

AAT-076, A Unique Novel COX-2 Inhibitor for Acute Inflammatory Pain



2026 January

AskAt Inc.

Non-confidential Information



1. Executive Summary: AAT-076

- AAT-076 is a unique COX-2 inhibitor (COXIB) with potent analgesic and anti-inflammatory activities along with excellent safety profile.
 - A chromene (1-benzopyran) chemical structure different from existing COX-2 inhibitors (celecoxib, valdecoxib, rofecoxib, and etoricoxib)
 - Faster onset and longer-lasting efficacy than ibuprofen in Phase 2 post-operative dental pain study
 - Well-tolerated and safe following over 790 subjects dosed in Phase 1 and Phase 2 studies
 - Demonstrated analgesic efficacy in animal models of neuropathic pain
 - Penetrant to CNS in rats and decreased PGE2 levels in the brain of arthritic rats
 - A superior renal safety profile to non-steroidal anti-inflammatory drugs (NSAIDs) and other COXIBs in animals
- AAT-076 has an opioid sparing potential due to stronger analgesic efficacy than ibuprofen in post-operative dental pain (Phase 2)
- A potassium salt of AAT-076 was identified as the drug substance for further development to improve the solubility
 - The salt and crystal form patent was already registered
 - A novel composition of matter was developed
- IP status (as of January 28, 2026)
 - Salt & Crystal Forms (WO 2014/104414) filed on January 6, 2014
 - » Granted: CN, EP (FR, DE, GB, IE, IT, ES, CH), JP, KR, RU, TW, US
 - Pharmaceutical Composition (WO 2013/058303) filed on October 18, 2012
 - » Granted: BR, CA, CN, EP (FR, DE, GB, IE, IT, ES, CH), IN, JP, KR, MX, US
 - Photo-Deracemization Process (WO 2020/153279) filed on January 20, 2020
 - » Granted: BR, CA, CN, EP (GB, FR, DE, IT, ES, IE, CH), IN, JP, KR, MX, RU, US

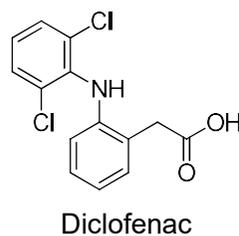
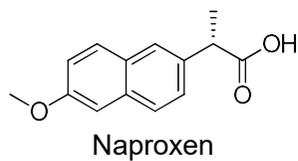
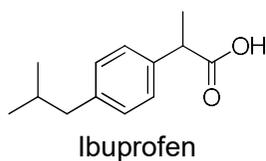


2. Table of Contents

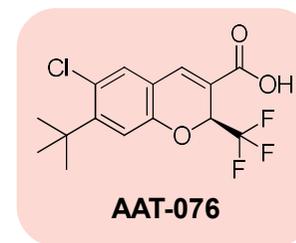
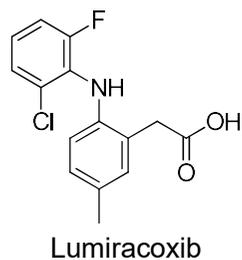
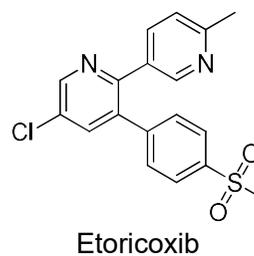
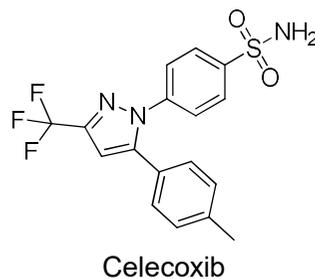
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3. A Unique Novel COX-2 Inhibitor AAT-076

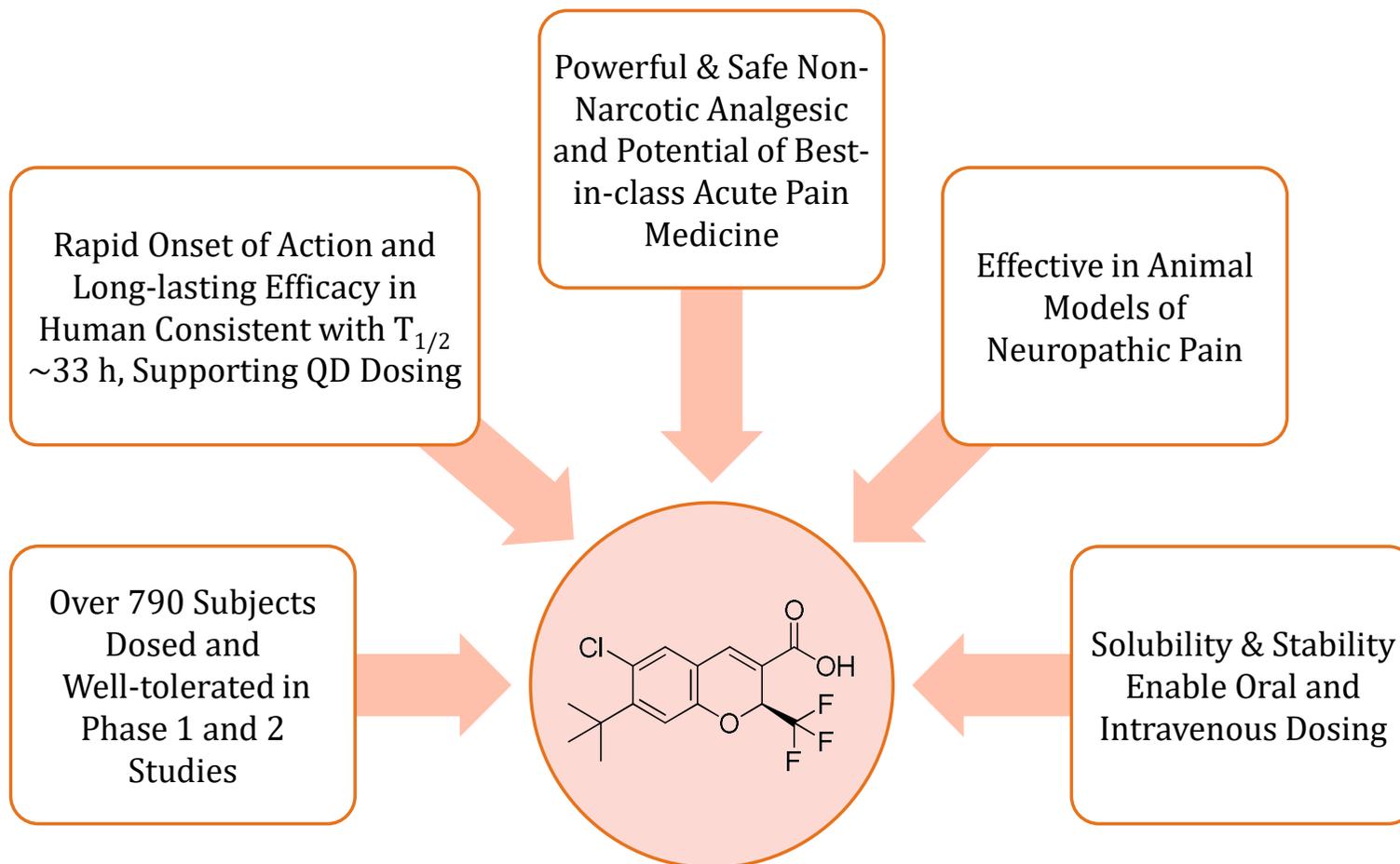
NSAIDs



COXIBs



4. Key Attributes of AAT-076





5. AAT-076 Product Concept

- **Mechanism of Action**
 - A Selective COX-2 inhibitor
- **Product Concept: “Powerful and safe analgesic uniquely differentiated from non-steroidal and non-narcotic drugs”**
 - Superior pain relief profile vs. existing NSAIDs/COXIBs
 - Opioid-sparing profile
 - Better safety and tolerability, e.g., renal, gastro-intestinal (GI) than NSAIDs/COXIBs
 - Oral and intravenous formulations meet the therapeutic need for acute pain management
 - Covering a wide range of pain indications, including acute to chronic, inflammatory and neuropathic pain
- **Mode of Therapy**
 - Once-a-day oral dosing
 - Intravenous dosing
- **Target Indications**
 - Primary indication: Post-operative pain
 - Expanded indication in acute pain: Non-surgical acute pain, Post-traumatic pain
 - Additional opportunity: Cancer pain, Chronic inflammatory pain, Neuropathic pain

6. Primary Indication - 1

Post-operative pain is the most suitable for market entry based on the key attributes of AAT-076

Potent and rapid analgesic action in human

Half Life ~33 h in human supporting once-a-day dosing and long-lasting efficacy

Renal safety shown in animal models

Effective in pre-clinical models of neuropathic pain

Well-tolerated and safe following over 790 subjects dosed

Solubility & stability profiles enable oral and intravenous dosing

Target Product Profile for Post-operative pain

- Superior pain relief profile to existing non-opioid analgesics
- Rapid onset and long-acting analgesics
- Superior opioid-sparing profile to existing non-opioid analgesics
- Superior safety and tolerability

- Oral and intravenous forms for the entire peri-operative pain management

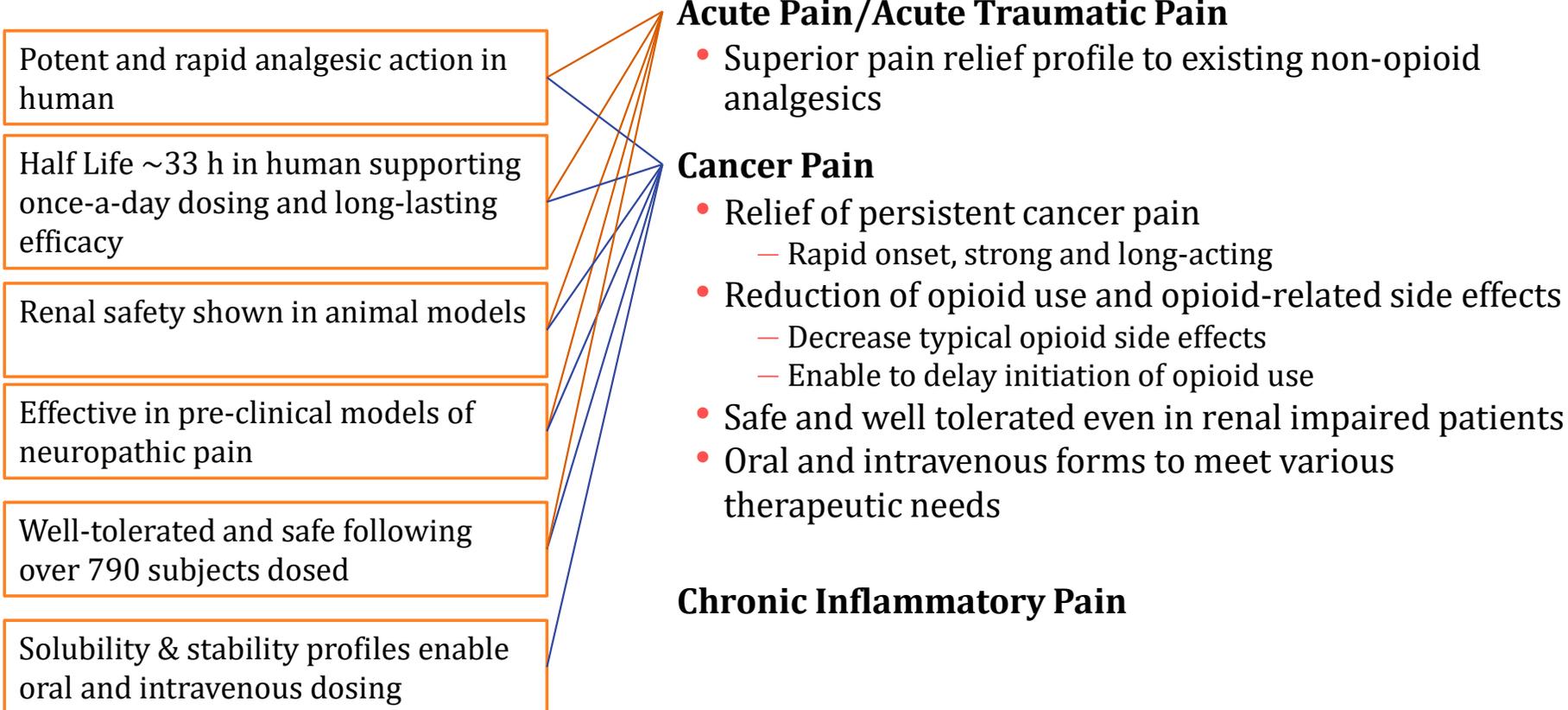
6. Primary Indication - 2

- Current therapies for post-operative pain
 - NSAIDs and COXIBs are widely used for the treatment of post-operative pain.
 - Opioids are used as the first-line agents for moderate-to-severe post-operative pain in combination with NSAIDs or COXIBs.

- Unmet medical needs in post-operative pain
 - Long lasting analgesic effect
 - » NSAIDs and COXIBs need BID or TID dosing due to short half-life and duration of action.
 - Opioid sparing effect
 - » Common opioid side effects include nausea, vomiting, sedation, constipation, and respiratory depression.
 - » A more potent NSAID can reduce opioid dose when combined.
 - Safety and tolerability of NSAID and COXIB
 - » NSAIDs and COXIBs have dose-limiting GI and renal side effects.
 - » NSAIDs are known to increase the risk of excess bleeding and asthma (aspirin).
 - Availability of oral and intravenous dosing formulations

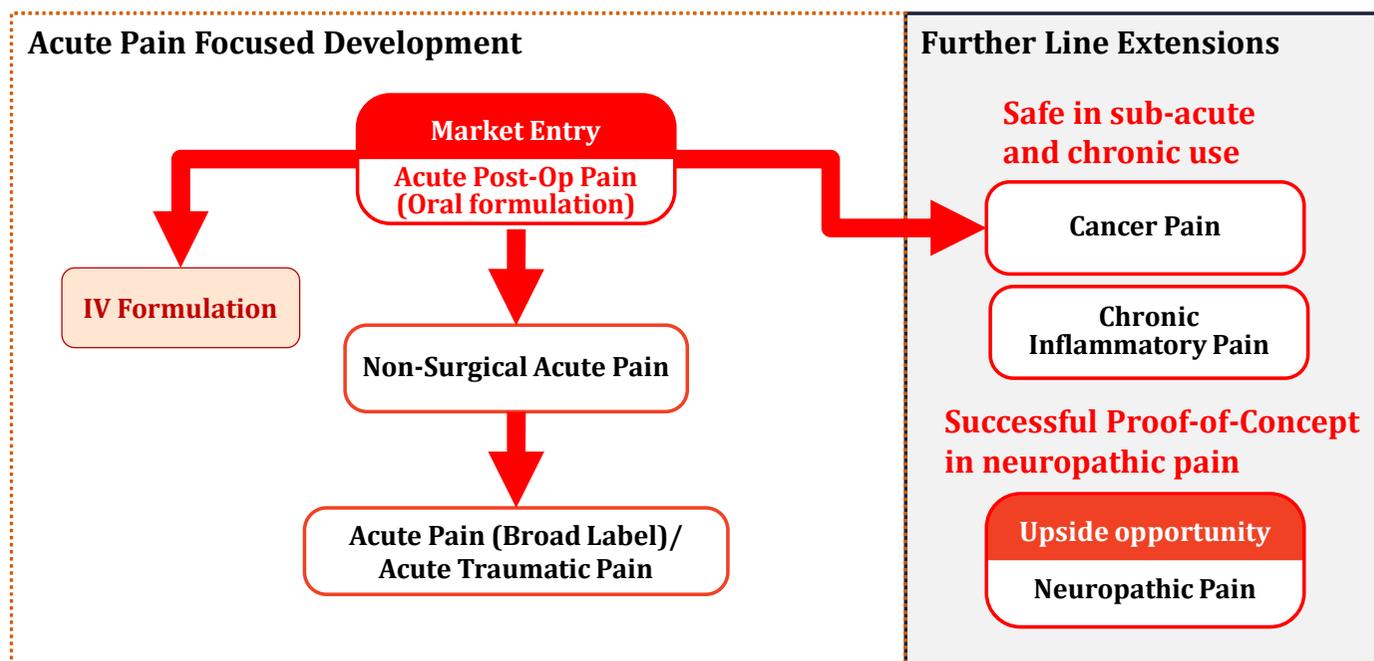
7. Additional Indications

Subsequent line extension in acute pain, cancer pain, chronic inflammatory pain and neuropathic pain is expected according to the key attributes of AAT-076



8. Market Entry and Expansion Strategy

- Development of oral formulation in acute post-operative pain is a rapid and low-risk pathway to the market.
- Indications will be expanded to non-surgical acute pain in various settings.
- Other opportunity includes cancer pain, chronic inflammatory pain and neuropathic pain.





9. Compound Attributes

- 9.1. Compound Information
- 9.2. Non-Clinical – Pharmacology
- 9.3. Non-Clinical – Safety Pharmacology
- 9.4. Non-Clinical – Safety Pharmacology Studies
- 9.5. Non-Clinical – Toxicology
- 9.6. Non-Clinical – Toxicology Studies
- 9.7. Non-Clinical – Pharmacokinetics
- 9.8. Non-Clinical – Pharmacokinetic Studies
- 9.9. Clinical – Phase 1
- 9.10. Clinical – Phase 2
- 9.11. Clinical Efficacy (AAT-076 vs. existing drugs)
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9.1. Compound Information

- Compound Code

- AAT-076

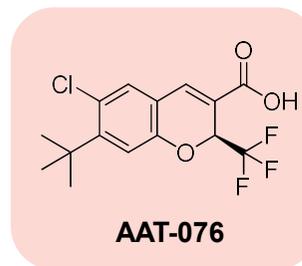
- Chemistry, Manufacturing and Control (CMC)

- Drug Substance

- » Biopharmaceutics Classification System of the free acid: Class II (low solubility/high permeability)
 - » A potassium salt was identified as the drug substance for further development to improve the aqueous solubility of the free acid
 - Aqueous Solubility; Free acid 1.83 mg/mL at pH6.37, Potassium salt >129.5 mg/mL at pH6.8
 - » Drug substance (Free acid: ~18 kg, Potassium salt: ~10 kg) production was completed under GMP conditions without problems

- Drug Product:

- » Oral solution and tablets of the free acid were used for clinical studies
 - » Advanced tablet formulation of the free acid bioequivalent to the oral solution was identified
 - » Immediate release (IR) formulation of the potassium salt is under development
 - A novel composition of matter, which facilitates a rapid dissolution without reprecipitation at acidic pH has been discovered



9.2. Non-Clinical – Pharmacology

- AAT-076 is a potent and selective inhibitor of COX-2.

Compound	Human Recombinant Enzyme Assay			Human Whole Blood Assay		
	COX-2 IC ₅₀ (μM)	COX-1 IC ₅₀ (μM)	Selectivity for COX-2	COX-2 IC ₅₀ (μM)	COX-1 IC ₅₀ (μM)	Selectivity for COX-2
Celecoxib	0.05	15	300×	0.3	8.3	28×
AAT-076	0.25	49.6	198×	1.4	>200	>143×



9.2. Non-Clinical – Pharmacology

Inflammatory Pain

- AAT-076 demonstrated anti-inflammatory and analgesic effects, and was more potent than celecoxib in animal models

Compound	Carrageenan-Induced Edema ED ₅₀ (mg/kg)	Carrageenan-Induced Hyperalgesia ED ₅₀ (mg/kg)	Adjuvant Arthritis ED ₅₀ (mg/kg)
Celecoxib	7	35	0.3
AAT-076	2.7	4.0	0.08

9.2. Non-Clinical – Pharmacology

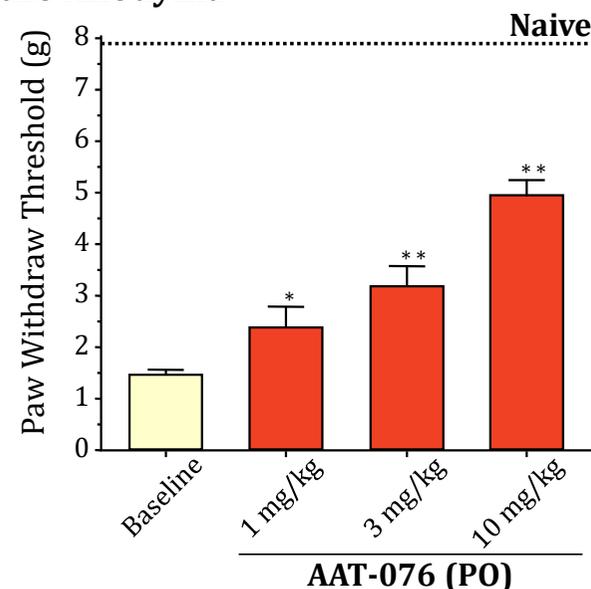
Neuropathic Pain

- AAT-076 dose-dependently reversed tactile allodynia induced by spinal nerve ligation (SNL) in rats.

Compound	Neuropathic Pain (SNL) ED ₅₀ (mg/kg)
Naproxen	No effect (@30 mg/kg)
Acetaminophen	No effect (@100 mg/kg)
Gabapentin	30
Morphine	0.5
AAT-076	10

Gierse J., *et al.*:
European Journal of Pharmacology, 588, 93 (2008)

Tactile Allodynia



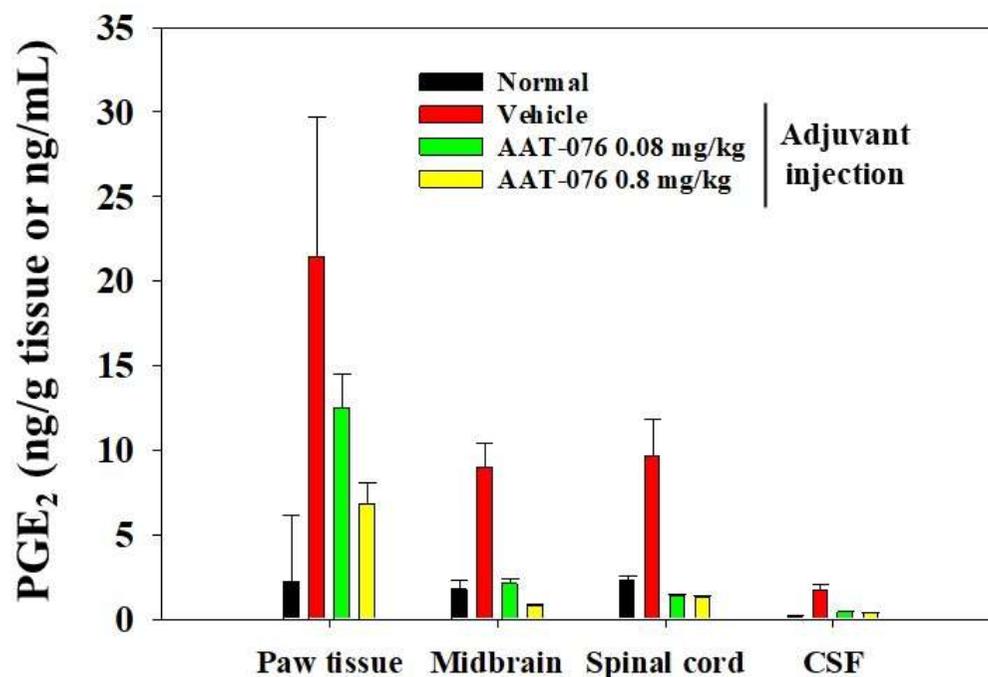
Data represent mean \pm S.E.M. of 5 rats. **P<0.01, *P<0.05 vs. baseline using ANOVA followed by Dunnett's test.

- AAT-076 also exhibited significant analgesic effects in rat models of CCI (chronic constriction injury) and SNI (spared nerve injury).

9.2. Non-Clinical – Pharmacology

Effect of single oral dose of AAT-076 on PGE₂ levels in CNS and paw tissues on rat adjuvant arthritis

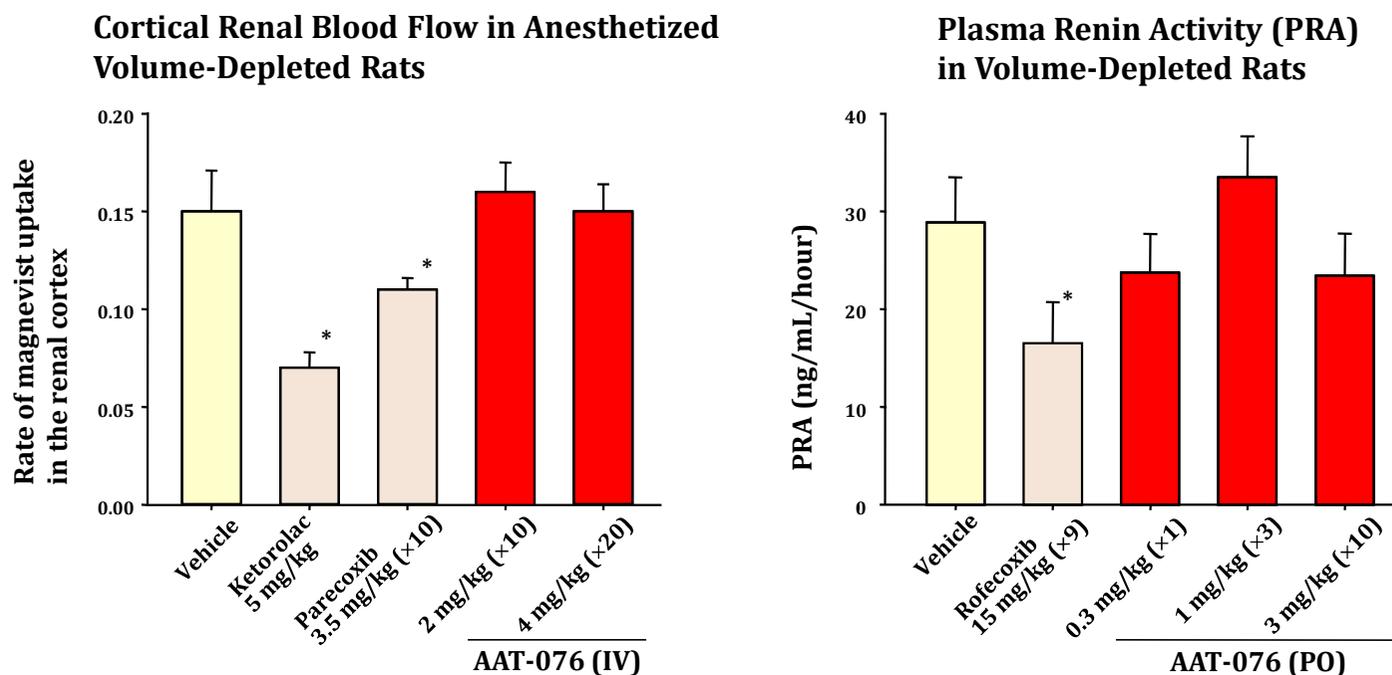
- AAT-076 completely inhibited PGE₂ levels in the CNS tissues whereas partially in the peripheral inflammatory tissues at ED₅₀ and 10 times of ED₅₀ on paw swelling of adjuvant arthritis.



AAT-076 at 0.08 (ED₅₀ on paw swelling) and 0.8 (10 times of ED₅₀) mg/kg or vehicle was orally administered at day 20 after adjuvant injection. PGE₂ level was measured at 4 hr after single dosing. Data represent mean \pm S.E.M. of 4-5 rats/group.

9.3. Non-Clinical – Safety Pharmacology

- No clinically significant effect on CNS, CVS, and respiratory system
- Superior renal safety profile compared with NSAIDs and current COX-2 inhibitors in rats and dogs



Volume depletion was induced by furosemide.

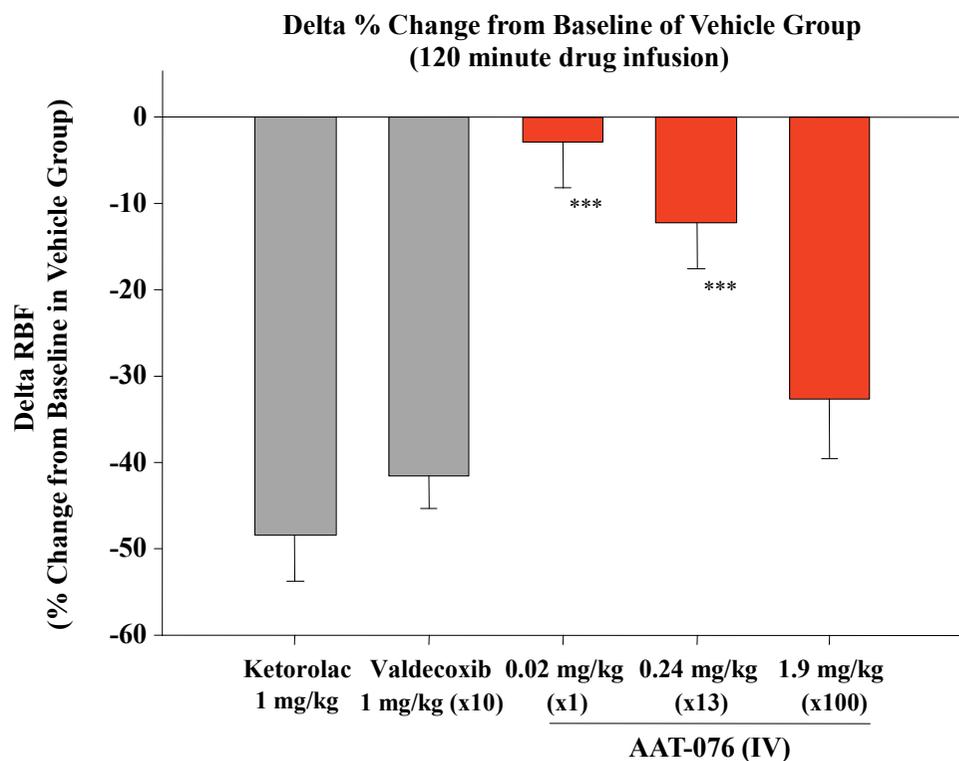
Data are expressed as Mean + SEM. *: $p < 0.05$ compared to Vehicle group by t-test.

× = fold the estimated anti-inflammatory exposure at the ED_{80} in the rat adjuvant arthritis model.

9.3. Non-Clinical – Safety Pharmacology

Effect of COX Inhibitors on RBF in Volume-Depleted Anesthetized Dogs

- AAT-076 sodium salt at 1.9 mg/kg produced an RBF decrease of ~33% at a 100-fold exposure multiple of the estimated C_{max} at the ED_{80} in the rat adjuvant arthritis model
- In contrast, greater diminution was seen with valdecoxib (~42%) and ketorolac (~48%) at only 10-fold their respective estimated anti-inflammatory exposures



All compounds were given as an intravenous bolus followed by continuous infusion to maintain constant exposure throughout the experimental period

× = fold the estimated anti-inflammatory exposure at the ED_{80} in the rat adjuvant arthritis model

*** indicates $p < 0.001$ compared to ketorolac and valdecoxib groups (t-Test analysis)



9.4. Non-Clinical – Safety Pharmacology Studies

Study Type			Route of Administration	Species/ Cell Line
Core Battery	CNS		PO	Rat
	CVS		PO	Dog
	Respiratory System		PO	Rat
	hERG Assay		–	hERG Expressing Cell Line
Follow-Up	CVS	Purkinje Fiber	–	Dog Isolated Heart Tissue
Supplemental	Renal System	Renal Blood Flow	IV	Rat, Dog
		Plasma Renin Activity	PO	Rat
	GI and Renal System	7-Day	PO	Rat
	Broad Ligand Assay		–	Human

9.5. Non-Clinical – Toxicology

- General Toxicity
 - In rats (13-week dose), death due to GI-related toxicities has been observed and NOAEL was determined to be 2.5/1 mg/kg (male/female)
 - In Monkeys (13-week dose), NOAEL was determined to be 200 mg/kg (no remarkable toxicities observed at the highest dose in the study)
 - In Dogs (single dose), no remarkable effects were observed at doses up to 100 mg/kg
- Genotoxicity
 - All “negative” in Ames, *in vitro* Chromosomal aberration, and *in vivo* micronucleus test
- Developmental and Reproductive Toxicity
 - In rats, did not induce developmental toxicity and teratogenicity at any doses up to 5 mg/kg
 - In rabbits, developmental toxicity including malformation were observed at 10 mg/kg or more, which was considered equivocal due to lack of dose dependency



9.6. Non-Clinical – Toxicology Studies

Study Type and Duration		Route of Administration	Species/Cell Line
Single-Dose Toxicity		PO	Dog, Monkey
Repeated-Dose Toxicity	7-Day Range-Finding	PO	Rat
	2-Week	PO	Rat, Monkey
	3-Month	PO	Rat, Monkey
Genotoxicity	Ames Assay	–	S. typhimurium
	Cytogenetic Assay	–	Human Lymphocyte
	In Vivo Micronucleus Assay	PO	Rat
Reprotoxicity	Range-Finding in Pregnant Animals	PO	Rat, Rabbit
	Embryo-Fetal Development	PO	Rat, Rabbit

9.7. Non-Clinical – Pharmacokinetics

- Rapid absorption and high oral bioavailability
- Low total body clearance across all species studied (rats, dogs, and monkeys)
 - Renal clearance is a minor component of the overall elimination (renal clearance <0.001% of total clearance)
- No marked accumulation in plasma (rats and monkeys)
- High plasma protein binding (99.4% to 99.8%) in rats, dogs, monkeys, and humans
- Low risk of 5 major CYPs mediated drug-drug interaction (DDI)
 - $IC_{50} > 100 \mu M$ against CYPs (1A2, 2D6, 2C19, 3A4)
 - CYP2C8 ($IC_{50} = 3 \mu M$), CYP2C9 ($IC_{50} = 35 \mu M$)
- Major excretion route
 - Rats: Biliary

9.8. Non-Clinical – Pharmacokinetic Studies

Study Type		Route of Administration	Species/Cell Line
Absorption	Single Dose	IV and PO	Rat, Dog, Monkey
	Multiple Dose	PO	Rat, Monkey
Distribution	Tissue Distribution	PO	Rat
	Plasma Protein Binding	–	Rat, Dog, Monkey, Human
Metabolism	In Vivo Metabolism	IV	Rat, Dog, Monkey, Minipig
	In Vitro Metabolism	–	Rat, Dog, Monkey, Human Hepatocytes
	Inhibition of Drug Metabolizing Enzymes (DDI)	–	Human
Excretion	Excretion into Urine	IV	Rat, Dog, Monkey
Others	Cell Permeability Assay	–	Caco-2



9.9. Clinical – Phase 1

- Well-tolerated at single doses up to 360 mg and multiple doses for 10 days up to 180 mg
- Systemic exposure increased in dose-proportional manner after single- and multiple-dose administration
- No serious adverse events were observed
- Advanced tablet formulation bioequivalent to oral solution was identified

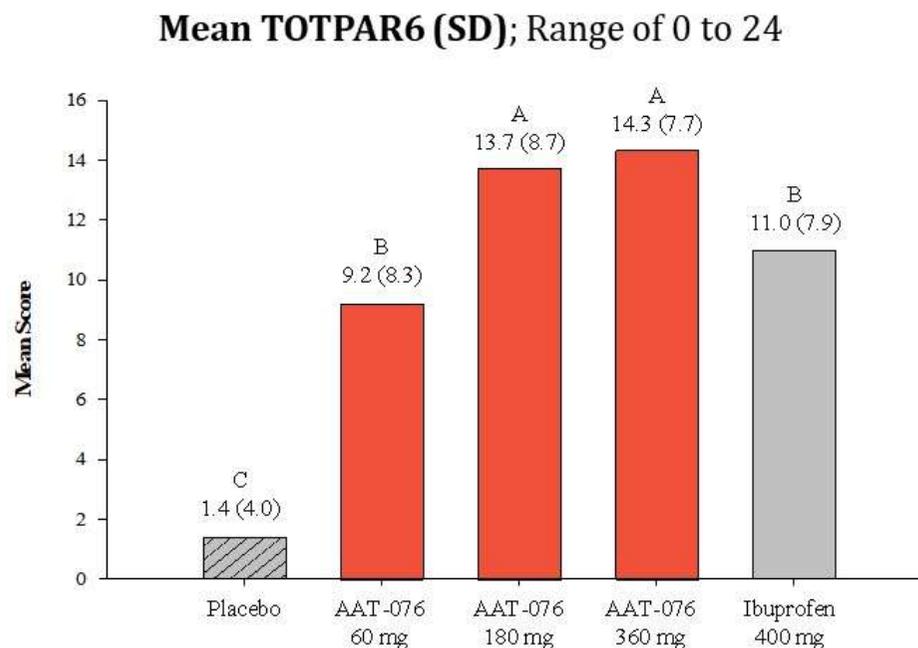


9.10. Clinical – Phase 2

- Two Phase 2 post-operative dental pain studies were conducted in the US
- A single oral 60 mg dose of AAT-076 with capsule formulation demonstrated superior overall efficacy compared with placebo in regards to time-to-analgesia and time-to-rescue medication
- A single oral dose of 180 or 360 mg AAT-076 with oral solution formulation provided significantly greater analgesic efficacy, faster onset, and longer duration compared with 400 mg ibuprofen
- AAT-076 was safe and well-tolerated; no dose-related safety findings were evident

9.10. Clinical – Phase 2

- Primary Endpoint: Total Pain Relief through 6 hours
 - AAT-076 60, 180, and 360 mg groups had a significantly higher TOTPAR(6) score (improvement) compared with placebo group
 - Additionally, AAT-076 180 and 360 mg groups had a significantly higher TOTPAR(6) score compared with ibuprofen 400 mg group



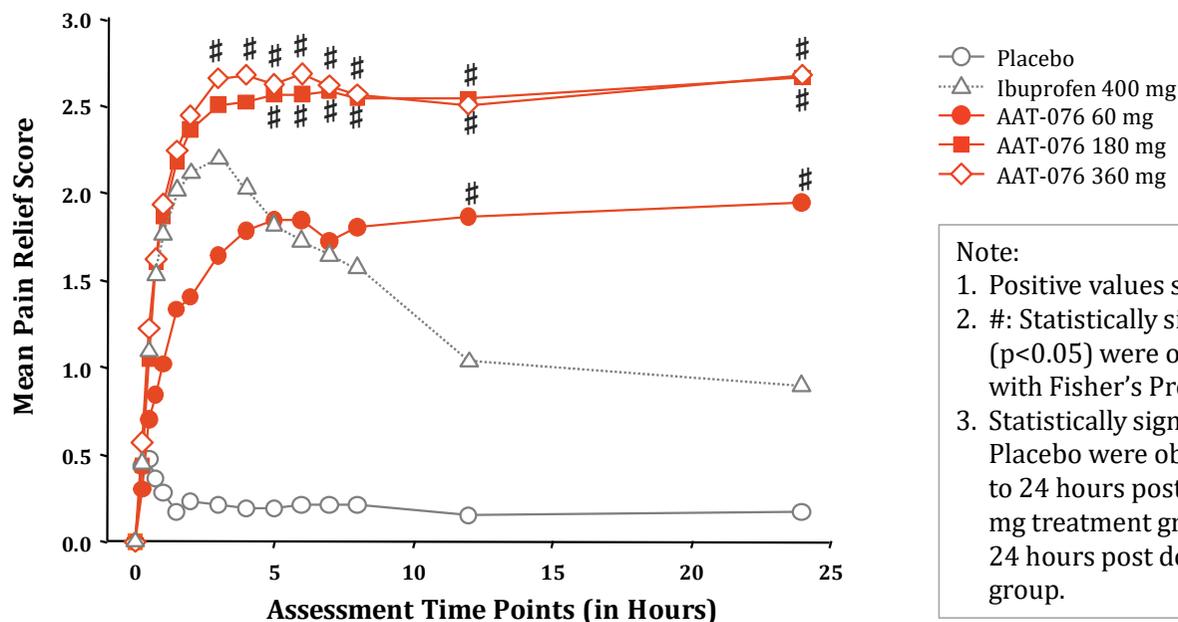
Treatments with the same letter code are not significantly different from each other. (Comparisons are made at 5% level of significance. Type I error is protected with Fisher's protected LSD.)

9.10. Clinical – Phase 2

- Pain Relief (PR)

- Subjects who received 180 mg AAT-076 had significantly greater PR from Hour 5 through 24 compared with subjects who received ibuprofen
- Subjects treated with 360 mg AAT-076 had significantly greater PR from Hour 3 through 24 compared with subjects treated with ibuprofen

Mean Pain Relief (0-24 Hours), Categorical (Range 0-4), LOCF



Note:

1. Positive values signify improvement.
2. #: Statistically significant differences ($p < 0.05$) were observed vs. Ibuprofen with Fisher's Protected LSD Comparisons.
3. Statistically significant differences vs. Placebo were observed after 30 minutes to 24 hours post dosing at 180 and 360 mg treatment groups, after 45 minutes to 24 hours post dosing at 60 mg treatment group.

9.10. Clinical – Phase 2

- Time to Onset of Analgesia
 - Significantly faster in the 360 mg AAT-076 treatment group (00:20 min) compared with 400 mg ibuprofen (00:28 min), 60 mg AAT-076 (00:55 min), and placebo treatment group (>24 hours)
 - A clear dose response was observed in onset of analgesia for AAT-076-treated subjects

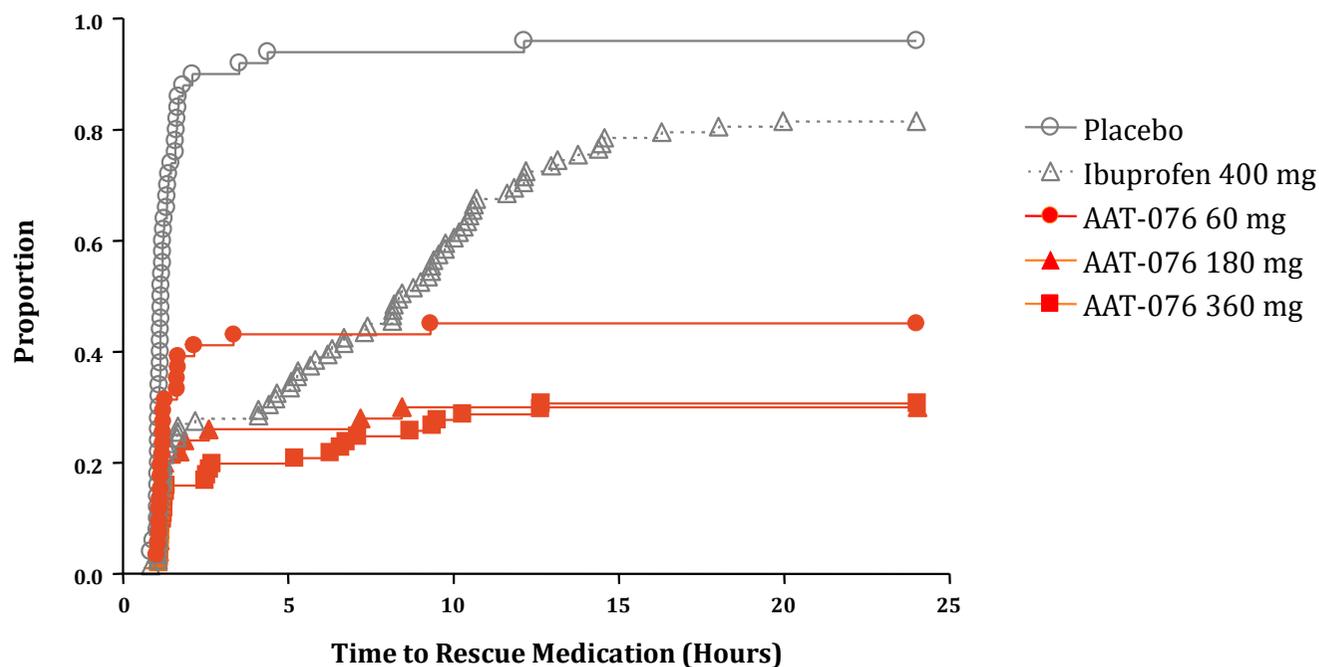
Treatment Group	Median Time (Hour:Minute)	Statistically Significant Group Differences ^a
Placebo	>24:00	C
Ibuprofen, 400 mg	00:28	B
AAT-076, 60 mg	00:55	B
AAT-076, 180 mg	00:28	AB
AAT-076, 360 mg	00:20	A

^a Log Rank test applied. Type I error is protected with Fisher's protected LSD. Treatments with the same letter are not significantly different from each other. Subjects not experiencing onset of analgesia were censored at 24 hours. Subjects who dropped out for reasons other than rescue medication were censored at the drop out time.

9.10. Clinical – Phase 2

- Time to Rescue Medication

- The median time to rescue medication was significantly longer in the 360 mg AAT-076 treatment group (>24 hours) compared with the 400 mg ibuprofen group (08:26 hr:min)
- The median time to rescue medication was >24 hours for all AAT-076 dose groups



9.11. Clinical Efficacy (AAT-076 vs. existing drugs)

- AAT-076 showed superior analgesic profile over celecoxib and ibuprofen in postoperative dental pain clinical trials

Treatment Group (No of subjects)	Total Pain Relief TOTPAR 8	Total Pain Relief TOTPAR 12	Median Time to Perceptible Pain Relief (min)	Median Time to Rescue Medication (h)	Requiring Rescue Medication (%)	Reference*
Placebo (N = 50)	1.82	2.41	>1440	1.17	96.0	a
Placebo (N = 45)	0.7	0.8	>240	1.6	97.8	b
Celecoxib, 400 mg (N = 151)	15.0	21.0	54	10.6	65.6	b
Celecoxib, 200 mg (N = 90)	11.5	16.7	72	6.8	68.9	b
Ibuprofen, 400 mg (N = 100)	14.22	18.34	27	8.43	82.0	a
Ibuprofen, 400 mg (N = 45)	14.7	18.3	30	10.0	86.7	b
AAT-076, 180 mg (N = 50)	18.77	28.93	28	>24	30.0	a
AAT-076, 360 mg (N = 101)	19.46	29.46	18	>24	31.7	a

* a: A6151012 CSR (unpublished), b: Malstrom K, *et al.*: Clinical Therapeutics, 24(10), 1549 (2002)

9.12. Clinical Studies Summary

	Phase 1	Phase 2
Studies	<ul style="list-style-type: none"> • Single dose tolerance and PK (up to 360 mg) • Food effect • Multiple dose tolerance and PK (up to 180 mg/day for 10 days) • Formulation development <ul style="list-style-type: none"> – Effect of stomach pH – Bioavailability of the prototype tablet formulations of free acid with the solution formulation 	<ul style="list-style-type: none"> • Single doses (3, 10, and 60 mg), rofecoxib (50 mg), and placebo in subjects with post-operative dental pain study with capsule formulation • Single doses (60, 180, and 360 mg), ibuprofen (400 mg) and placebo in subjects with post-operative dental pain study with oral solution formulation
Results	<ul style="list-style-type: none"> • Well-tolerated at doses up to 360 mg in single dose and 180 mg in multiple doses (QD for 10 days) • Dose proportionally increased systemic exposure after single- and QD multiple-dose administration up to 360 mg and 180 mg, respectively • No serious adverse events • Advanced tablet formulation of free acid identified 	<ul style="list-style-type: none"> • Efficacy in terms of onset, magnitude, and duration of analgesia confirmed at a single dose of 60 mg with capsule formulation • Significantly greater analgesic efficacy, faster onset, and longer duration at a single dose of 180 and 360 mg with oral solution compared with ibuprofen (400 mg) <ul style="list-style-type: none"> – Superior overall analgesic efficacy at a single oral dose of 60 mg with oral solution compared with placebo • Safe and well tolerated; no dose-related safety findings



“PRECISION” Trial

Prospective Randomized Evaluation of Celecoxib Integrated
Safety versus Ibuprofen or Naproxen

Publication:

Titled “Cardiovascular Safety of Celecoxib, Naproxen, or
Ibuprofen for Arthritis”

N Engl J Med 2016; 2519-2529



“PRECISION” Trial

Background

- Discussion at the FDA Advisory Committee Meeting on cardiovascular (CV) risk of COX-2 NSAIDs in 2015
- FDA mandated study - Commitment by Pfizer to FDA
- Funded by Pfizer

Organization

- Independent Executive Committee
 - Principal Investigator and Study Chair- Steven Nissen, MD – Cleveland Clinic
- Independent Data Monitoring Committee
 - Chair - Thomas R. Fleming, Ph.D. – University of Washington
- Experts in Cardiology, Rheumatology and Gastroenterology on both committees

Allocation

- Randomized

Intervention Model

- Parallel Assignment

Masking

- Double Blind (Subject, Caregiver, Investigator)

Subject

- Enrolled OA or RA patients who were over 18 years of age and who, as determined by the patient and physician, required daily treatment with NSAIDs for arthritis pain; patients whose arthritis pain was managed adequately with acetaminophen were not eligible
- A Key inclusion criterion was established cardiovascular disease or an increased risk of the development of cardiovascular disease

Group

- Celecoxib, 100 to 200 mg twice daily
- Ibuprofen, 600 mg to 800 mg three times daily
- Naproxen, 375 mg to 500 mg twice daily

Primary Objective

- To assess the relative cardiovascular effects of celecoxib, ibuprofen and naproxen in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA)

Primary Outcome

- Time-to-event analysis of the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (i.e. death from CV causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke)

Secondary Outcome

- Major adverse CV events, included the components of the primary outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack
- Clinically significant gastrointestinal (GI) events

Tertiary Outcome

- Clinically significant renal events, iron deficiency anemia of GI origin, and hospitalization for heart failure or hypertension

Non-adjudicated Secondary Outcome

- Assessment of the intensity of arthritis pain with the use of the Visual Analogue Scale for Pain



“PRECISION” Study Results-1

- A total of 24,081 OA and RA patients were randomly assigned to three groups
 - Celecoxib group, daily dose, 209 ± 37 mg (mean \pm SD)
 - Naproxen group, daily dose, 852 ± 103 mg
 - Ibuprofen group, daily dose, 2045 ± 246 mg
- Mean treatment duration of 20.3 ± 16.0 months
- Mean follow-up period of 34.1 ± 13.4 months

“PRECISION” Study Results-2

Cardiovascular safety

- Celecoxib noninferior to ibuprofen or naproxen
 - Intention-to- treatment analysis

Group	Number of patients of primary APTC end point (percent)	Adjusted Hazard Ratio (95% CI)	P Value vs. celecoxib
Celecoxib (N = 8072)	188 (2.3%)	-	-
Ibuprofen (N = 8040)	218 (2.7%)	0.85 (0.70-1.04)	0.12
Naproxen (N = 7969)	201 (2.5%)	0.93 (0.76-1.13)	0.45

- On-treatment analysis

Group	Number of patients of primary APTC end point (percent)	Adjusted Hazard Ratio (95% CI)	Noninferiority comparison, P Value vs. celecoxib
Celecoxib (N = 8030)	134 (1.7%)	-	-
Ibuprofen (N = 7990)	155 (1.9%)	0.81 (0.65-1.02)	<0.001
Naproxen (N = 7933)	144 (1.8%)	0.90 (0.71-1.15)	<0.001



“PRECISION” Study Results-3

Gastrointestinal events

- Significantly lower with celecoxib than with ibuprofen (P = 0.002) or naproxen (P = 0.01)

Renal events

- Significantly lower with celecoxib than with ibuprofen (P = 0.004) but was not significantly lower with celecoxib than with naproxen (P = 0.19)



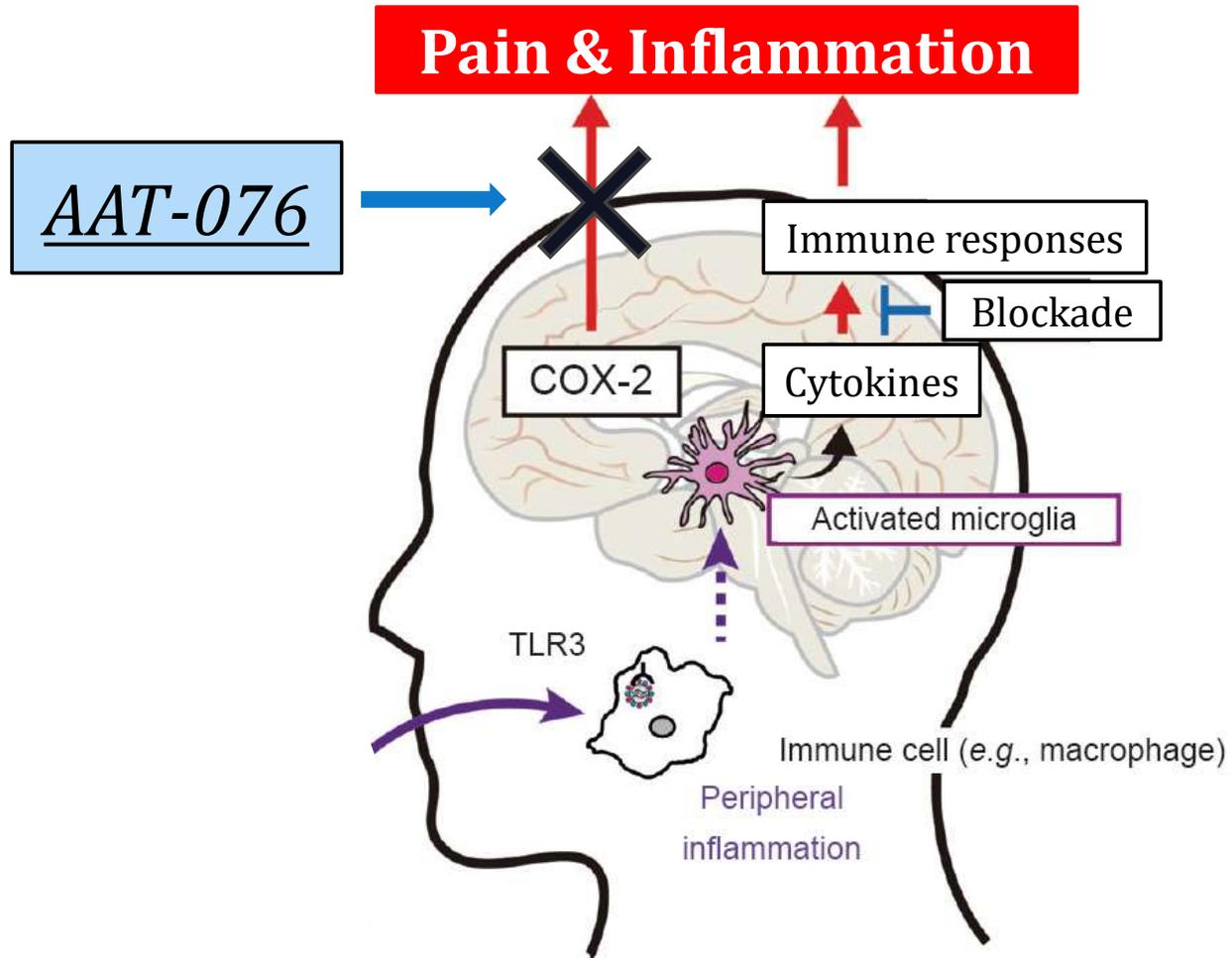
A Novel Opioid-Sparing Pain Therapy: Acute, Chronic and Neuropathic Pain

AAT-076: First and only CNS Active COX-2 Inhibitor



2026, AskAt Inc.

Non-confidential Information

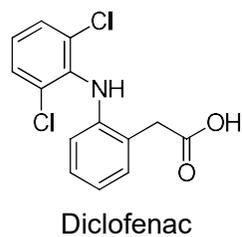
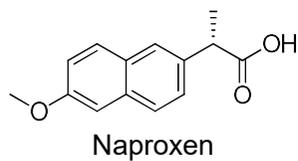
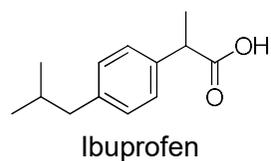


AAT-076 is the ***first*** and ***only*** compound presenting an opportunity to examine clinical significance of CNS COX-2 inhibition

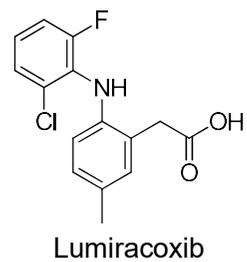
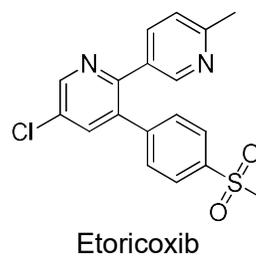
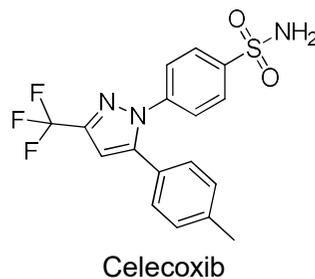
- Phase 1 and Phase 2 results in the US
 - Safe, well-tolerated up to 360 mg, 10 days up to 180 mg/day
 - Superior Efficacy vs Ibuprofen, i.e., onset, potency, and duration
 - Opioid sparing potential suggested
 - Safety advantages include Renal, GI and no platelet inhibition
- IP status (as of January 28, 2026)
 - Salt & Crystal Forms (WO 2014/104414) filed on January 6, 2014
 - » Granted: CN, EP (FR, DE, GB, IE, IT, ES, CH), JP, KR, RU, TW, US
 - Pharmaceutical Composition (WO 2013/058303) filed on October 18, 2012
 - » Granted: BR, CA, CN, EP (FR, DE, GB, IE, IT, ES, CH), IN, JP, KR, MX, US
 - Photo-Deracemization Process (WO 2020/153279) filed on January 20, 2020
 - » Granted: BR, CA, CN, EP (GB, FR, DE, IT, ES, IE, CH), IN, JP, KR, MX, RU, US

A Super NSAID AAT-076

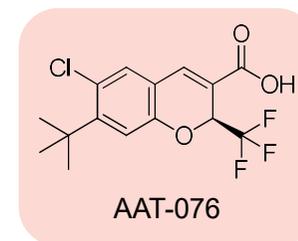
Non-Selective NSAIDs



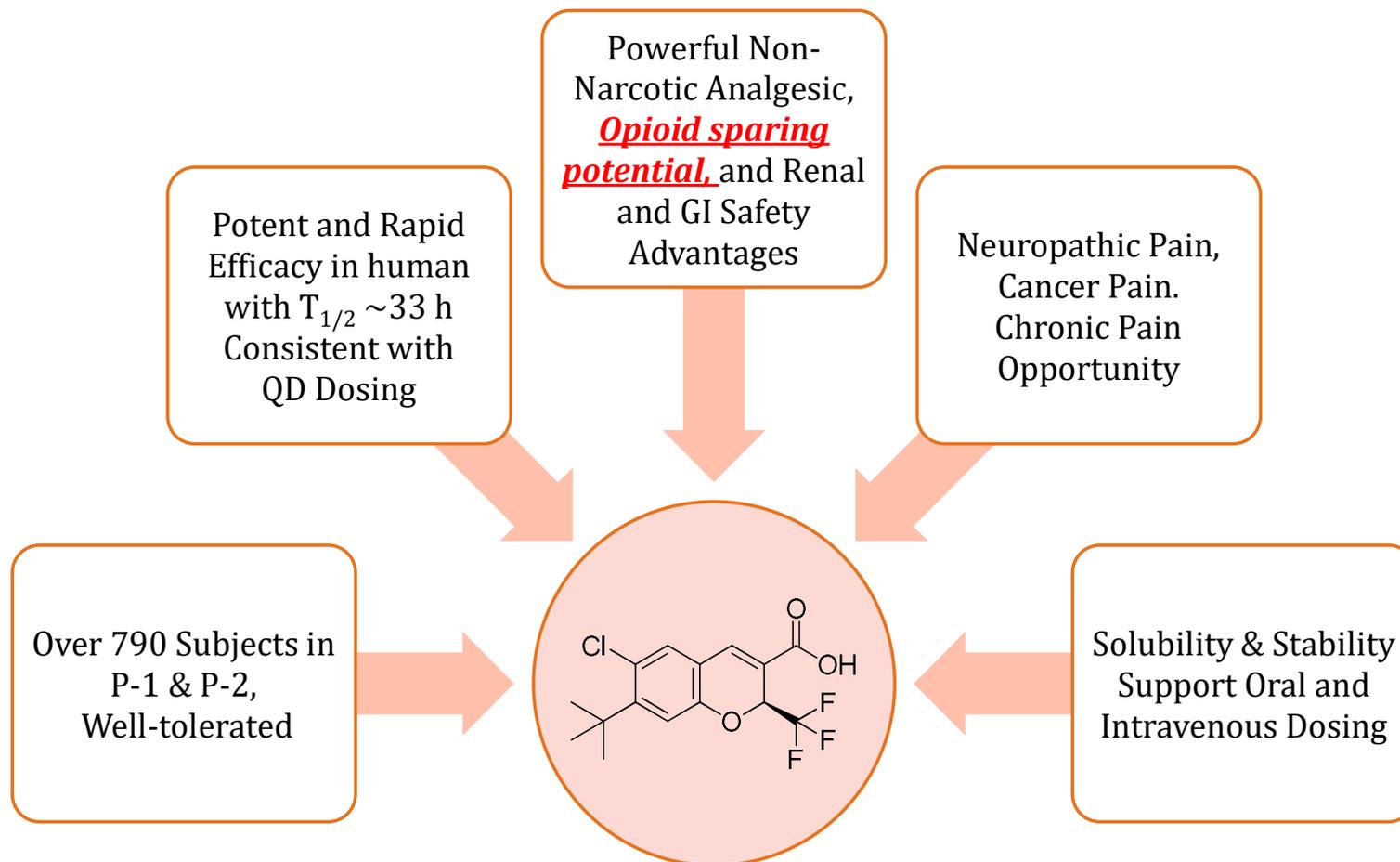
COXIBs



Super NSAID



Key Attributes of AAT-076





AAT-076 Product Concept

- Mechanism of Action
 - COX-2 inhibitor
- Product Concept: “Powerful and safe analgesic uniquely differentiated from non-steroidal and non-narcotic drugs”
 - Superior pain relief profile vs. existing non-opioid analgesics
 - Superior opioid-sparing profile vs. existing non-opioid analgesics
 - Superior Renal and GI safety
 - Oral and intravenous formulations meet therapeutic needs in pain management
 - Effective in neuropathic pain conditions
- Mode of Therapy
 - Once-a-day oral dosing
 - Opportunity for intravenous dosing
- Target Indication
 - Acute and Chronic Pain including Neuropathic Pain

- Potency and selectivity demonstrated in *in vitro* assays

Compound	Human Recombinant Enzyme Assay			Human Whole Blood Assay		
	COX-2 IC ₅₀ (μM)	COX-1 IC ₅₀ (μM)	Selectivity for COX-2	COX-2 IC ₅₀ (μM)	COX-1 IC ₅₀ (μM)	Selectivity for COX-2
Celebrex™	0.05	15	300×	0.3	8.3	28×
AAT-076	0.25	49.6	198×	1.4	>200	>143×



Non-Clinical – Pharmacology

- AAT-076 exhibited far more potent *in vivo* activities than those of Celebrex™ in animal models

Compound	Carrageenan-Induced Edema ED ₅₀ (mg/kg)	Carrageenan-Induced Hyperalgesia ED ₅₀ (mg/kg)	Adjuvant Arthritis ED ₅₀ (mg/kg)
Celebrex™	7	35	0.3
AAT-076	2.7	4.0	0.08

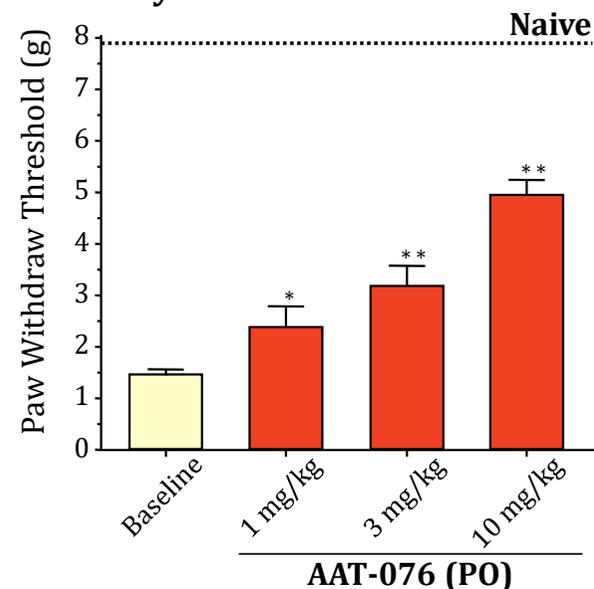
Neuropathic Pain – Spinal nerve ligation (SNL) model

- In a rat neuropathic pain model, AAT-076 dose-dependently reversed tactile allodynia induced by spinal nerve ligation

Compound	Neuropathic Pain (SNL) ED ₅₀ (mg/kg)
Naproxen	No effect (@30 mg/kg)
Acetaminophen	No effect (@100 mg/kg)
Gabapentin	30
Morphine	0.5
AAT-076	Approx. 10

Gierse J., *et al.*:
European Journal of Pharmacology, 588, 93 (2008)

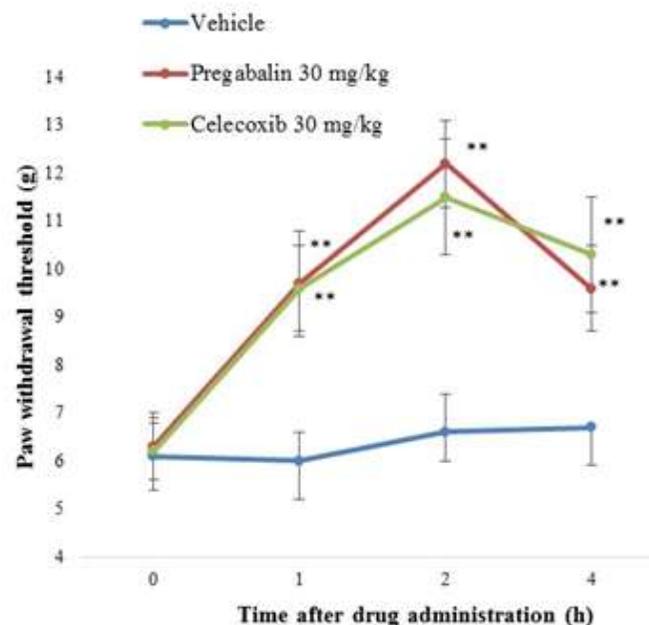
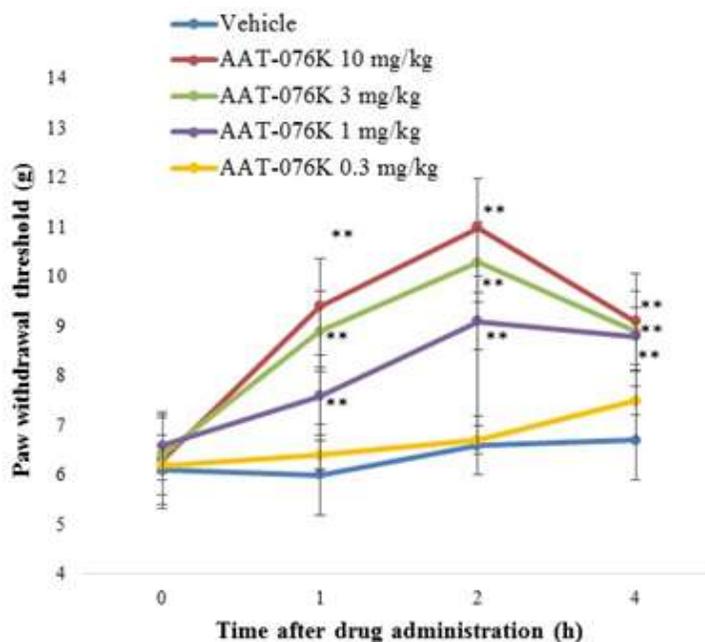
Tactile Allodynia



AAT-076 dose-dependently reversed tactile allodynia 2 h following oral administration. Baselines were taken on the day of the experiment before dosing. Withdrawal threshold is expressed as grams (g). For naive rats (no surgery) withdrawal threshold is 8 g. Data represent mean \pm S.E.M. of 5 rats. **P<0.01, *P<0.05 vs. baseline using ANOVA followed by Dunnett's test.

Neuropathic Pain – Chronic constriction injury (CCI) model

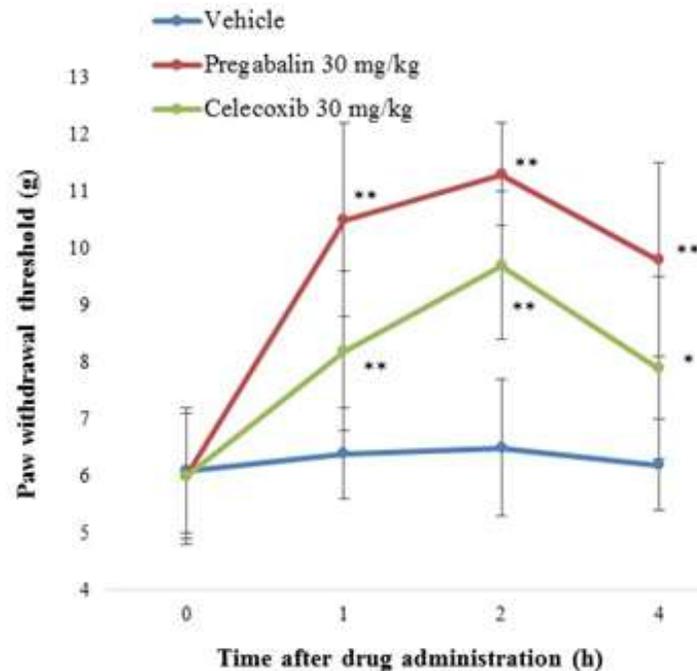
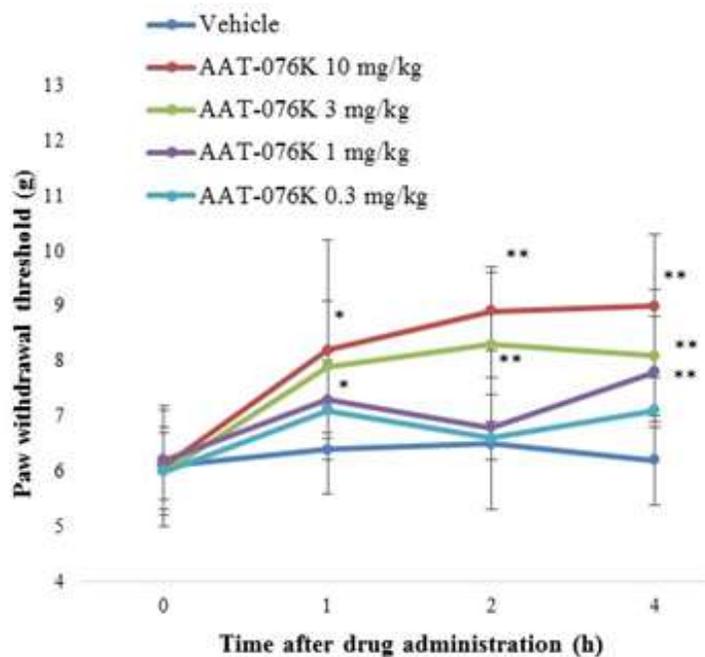
- Efficacy of AAT-076K, Pregabalin and Celecoxib



Data expressed mean \pm SD, **: $p < 0.01$, Doses of AAT-076K indicate equivalent doses as free-base.
 AAT-076K: one-way ANOVA Dunnett's test versus vehicle group.
 Pregabalin and celecoxib: Student t-test versus vehicle group

Neuropathic Pain - Spared nerve injury (SNI) model

- Efficacy of AAT-076K, Pregabalin and Celecoxib



Data expressed mean \pm SD, *: $p < 0.05$, **: $p < 0.01$, Doses of AAT-076K indicate equivalent doses as free-base.
 AAT-076K: one-way ANOVA Dunnett's test versus vehicle group.
 Pregabalin and celecoxib: Student t-test versus vehicle group

Clinical Dose for Neuropathic Pain

- Clinical doses of pregabalin and celecoxib are not adequate for optimal efficacy in the treatment neuropathic pain conditions
- AAT-076 at 60 mg QD is predicted to achieve optimal efficacy

	Neuropathic Pain Model Efficacy		Clinical Dose		Projected Neuropathic Pain Dose
	Dose (mg/kg)	C _{max} (mg/mL)	Dose (mg)	C _{max} (mg/mL)	
Pregabalin (Lyrica)	30	~30	300 BID	9.1*	≥900 mg BID (AE dose limiting)
Celecoxib (Celebrex)	30	9	200 BID	1.1*	≥1600 mg BID (AE dose limiting)
AAT-076	10	16	60 QD	17#	60 mg QD

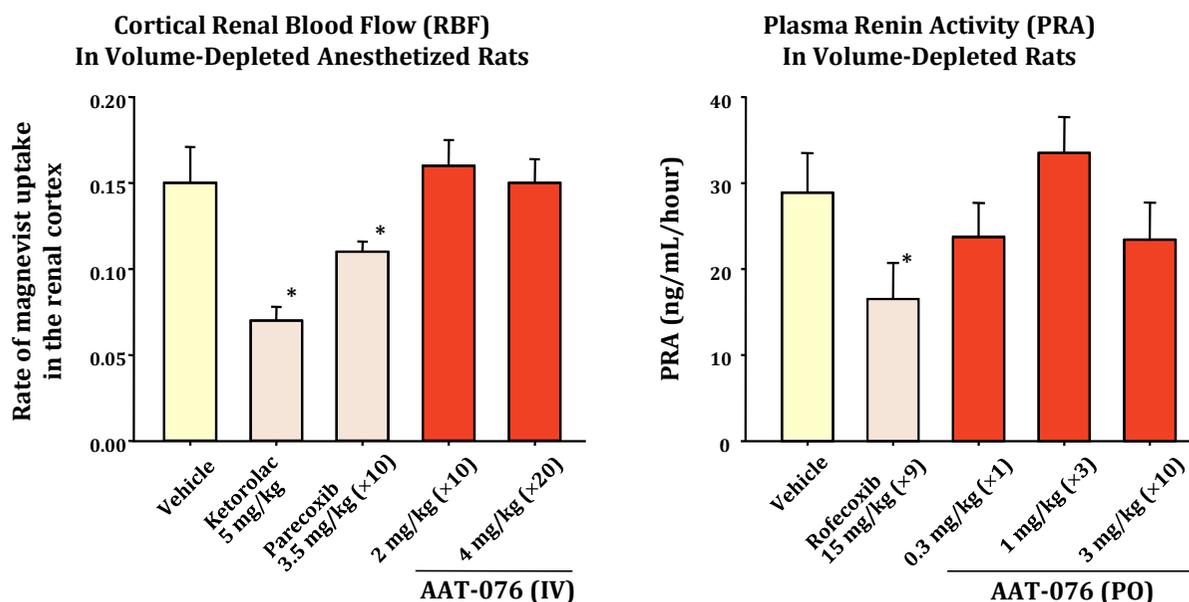
*: US NDA Clinical Pharmacology, Healthy Subjects

#: Phase I, Multiple Dose Study, Healthy Subjects

- No clinically significant effect on CNS, CVS, and respiratory system
 - CNS (rats)
 - » Did not observe significant effects up to 100 mg/kg
 - CVS (*in vitro* and dogs)
 - » No clinically significant inhibition of hERG current up to 30 μ M (approximately 33-fold concentrations over that achieved free fraction of C_{max} at 180 mg QD in clinic)
 - » A dose-related decrease in mean arterial pressure observed at 30 mg/kg or more
 - » No biologically significant effects on QT/QTc up to 100 mg/kg
 - Respiratory (rats)
 - » Did not induce any meaningful effects up to 100 mg/kg

Effect of COX Inhibitors on RBF and PRA in Volume-Depleted Anesthetized Rats

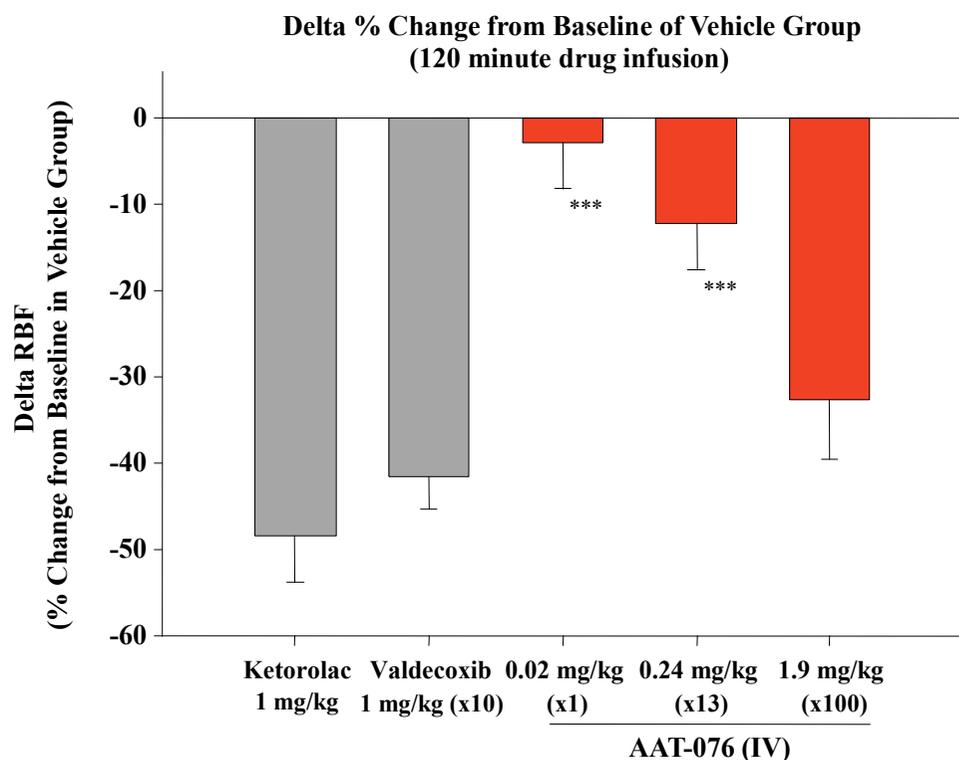
- AAT-076 had no effect on cortical renal blood flow (cRBF) while ketorolac and parecoxib caused a significant reduction in cRBF in anesthetized volume-depleted rats
- AAT-076 did not inhibit plasma renin activity (PRA) during administration of loop diuretic furosemide suggesting that AAT-076 may have renal sparing properties which may be due to low tissue penetration, however significant decrease in PRA levels with the Rofecoxib indicated that this mechanism was COX-2 dependent
- These results suggest AAT-076 has superior renal safety when compared to NSAIDs and current COX-2 inhibitors



Data are expressed as Mean + SEM. *: $p < 0.05$ compared to Vehicle group by t-test
 \times = fold the estimated anti-inflammatory exposure at the ED_{80} in the rat adjuvant arthritis model

Effect of COX Inhibitors on RBF in Volume-Depleted Anesthetized Dogs

- AAT-076 sodium salt at 1.9 mg/kg produced an RBF decrease of ~33% at a 100-fold exposure multiple of the estimated C_{max} at the ED_{80} in the rat adjuvant arthritis model
- In contrast, greater diminution was seen with valdecoxib (~42%) and ketorolac (~48%) at only 10-fold their respective estimated anti-inflammatory exposures



All compounds were given as an intravenous bolus followed by continuous infusion to maintain constant exposure throughout the experimental period

× = fold the estimated anti-inflammatory exposure at the ED_{80} in the rat adjuvant arthritis model

*** indicates $p < 0.001$ compared to ketorolac and valdecoxib groups (t-Test analysis)



Non-Clinical – Safety Pharmacology Studies

Study Type			Route of Administration	Species/ Cell Line
Core Battery	CNS		PO	Rat
	CVS		PO	Dog
	Respiratory System		PO	Rat
	HERG Assay		–	HERG Expressing Cell Line
Follow-Up	CVS	Purkinje Fiber	–	Dog Isolated Heart Tissue
Supplemental	Renal System	Renal Blood Flow	IV	Rat, Dog
		Plasma Renin Activity	PO	Rat
	GI and Renal System	7-Day	PO	Rat
	Broad Ligand Assay		–	Human

Non-Clinical – Pharmacokinetics

- Rapid absorption and high oral bioavailability
- Low total body clearance across all species studied (rats, dogs, and monkeys)
 - Renal clearance is a minor component of the overall elimination (renal clearance <0.001% of total clearance)
- No marked accumulation in plasma (rats and monkeys)
- High plasma protein binding (99.4% to 99.8%) in the rat, dog, monkey, and human
- Low risk of 5 major CYPs mediated drug-drug interaction (DDI)
 - $IC_{50} > 100 \mu\text{M}$ against CYPs (1A2, 2D6, 2C19, 3A4)
 - CYP2C8 ($IC_{50} = 3 \mu\text{M}$), CYP2C9 ($IC_{50} = 35 \mu\text{M}$)
- Major excretion route
 - Rats: Biliary

Non-Clinical – Pharmacokinetic Studies

	Study Type	Route of Administration	Species/Cell Line
Absorption	Single Dose	IV and PO	Rat, Dog, Monkey
	Multiple Dose	PO	Rat, Monkey
Distribution	Tissue Distribution (QWBA)	PO	Rat
	Plasma Protein Binding	–	Rat, Dog, Monkey, Human
	CNS Penetration	PO	Rat
Metabolism	In Vivo Metabolism	IV	Rat, Dog, Monkey
	In Vitro Metabolism	–	Rat, Dog, Monkey, Human Hepatocytes
	Inhibition of Drug Metabolizing Enzymes (DDI)	–	Human
Excretion	Excretion into Urine	IV	Rat, Dog, Monkey
Others	Cell Permeability Assay	–	Caco-2

- General Toxicity
 - In rats (13-week dose), death due to GI-related toxicities has been observed and NOAEL was determined to be 2.5/1 mg/kg (male/female)
 - In Monkeys (13-week dose), NOAEL was determined to be 200 mg/kg (no remarkable toxicities observed at the highest dose in the study)
 - In Dogs (single dose), no remarkable effects were observed at doses up to 100 mg/kg
- Genotoxicity
 - All “negative” in Ames, *in vitro* Chromosomal aberration, and *in vivo* micronucleus test
- Developmental and Reproductive Toxicity
 - In rats, did not induce developmental toxicity and teratogenicity at any doses up to 5 mg/kg
 - In rabbits, developmental toxicity including malformation were observed at 10 mg/kg or more, which was considered equivocal due to lack of dose dependency



Non-Clinical – Toxicology Studies

Study Type and Duration		Route of Administration	Species/ Cell Line
Single-Dose Toxicity		PO	Dog, Monkey
Repeated-Dose Toxicity	7-Day Range-Finding	PO	Rat
	2-Week	PO	Rat, Monkey
	3-Month	PO	Rat, Monkey
Genotoxicity	Bacterial Reverse Mutation (AMES)	–	S. typhimurium, E coli
	Chromosomal Aberration	–	Human Lymphocyte
	In Vivo Micronucleus Assay	PO	Rat
Reprotoxicity	Range-Finding in Pregnant Animals	PO	Rat, Rabbit
	Embryo-Fetal Development	PO	Rat, Rabbit



Clinical – Phase 1

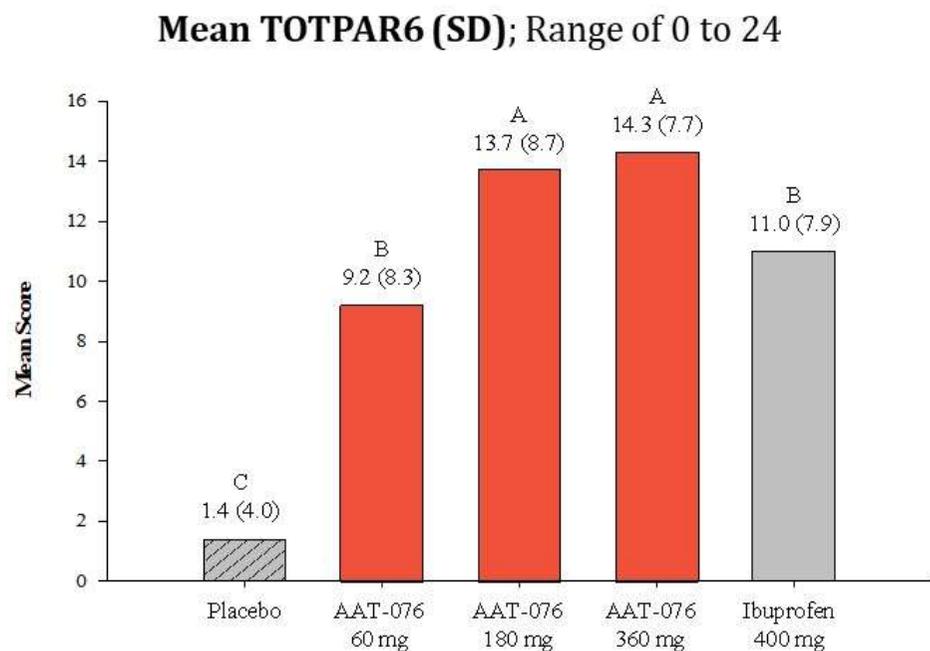
- Well-tolerated at single doses up to 360 mg and multiple doses for 10 days up to 180 mg
- Systemic exposure increased in dose-proportional manner after single- and multiple-dose administration
- No serious adverse events were observed
- Advanced tablet formulation bioequivalent to oral solution identified



Clinical – Phase 2

- Two Phase 2 post-operative dental pain studies were conducted in the US
- A single oral 60 mg dose of AAT-076 with capsule formulation demonstrated superior overall efficacy compared with placebo in regards to time-to-analgesia and time-to-rescue medication
- A single oral dose of 180 or 360 mg AAT-076 with oral solution formulation provided significantly greater analgesic efficacy, faster onset, and longer duration compared with 400 mg ibuprofen
- AAT-076 was safe and well-tolerated; no dose-related safety findings were evident

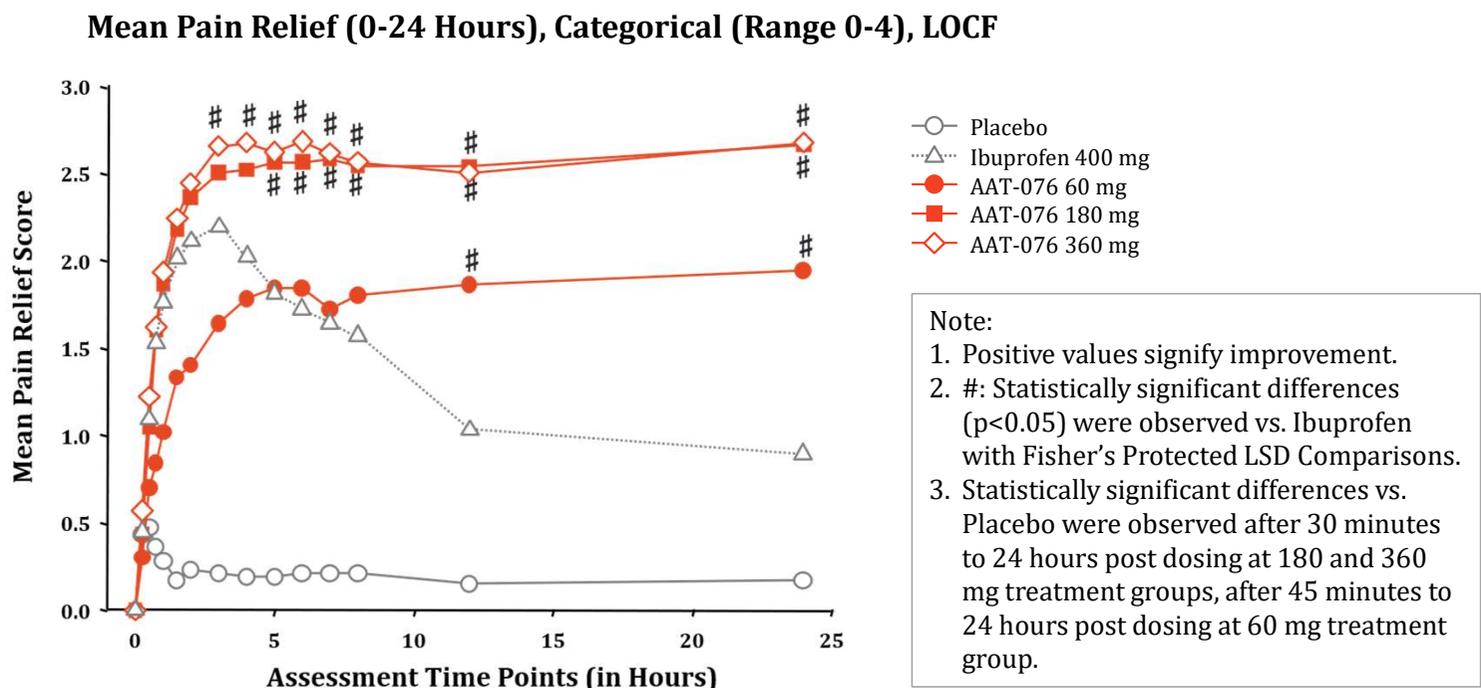
- Primary Endpoint: Total Pain Relief through 6 hours
 - AAT-076 60, 180, and 360 mg groups had a significantly higher TOTPAR(6) score (improvement) compared with placebo group
 - Additionally, AAT-076 180 and 360 mg groups had a significantly higher TOTPAR(6) score compared with ibuprofen 400 mg group



Treatments with the same letter code are not significantly different from each other. (Comparisons are made at 5% level of significance. Type I error is protected with Fisher's protected LSD.)

- Pain Relief (PR)

- Subjects who received 180 mg AAT-076 had significantly greater PR from Hour 5 through 24 compared with subjects who received ibuprofen
- Subjects treated with 360 mg AAT-076 had significantly greater PR from Hour 3 through 24 compared with subjects treated with ibuprofen



- Time to Onset of Analgesia

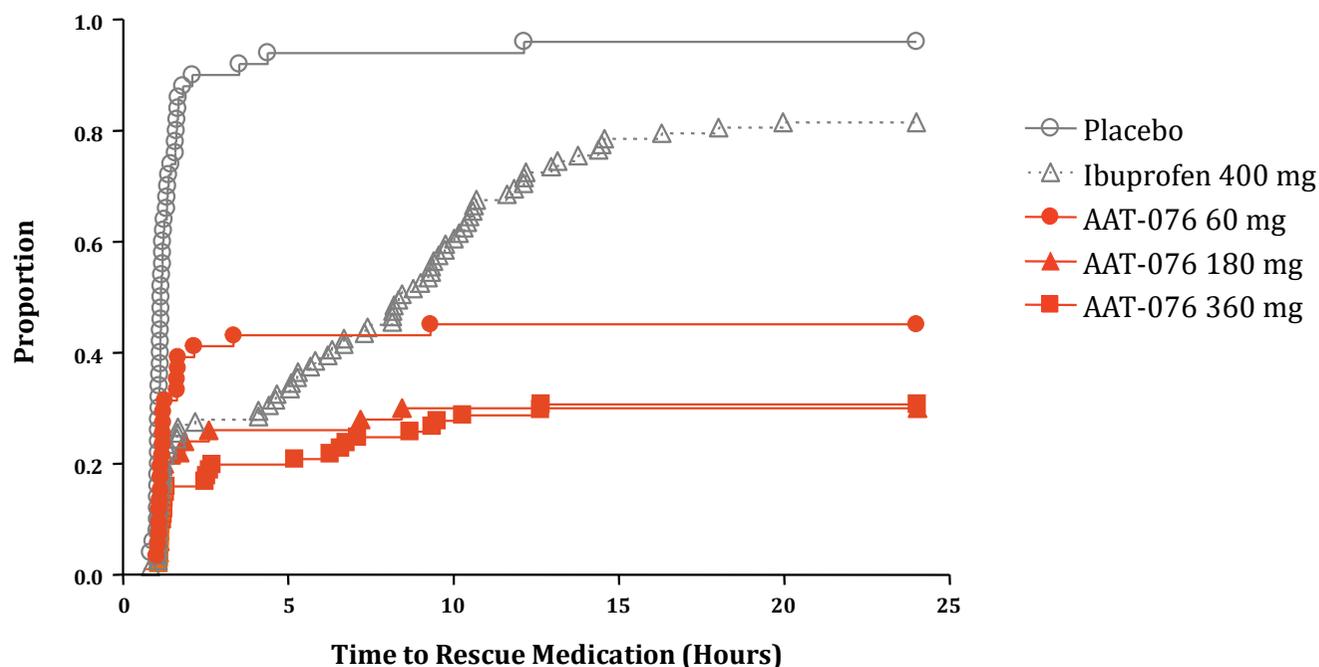
- Significantly faster in the 360 mg AAT-076 treatment group (00:20 min) compared with 400 mg ibuprofen (00:28 min), 60 mg AAT-076 (00:55 min), and placebo treatment group (>24 hours)
- A clear dose response was observed in onset of analgesia for AAT-076-treated subjects

Treatment Group	Median Time (Hour:Minute)	Statistically Significant Group Differences ^a
Placebo	>24:00	C
Ibuprofen, 400 mg	00:28	B
AAT-076, 60 mg	00:55	B
AAT-076, 180 mg	00:28	AB
AAT-076, 360 mg	00:20	A

^a Log Rank test applied. Type I error is protected with Fisher’s protected LSD. Treatments with the same letter are not significantly different from each other. Subjects not experiencing onset of analgesia were censored at 24 hours. Subjects who dropped out for reasons other than rescue medication were censored at the drop out time.

- Time to Rescue Medication

- The median time to rescue medication was significantly longer in the 360 mg AAT-076 treatment group (>24 hours) compared with the 400 mg ibuprofen group (08:26 hr:min)
- The median time to rescue medication was >24 hours for all AAT-076 dose groups



Clinical Efficacy (AAT-076 vs. existing drugs)

- AAT-076 showed superior analgesic profile over celecoxib and ibuprofen in postoperative dental pain clinical trials

Treatment Group (No of subjects)	Total Pain Relief TOTPAR 8	Total Pain Relief TOTPAR 12	Median Time to Perceptible Pain Relief (min)	Median Time to Rescue Medication (h)	Requiring Rescue Medication (%)	Reference*
Placebo (N = 50)	1.82	2.41	>1440	1.17	96.0	a
Placebo (N = 45)	0.7	0.8	>240	1.6	97.8	b
Celecoxib, 400 mg (N = 151)	15.0	21.0	54	10.6	65.6	b
Celecoxib, 200 mg (N = 90)	11.5	16.7	72	6.8	68.9	b
Ibuprofen, 400 mg (N = 100)	14.22	18.34	27	8.43	82.0	a
Ibuprofen, 400 mg (N = 45)	14.7	18.3	30	10.0	86.7	b
AAT-076, 180 mg (N = 50)	18.77	28.93	28	>24	30.0	a
AAT-076, 360 mg (N = 101)	19.46	29.46	18	>24	31.7	a

* a: A6151012 CSR (unpublished), b: Malstrom K, *et al.*: Clinical Therapeutics, 24(10), 1549 (2002)



Clinical Studies Summary

	Phase 1	Phase 2
Studies	<ul style="list-style-type: none"> • Single dose tolerance and PK (up to 360 mg) • Food effect • Multiple dose tolerance and PK (up to 180 mg/day for 10 days) • Formulation development <ul style="list-style-type: none"> – Effect of stomach pH – Bioavailability of the prototype tablet formulations with the solution formulation 	<ul style="list-style-type: none"> • Single doses (3, 10, and 60 mg), rofecoxib (50 mg), and placebo in subjects with post-operative dental pain study with capsule formulation • Comparative efficacy at single doses at 60, 180, and 360 mg as well as ibuprofen (400 mg) and placebo in subjects with post-operative dental pain study with oral solution formulation
Results	<ul style="list-style-type: none"> • Well-tolerated at doses up to 360 mg in single dose and 180 mg in multiple doses (QD for 10 days) • Dose proportionally increased systemic exposure after single- and QD multiple-dose administration up to 360 mg and 180 mg, respectively • No serious adverse events • Advanced tablet formulation for the next step identified 	<ul style="list-style-type: none"> • Efficacy in terms of onset, magnitude, and duration of analgesia confirmed at a single dose of 60 mg with capsule formulation • Significantly greater analgesic efficacy, faster onset, and longer duration at a single dose of 180 and 360 mg with oral solution compared with ibuprofen (400 mg) <ul style="list-style-type: none"> – Superior overall analgesic efficacy at a single oral dose of 60 mg compared with placebo • Safe and well tolerated; no dose-related safety findings



“PRECISION” Trial

Prospective Randomized Evaluation of Celecoxib Integrated
Safety versus Ibuprofen or Naproxen

Publication:

Titled “Cardiovascular Safety of Celecoxib, Naproxen, or
Ibuprofen for Arthritis”

N Engl J Med 2016; 2519-2529



“PRECISION” Trial

Background

- Discussion at the FDA Advisory Committee Meeting on cardiovascular (CV) risk of COX-2 NSAIDs in 2015
- FDA mandated study - Commitment by Pfizer to FDA
- Funded by Pfizer

Organization

- Independent Executive Committee
 - Principal Investigator and Study Chair- Steven Nissen, MD – Cleveland Clinic
- Independent Data Monitoring Committee
 - Chair - Thomas R. Fleming, Ph.D. – University of Washington
- Experts in Cardiology, Rheumatology and Gastroenterology on both committees



“PRECISION” Study Design-1

Allocation

- Randomized

Intervention Model

- Parallel Assignment

Masking

- Double Blind (Subject, Caregiver, Investigator)

Subject

- Enrolled OA or RA patients who were over 18 years of age and who, as determined by the patient and physician, required daily treatment with NSAIDs for arthritis pain; patients whose arthritis pain was managed adequately with acetaminophen were not eligible
- A Key inclusion criterion was established cardiovascular disease or an increased risk of the development of cardiovascular disease

Group

- Celecoxib, 100 to 200 mg twice daily
- Ibuprofen, 600 mg to 800 mg three times daily
- Naproxen, 375 mg to 500 mg twice daily

Primary Objective

- To assess the relative cardiovascular effects of celecoxib, ibuprofen and naproxen in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA)

Primary Outcome

- Time-to-event analysis of the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (i.e. death from CV causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke)

Secondary Outcome

- Major adverse CV events, included the components of the primary outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack
- Clinically significant gastrointestinal (GI) events

Tertiary Outcome

- Clinically significant renal events, iron deficiency anemia of GI origin, and hospitalization for heart failure or hypertension

Non-adjudicated Secondary Outcome

- Assessment of the intensity of arthritis pain with the use of the Visual Analogue Scale for Pain



“PRECISION” Study Results-1

- A total of 24,081 OA and RA patients were randomly assigned to three groups
 - Celecoxib group, daily dose, 209 ± 37 mg (mean \pm SD)
 - Naproxen group, daily dose, 852 ± 103 mg
 - Ibuprofen group, daily dose, 2045 ± 246 mg
- Mean treatment duration of 20.3 ± 16.0 months
- Mean follow-up period of 34.1 ± 13.4 months

“PRECISION” Study Results-2

Cardiovascular safety

- Celecoxib noninferior to ibuprofen or naproxen
 - Intention-to- treatment analysis

Group	Number of patients of primary APTC end point (percent)	Adjusted Hazard Ratio (95% CI)	P Value vs. celecoxib
Celecoxib (N = 8072)	188 (2.3%)	-	-
Ibuprofen (N = 8040)	218 (2.7%)	0.85 (0.70-1.04)	0.12
Naproxen (N = 7969)	201 (2.5%)	0.93 (0.76-1.13)	0.45

- On-treatment analysis

Group	Number of patients of primary APTC end point (percent)	Adjusted Hazard Ratio (95% CI)	Noninferiority comparison, P Value vs. celecoxib
Celecoxib (N = 8030)	134 (1.7%)	-	-
Ibuprofen (N = 7990)	155 (1.9%)	0.81 (0.65-1.02)	<0.001
Naproxen (N = 7933)	144 (1.8%)	0.90 (0.71-1.15)	<0.001

Gastrointestinal events

- Significantly lower with celecoxib than with ibuprofen (P = 0.002) or naproxen (P = 0.01)

Renal events

- Significantly lower with celecoxib than with ibuprofen (P = 0.004) but was not significantly lower with celecoxib than with naproxen (P = 0.19)

