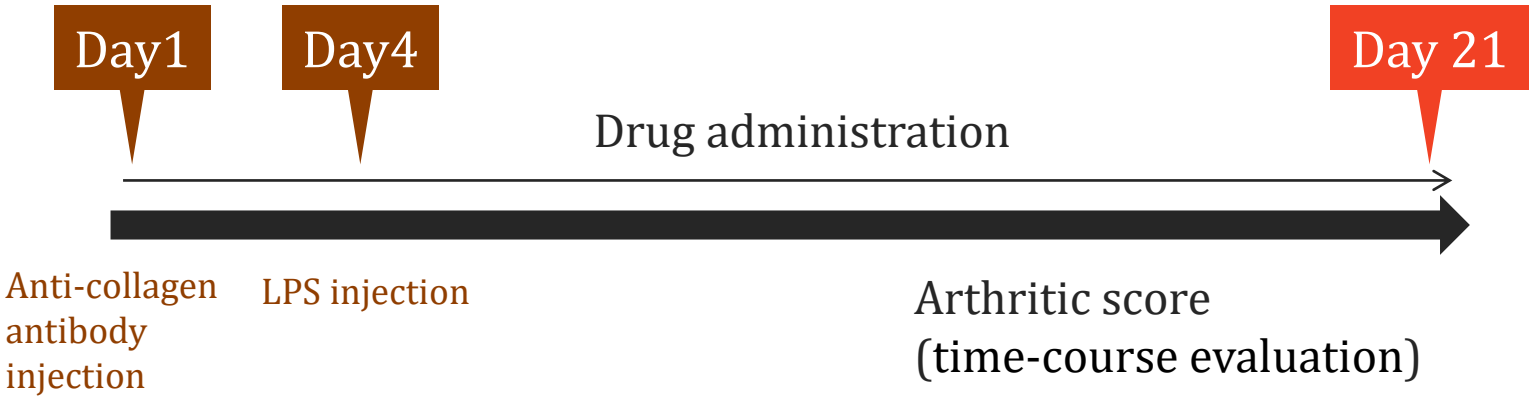
7.8. Paw Swelling in Rats with Adjuvant-Induced Arthritis - Therapeutic Treatment -



Data represent mean + SE (N = 8)
** p <0.01 versus disease control by One-way ANOVA, Dunnett post test
p <0.001 versus disease control by t-test

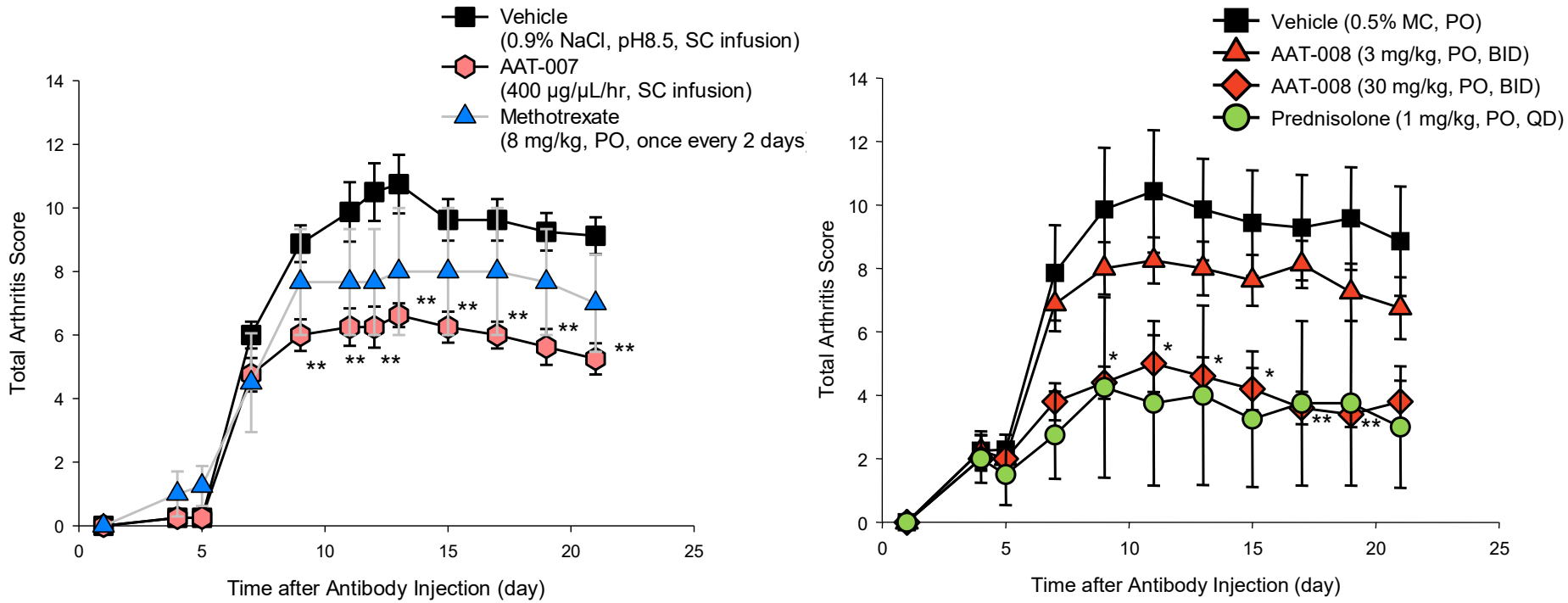
AAT-008 suppressed paw swelling in the rat adjuvant-induced arthritis with ED_{70} of 0.9 mg/kg, PO, BID.

7.9. Collagen Antibody-Induced Arthritis in Mice



Model	A well-characterized mouse poly-arthritis model, which is also utilized as non-clinical model of rheumatoid arthritis
Dose (Duration)	AAT-007: 400 µg/µL/hr, continuously SC injection using osmotic pump (ALZET, #2001) from Day0 to Day21. AAT-008: 3, 30 mg/kg, PO, BID from Day1 to Day21.
Endpoint	Total arthritic score: sum of arthritic score by each paw (as maximum 16 points)
Positive control	Prednisolone: 1 mg/kg, PO, QD from Day1 to Day21. Methotrexate: 8 mg/kg, PO, once every 2 days from Day1 to Day21.

7.9. Collagen Antibody-Induced Arthritis in Mice



Data represent mean +/- SEM (N = 3-8).
##: $p<0.01$ versus disease control group by t-test, *: $p<0.05$, **: $p<0.01$ versus disease control group by One-way ANOVA, Bonferroni test.

AAT-007 and AAT-008 suppressed total arthritis score in the mouse collagen antibody-induced arthritis.

8. Potential Indications for EP4 Antagonist

Pharmacological activities of EP4 antagonists support multiple therapeutic opportunities

	IBD	Psoriasis	RA	MS	Type IV Allergy
Animal Model	DSS-Induced Colitis	PCl-Induced CHS	Adjuvant Arthritis, Collagen Antibody-Induced Arthritis		PCl-Induced CHS
Mechanism	Down regulation of immune responses, e.g., Inhibition of IL-6, IL-23, and IL-17 Production				

EP4 antagonists provide attractive opportunities for the treatment of autoimmune diseases and type IV allergic diseases.

9. IP Status of EP4 Antagonist, AAT-007 and AAT-008

Patent	Int'l Publication No. (Int'l Application No.)	Int'l Filing Date	Status as of January 28, 2026
AAT-007 Crystal Forms	WO 2006/095268 (PCT/IB2006/000754)	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
AAT-007 & AAT-008 Use for Immune	WO 2011/102149 (PCT/JP2011/000994)	February 22, 2011	Granted: CA, EP (FR, DE, GB, IT, IE, ES), JP, KR, MX, RU, US Under examination: BR, BR-Div.
AAT-007 Synthesis Thereof (Impurity)	WO 2020/014445 (PCT/US2019/041351)	July 11, 2019	Granted: - Under examination: US
AAT-007 Additional Crystal Forms	WO 2020/014465 (PCT/US2019/041378)	July 11, 2019	Granted: US

* Five-year patent term extension for Galliprant: GB, FR, DE, IE, IT, ES, GR, PL, NL, BE, JP, US

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1. Yao C, Sakata D, Esaki Y, *et al.* (2009). Prostaglandin E_2-EP4 signaling promotes immune inflammation through T_H1 cell differentiation and T_H17 cell expansion. *Nat Med* **15**: 633-640.
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3. Zeng LI, AN S, Goetzl EJ, *et al.* (1998). EP_4/EP_2 Receptor-Specific Prostaglandin E_2 Regulation of Interleukin-6 Generation by Human HSB.2 Early T Cells. *J Pharmacol Exp Ther* **286:** 1420-1426.
4. Kabashima K, Sakata D, Nagamachi M, *et al*. (2003). Prostaglandin E_2-EP4 signaling initiates skin immune response by promoting migration and maturation of Langerhans cells. *Nat Med* **9**: 744-749.
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8. Kotake S, Udagawa N, Takahashi N, *et al*. (1999). IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest* **103**: 1345-1352.
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11. Mark S, Kate M Drugs (2015). Secukinumab: First Global Approval. *Drugs* **75**: 329-338
12. Krueger GG, Langley RG, Leonardi C, *et al.* (2007). A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* **356**: 580-592.

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13. Sandborn WJ, Feagan BG, Fedorak RN, et al. (2008). A Randomized Trial of Ustekinumab, a Human Interleukin-12/23 Monoclonal Antibody, in Patients With Moderate-to-Severe Crohn's Disease. Gastroenterology 135: 1130-1141.

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15. Kabashima K, Saji T, Murata T, *et al*. (2002). The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. *J Clin Invest* **109**: 883-893.

16. Honda T, Matsuoka T, Ueta M, *et al*. (2009). Prostaglandin E_2-EP_3 signaling suppresses skin inflammation in murine contact hypersensitivity. *J Allergy Clin Immmol* **124**: 809-818.

17. Chen Q, Muramoto K, *et al*. (2010). A novel antagonist of the prostaglandin E(2) EP(4) receptor inhibits Th1 differentiation and Th17 expansion and is orally active in arthritis models. *Br J Pharmacol* **160**: 292-310

11. Appendixes, Table of Contents

12.1. Compound Information of AAT-007

- Compound Code
  - AAT-007 (grapiprant, RQ-00000007, CJ-023423)

- 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 clinical studies

12.2. 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

AAT-007 is >200-fold selective against other prostanoid receptors

12.3. 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

12.4. 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

11.5. Non-Clinical Toxicology Studies of AAT-007

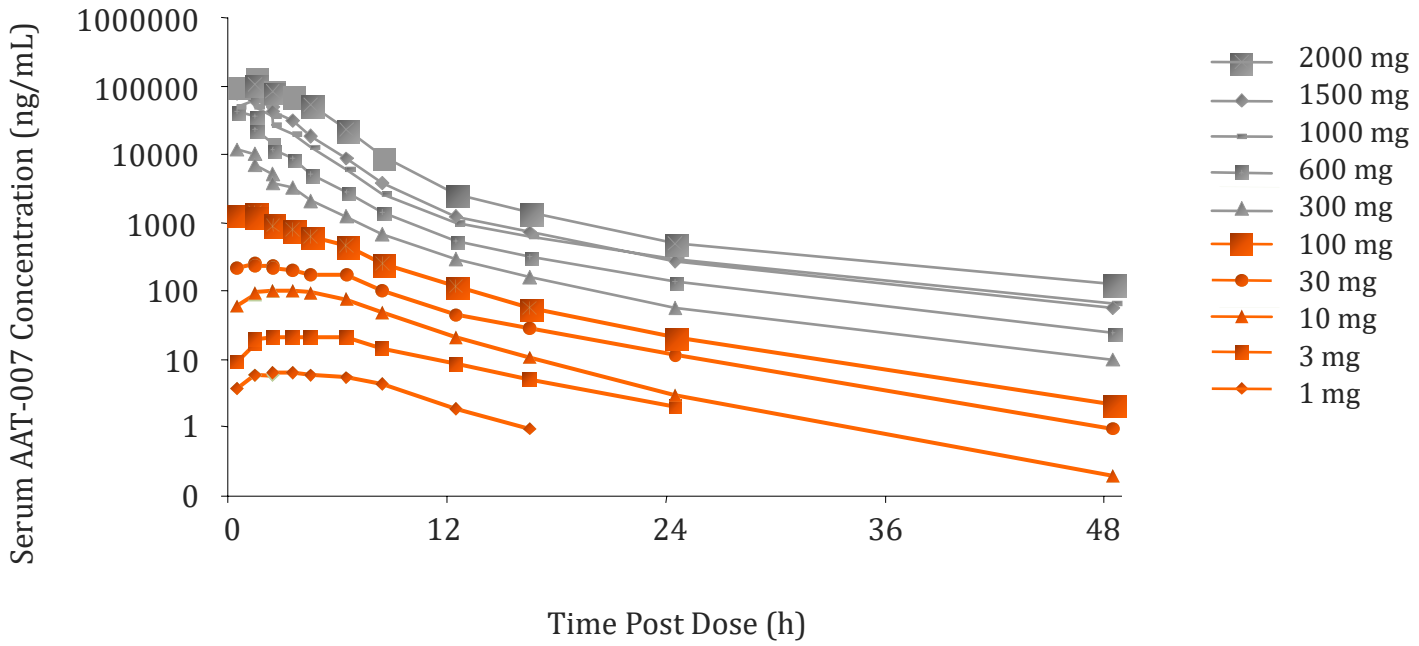
Study Type and Duration		Route of Administration	Species
Single-Dose Toxicity		PO	Rat, Dog
Repeated-Dose Toxicity	10-Day Range-Finding	PO	Rat, Dog
	1-Month	PO	Rat, Dog
	3-Month	PO	Rat
	9-Month	PO	Dog
Genotoxicity	Mutagenicity Assay (Ames)	-	Bacteria
	Clastogenicity Assay (Human Lymphocyte)	-	Human
	In 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

13.1. 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)

13.2. 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



13.2. 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

13.3. 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

14.1. Compound Information of AAT-008

- Compound Code
  - AAT-008 (RQ-00000008, CJ-043346)

- 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

14.2. Non-Clinical Safety Pharmacology Studies of AAT-008

Study Type			Route of Administration	Species
Core Battery	CNS		PO	Rat
	CVS		PO	Dog
	Respiratory System		PO	Rat
	CVS	hERG Assay	-	Human
Supplemental	Broad Ligand Assay		-	Human

14.3. Non-Clinical Pharmacokinetic Studies of AAT-008

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	Plasma Protein Binding	-	Rat, Dog, Monkey, Human
	RBC Partitioning (Blood / Plasma Ratio)	-	Rat, Dog, Human
	Brain Penetration	PO	Rat
Metabolism	*In vivo* Metabolism	IV	Rat
	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

14.4. Non-Clinical Toxicology Studies of AAT-008

Study Type and Duration		Route of Administration	Species
Repeated-Dose Toxicity	4-Day Tolerance	PO	Rat, Dog
	10-Day Range-Finding	PO	Rat, Dog
	1-Month	PO	Rat, Dog
Genotoxicity Carcinogenicity	Mutagenicity Assay (Ames)	-	Bacteria
	Clastogenicity Assay (Human Lymphocyte)	-	Human
	In vivo Micronucleus Assay	PO	Rat

15. 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.

16. Publication List of AAT-008

1. Okumura Y, Yamagishi T, Nukui S and Nakao K (2017) Discovery of AAT-008, a novel, potent, and selective prostaglandin EP4 receptor antagonist. *Bioorg Med Chem Lett* **27(5)**:1186-1192.

The Chondroprotective Effect of EP4 Antagonists

ASKAT

2026, AskAt Inc.

Non-confidential Information

Summary

- AAT-007 and AAT-008 (both EP4 antagonists) inhibited release of a catabolic biomarker in a bovine cartilage explant model without loss of cell viability.

- Evaluation of the observed chondroprotective effects using appropriate biomarkers in clinical studies will determine the therapeutic significance and potential differentiation of EP4 antagonist from COX-2 and NSAIDs.

Chondroprotective effects of AAT-007 and AAT-008

- Effects of AAT-007 and AAT-008 on cartilage turnover were investigated using a bovine cartilage explant model *in vitro*.

- AAT-007 and AAT-008 are referred to as RQ-007 and RQ-008, respectively.

Bovine cartilage explant study - Method

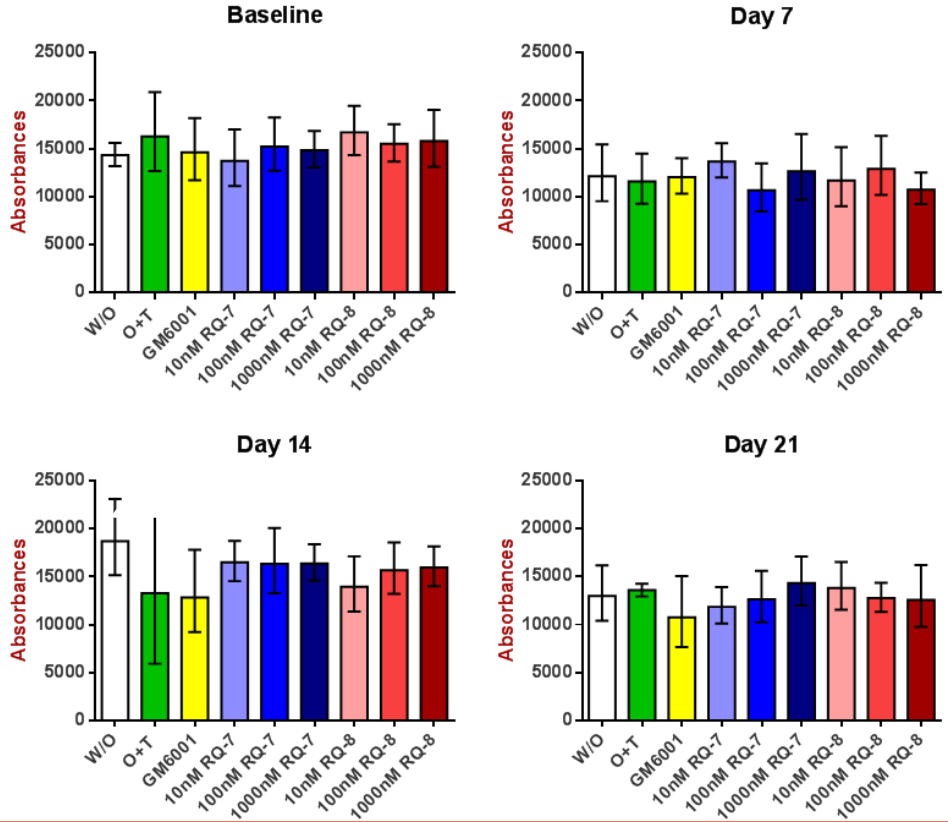
Experimental procedures:

- Full length cartilage (FDC) was excised from the knee of either of back legs of a cow aged less than 24 months.
- Those FDC explants were divided into treatment groups based on explant weight and metabolic activity (viability) measured by Alamar Blue in D-MEM/F-12.
- The explants were cultured in serum-free medium containing 10 ng/mL Oncostatin M and 20 ng/mL TNFα (O+T) on Day 0.
- 10, 100 and 1000 nmol/L of AAT-007 and AAT-008, or 10 μM of GM6001 (positive control, MMPs inhibitor) were freshly added to the explants at each media change (on Days 3, 5, 7, 10, 12, 14, 17, 19, and 21).
- Supernatants were collected from the culture at the time of media change and subjected to biomarkers analysis.
  a. P2NP: cartilage formation
  b. C2M: MMP-mediated type II collagen degradation
  c. AGNx1: Aggrecanase mediated aggrecan degradation
  d. AGNx2: MMP-mediated aggrecan degradation

Bovine cartilage explants study - Results

- **Cell viability**

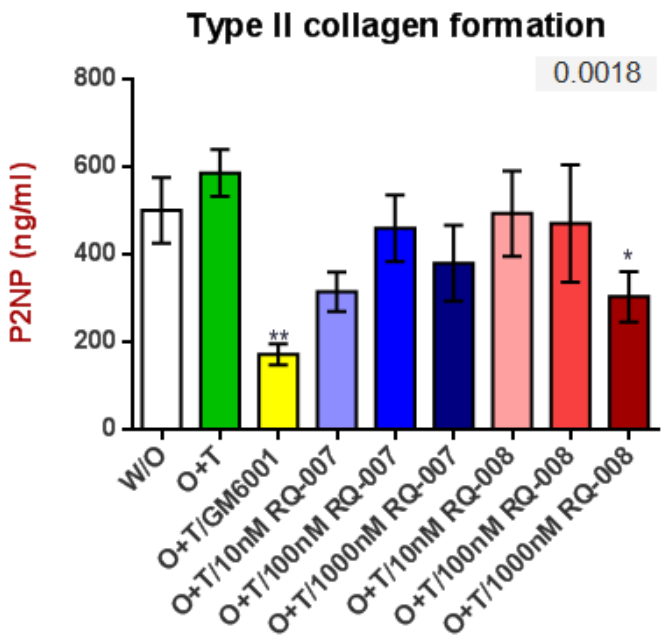
Chondrocyte viability was measured by Alamar Blue® by directly adding to the explants on baseline (pre compound treatment), Days 7, 14 and 21 (termination).



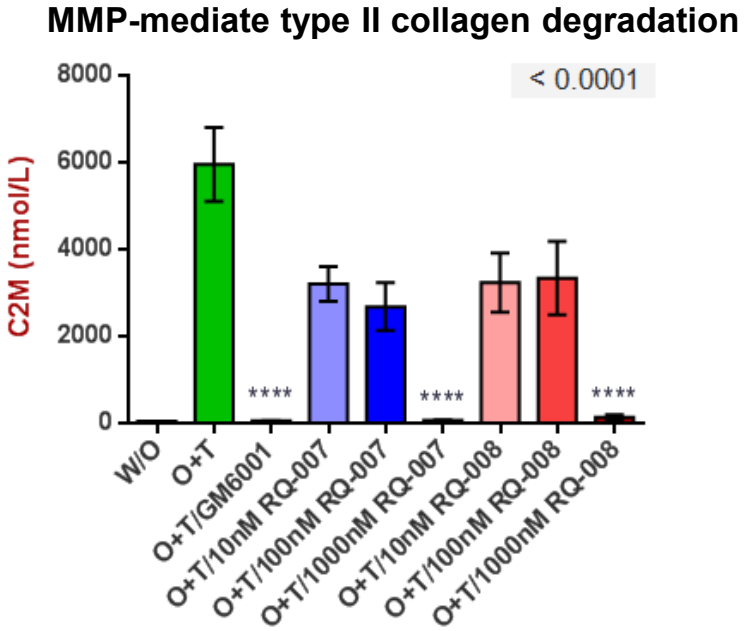
Neither AAT-007 nor AAT-008 affected the cellular viability following 21 days culture.

Bovine cartilage explants study - Results

- **Type II collagen turnover biomarkers**



Accumulated release of P2NP to the conditioned medium. P-value of the ANOVA test is shown in the right-hand corner. * p<0.05 and ** p<0.01. Mean±SEM

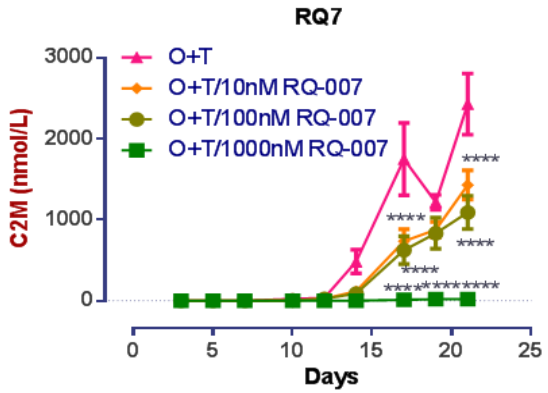


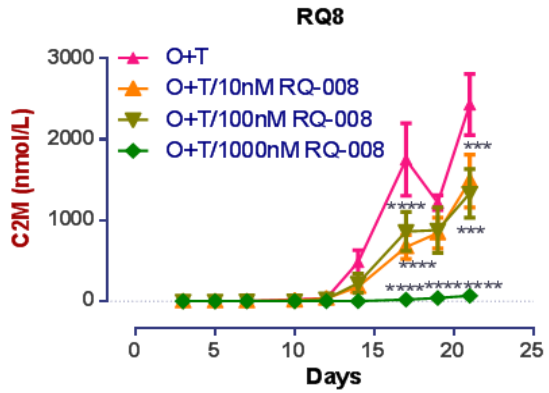
Accumulated release of the C2M to the conditioned medium. P-value of the ANOVA test is shown in the right-hand corner. **** p<0.0001. Mean±SEM

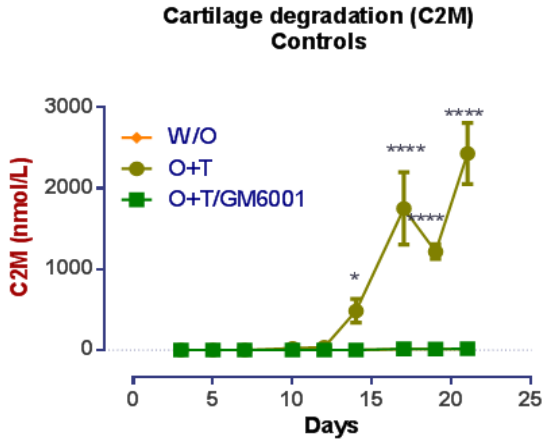
AAT-007 did not affect P2NP (type II collagen formation biomarker) but AAT-008 at 1000 nM slightly decreased P2NP (p<0.05).
Both of AAT-007 and AAT-008 at 1000 nM significantly reduced C2M (cartilage degradation biomarker) to the level of GM6001.

Bovine cartilage explants study - Results

- Time dependent effects of AAT-007 and AAT-008 on C2M (MMP-mediated type II collagen degradation marker) levels



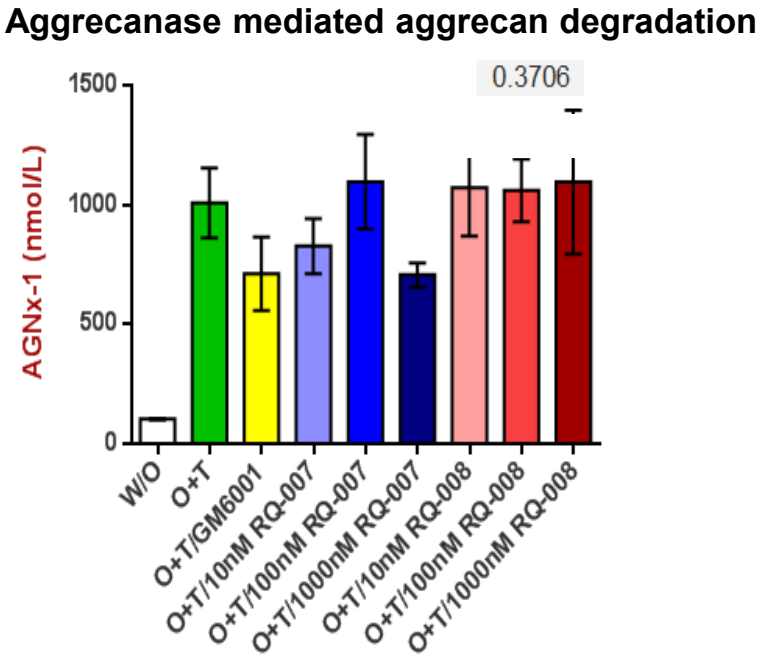




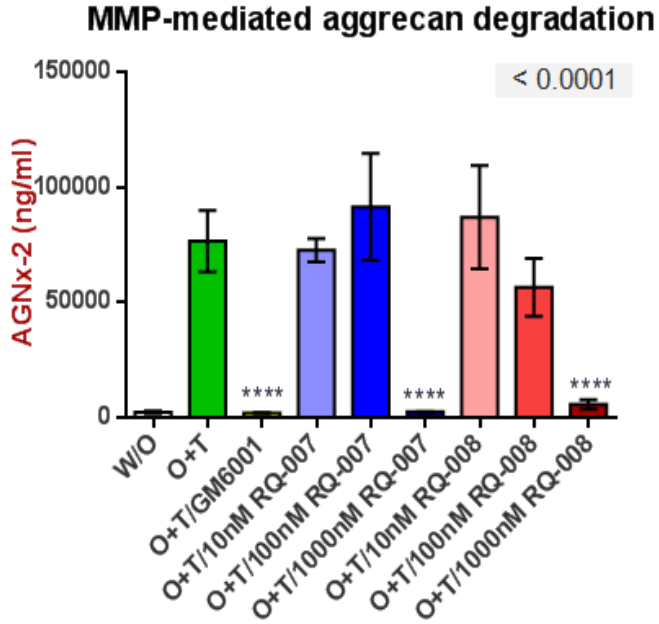
* p<0.05, ** p<0.01, *** p<0.001 and ****p<0.0001. Mean±SEM

Bovine cartilage explants study - Results

- **Aggrecan degradation**



Accumulated release of the AGNx1 to the conditioned medium. P-value of the ANOVA test is shown in the right-hand corner. Mean±SEM



Accumulated release of the AGNx2 to the conditioned medium. P-value of the ANOVA test is shown in the right-hand corner. **** p<0.0001. Mean±SEM

Neither AAT-007 nor AAT-008 affected AGNx-1 (aggrecanase mediated cartilage degradation biomarker) at up to 1000 nM.
Both of AAT-007 and AAT-008 at 1000 nM significantly decreased AGNx-2 (MMP-mediated aggrecan degradation biomarker) to the level of GM6001.

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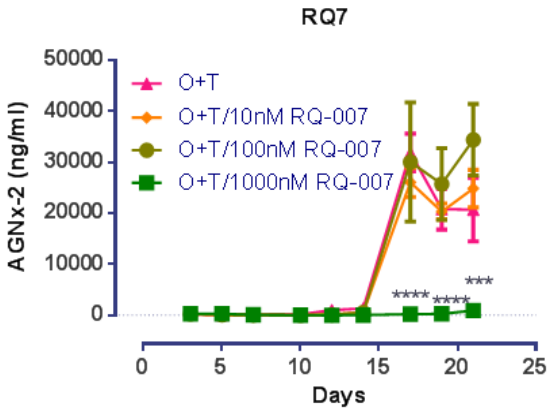
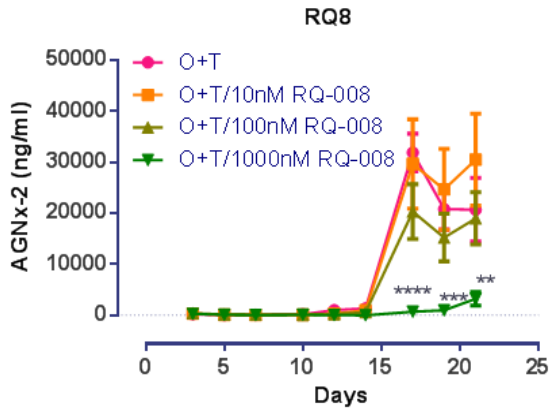
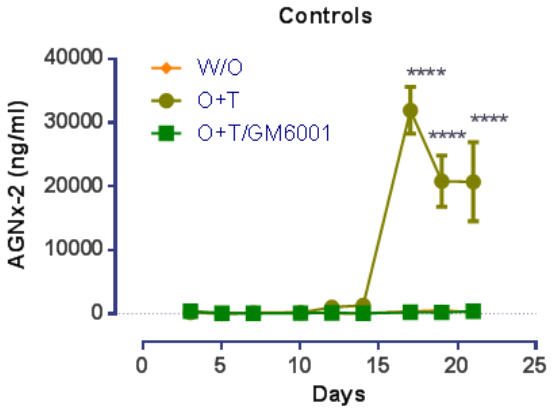
- Time dependent effect of AAT-007 and AAT-008 on AGNx-2 (MMP-mediated aggrecan degradation marker) levels







** p<0.01, ***p<0.001 and ****p<0.0001. Mean±SEM

Summary of the bovine cartilage explant study

- High dose (1000 nM) of AAT-007 and AAT-008 inhibited the release of C2M and AGNx-2 (catabolic biomarkers of cartilage).

- AAT-007 did not affect the release of P2NP at up to 1000 nM, and AAT-008 slightly decreased it at 1000 nM. The results strongly suggest that the effect of EP4 antagonists favors anti-catabolic but not anti-anabolic.

- AAT-007 and AAT-008 at up to 1000 nM did not affect cell viability.