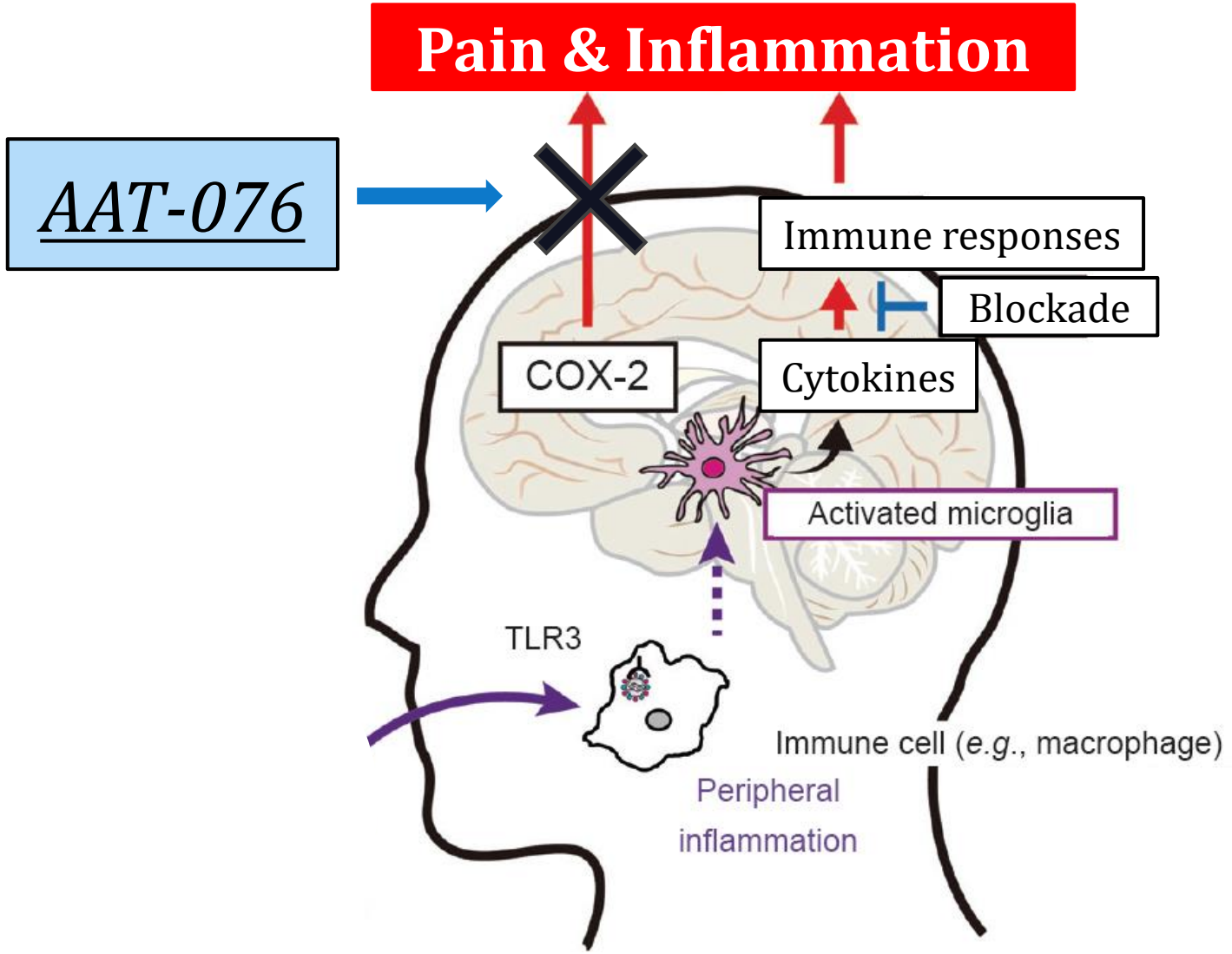
A Novel Opioid-Sparing Pain Therapy: Acute, Chronic and Neuropathic Pain

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

ASKAT

Non-confidential Information



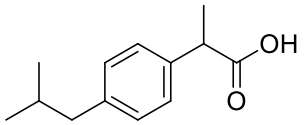
Executive Summary

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

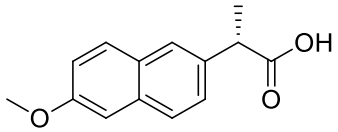
- Phase 1 and Phase 2 results in the US
  - Safe, well-tolerated up to 360 mg, 10 days up to 180 mg/day
  - Superior Efficacy vs Ibuprofen, i.e., onset, potency, and duration
  - Opioid sparing potential suggested
  - Safety advantages include Renal, GI and no platelet inhibition
- IP status (as of January 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

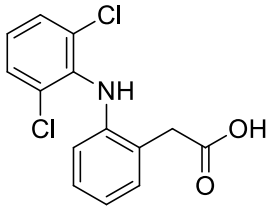
Non-Selective NSAIDs



Ibuprofen

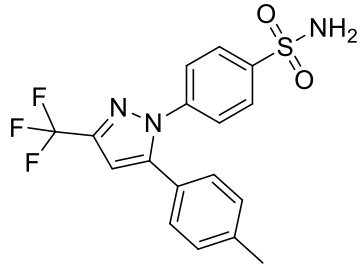


Naproxen

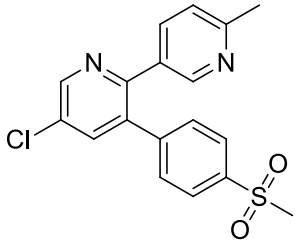


Diclofenac

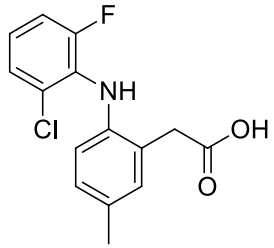
COXIBs



Celecoxib

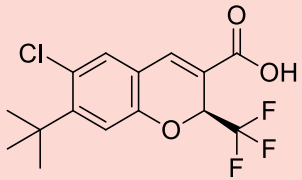


Etoricoxib



Lumiracoxib

Super NSAID



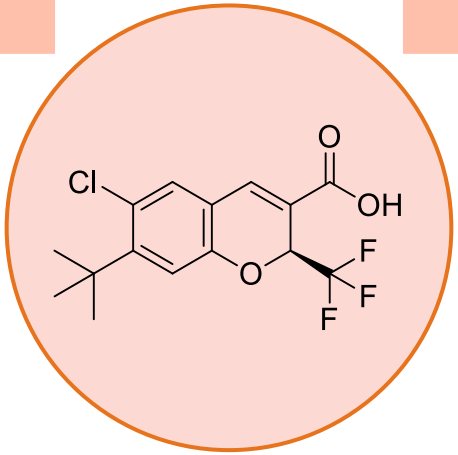
AAT-076

Key Attributes of AAT-076

Powerful Non-Narcotic Analgesic, ***Opioid sparing potential,*** and Renal and GI Safety Advantages

Potent and Rapid Efficacy in human with $T_{1/2}$ ~33 h Consistent with QD Dosing

Neuropathic Pain, Cancer Pain. Chronic Pain Opportunity



Over 790 Subjects in P-1 & P-2, Well-tolerated

Solubility & Stability Support Oral and Intravenous Dosing

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

Non-Clinical – Pharmacology

- 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**

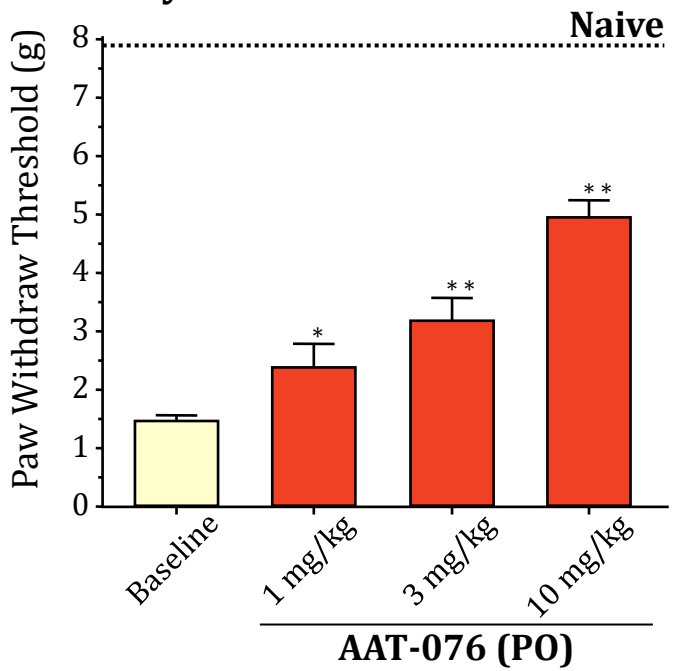
Neuropathic Pain – Spinal nerve ligation (SNL) model

- 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)

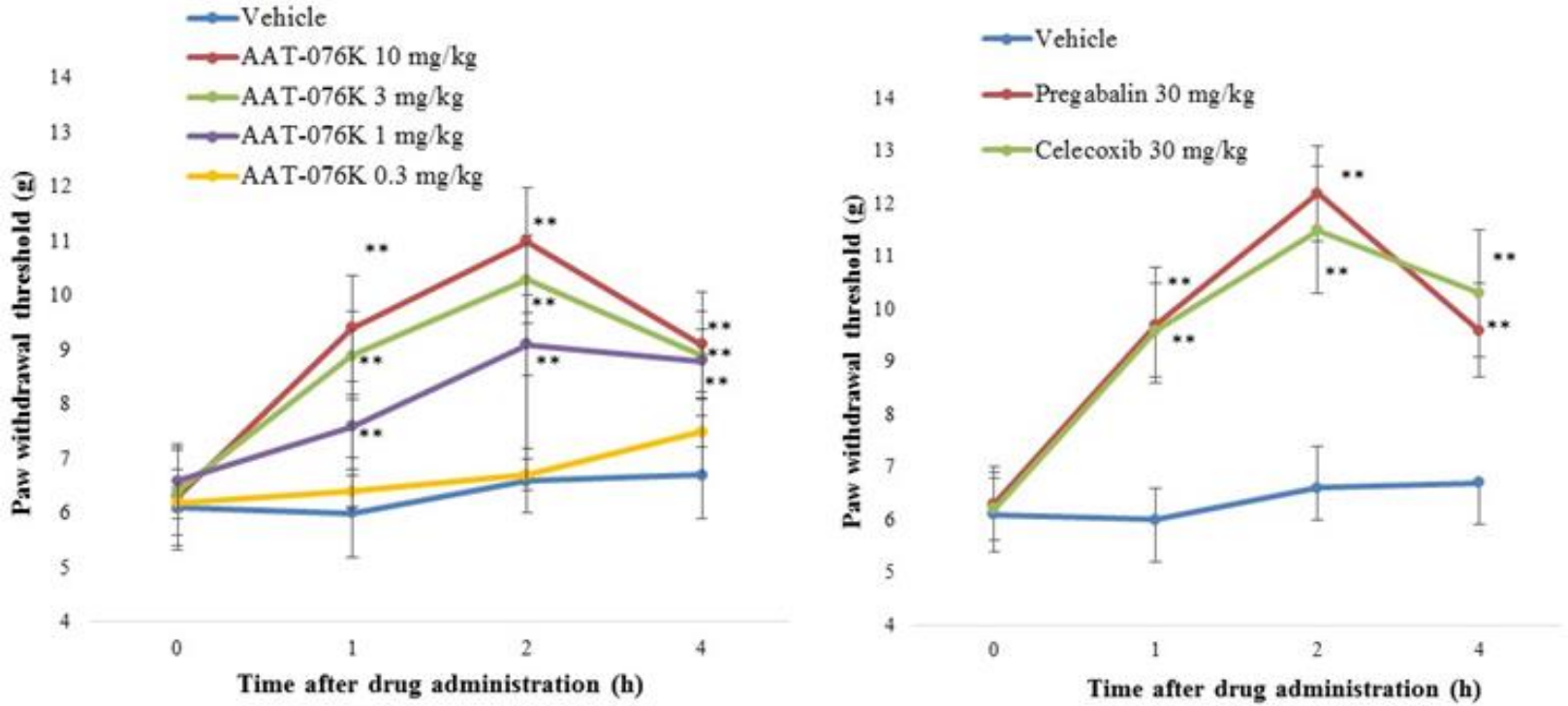
Tactile Allodynia



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 ± 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

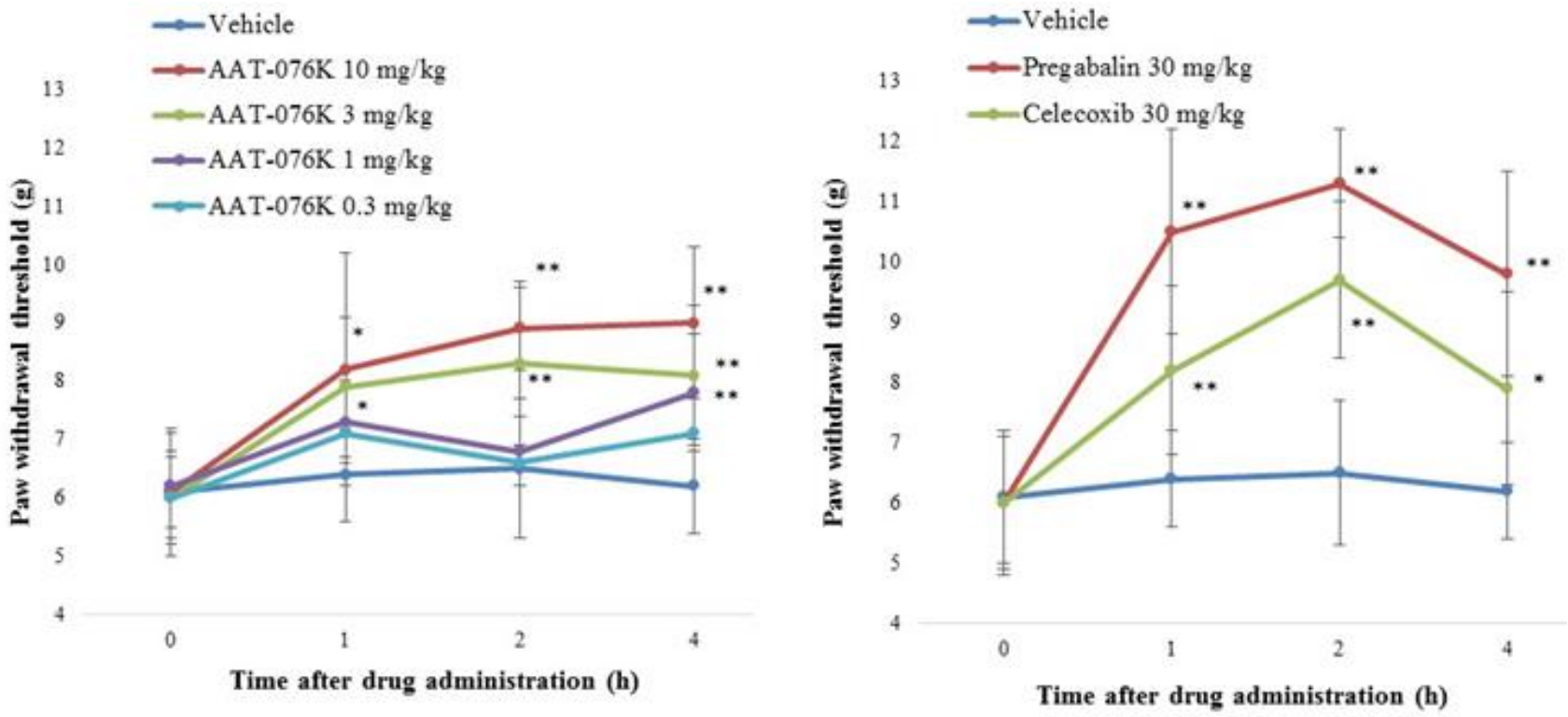
- Efficacy of AAT-076K, Pregabalin and Celecoxib



Data expressed mean ± 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 ± 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**

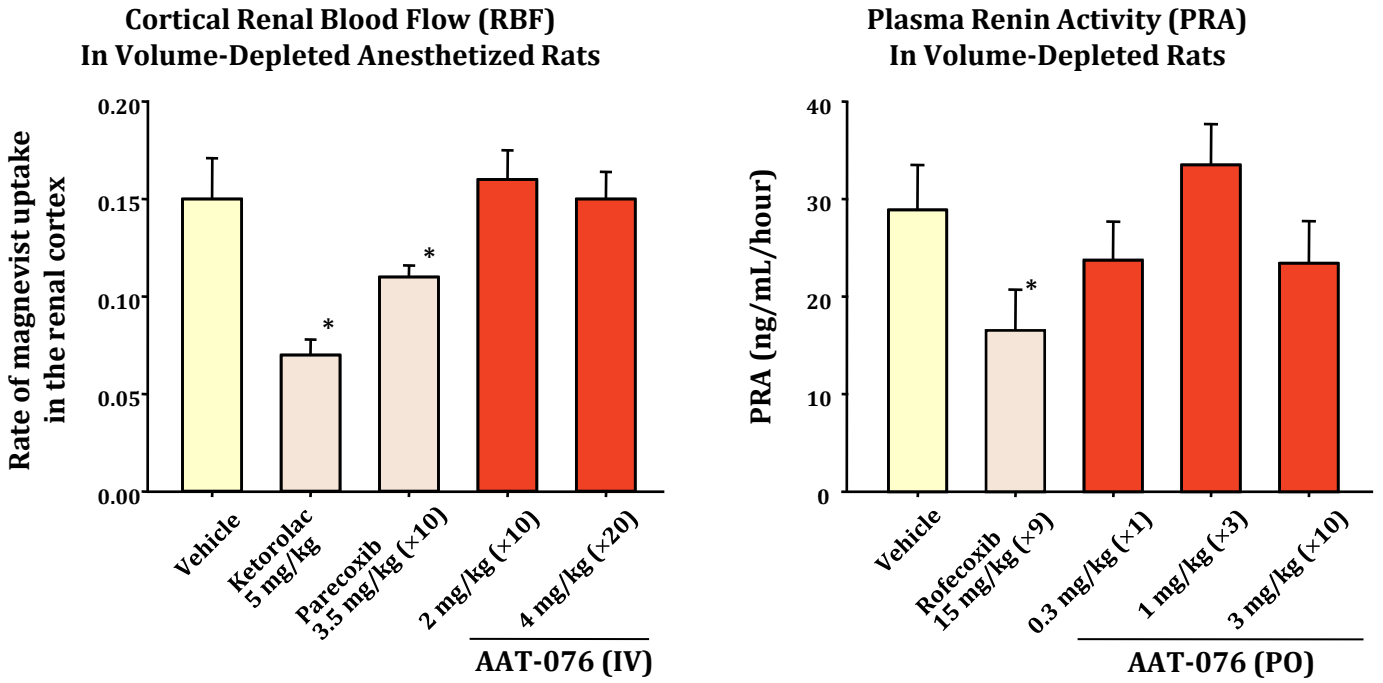
*: US NDA Clinical Pharmacology, Healthy Subjects
#: Phase I, Multiple Dose Study, Healthy Subjects

Non-Clinical – Safety Pharmacology

- 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 μM (approximately 33-fold concentrations over that achieved free fraction of Cmax 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

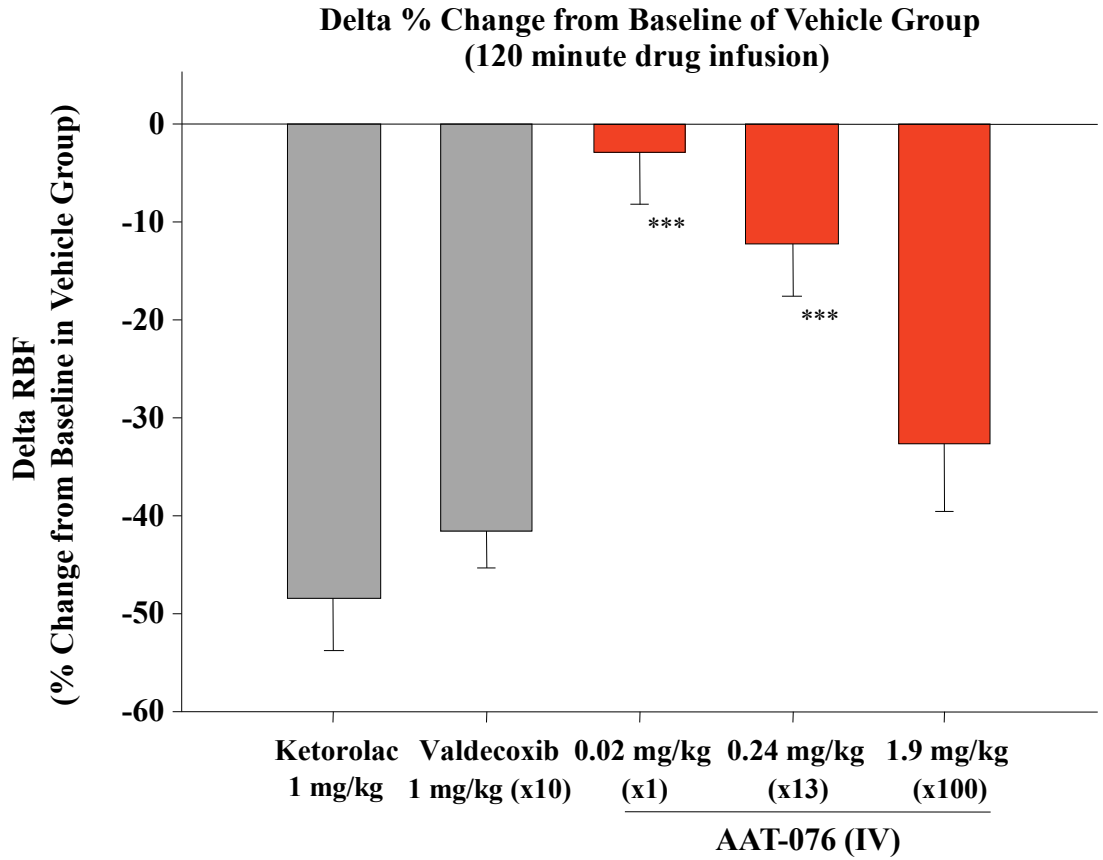
- AAT-076 had no effect on cortical renal blood flow (cRBF) while ketorolac and parecoxib caused a significant reduction in cRBF in anesthetized volume-depleted rats
- AAT-076 did not inhibit plasma renin activity (PRA) during administration of loop diuretic furosemide suggesting that AAT-076 may have 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
× = 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 μM against CYPs (1A2, 2D6, 2C19, 3A4)
  - CYP2C8 (IC_{50} = 3 μM), CYP2C9 (IC_{50} = 35 μM)
- 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

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

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

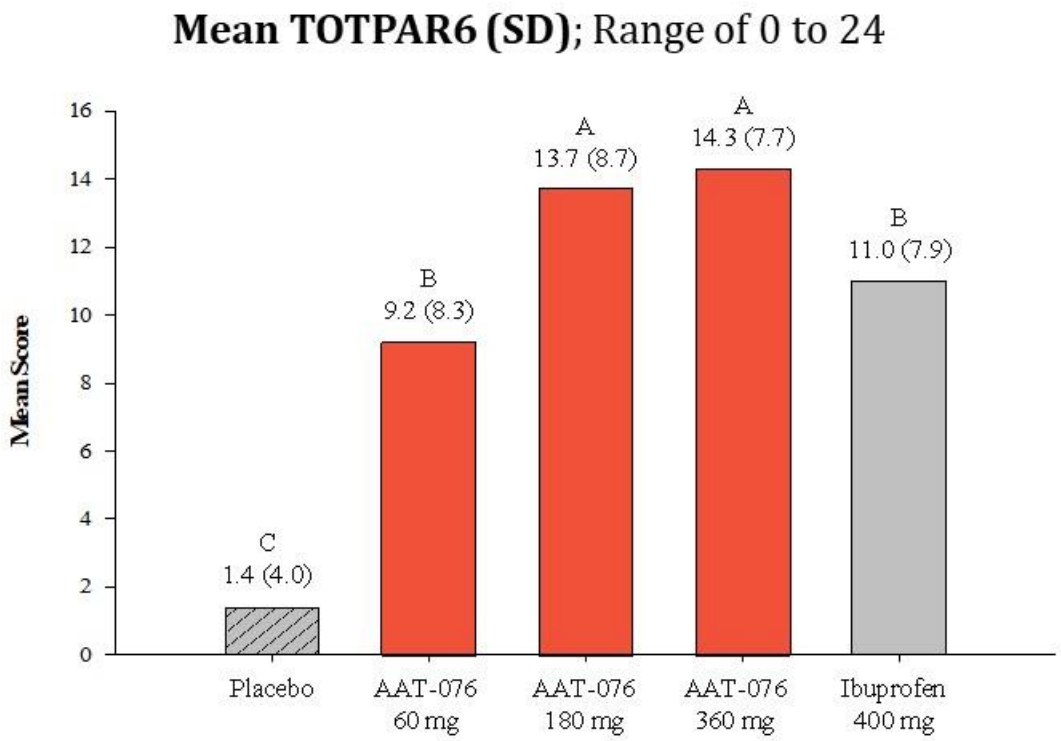
- Well-tolerated at single doses up to 360 mg and multiple doses for 10 days up to 180 mg
- Systemic exposure increased in dose-proportional manner after single- and multiple-dose administration
- No serious adverse events were observed
- Advanced tablet formulation bioequivalent to oral solution identified

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

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

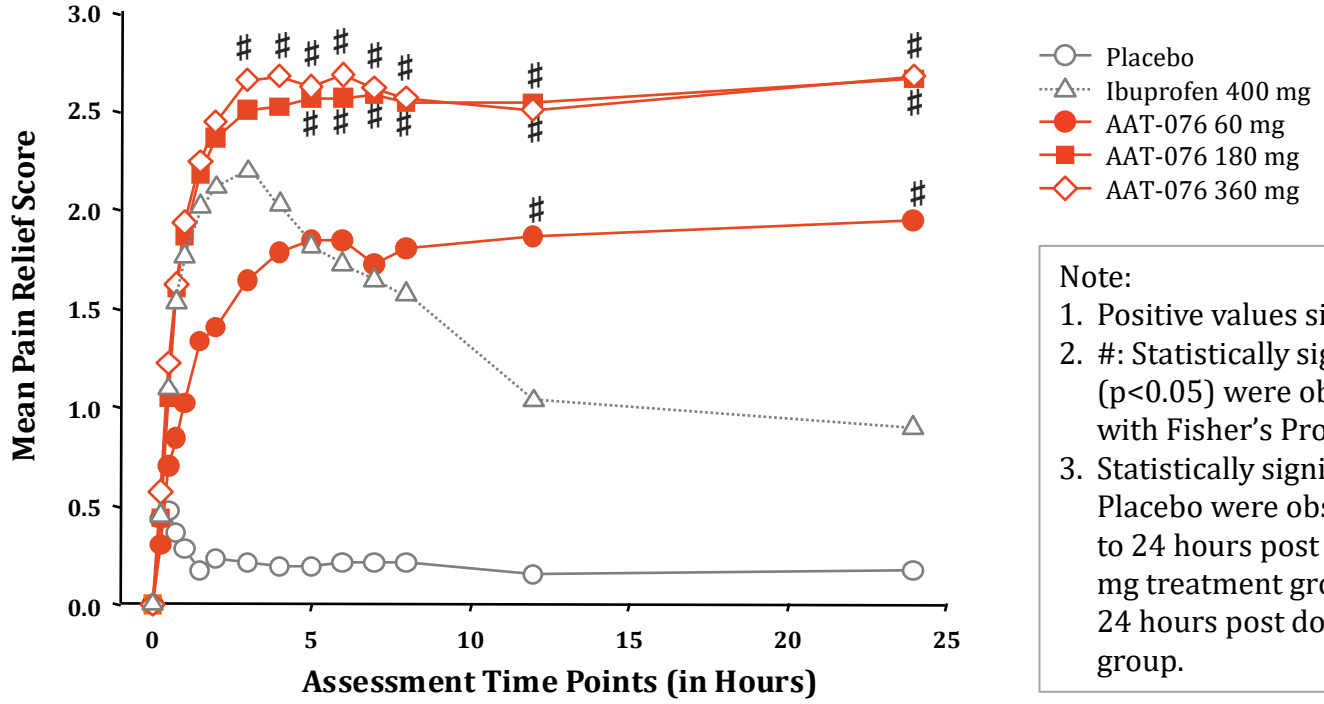


Treatments with the same letter code are not significantly different from each other. (Comparisons are made at 5% level of significance. Type I error is protected with Fisher's protected LSD.)

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.

Clinical – Phase 2

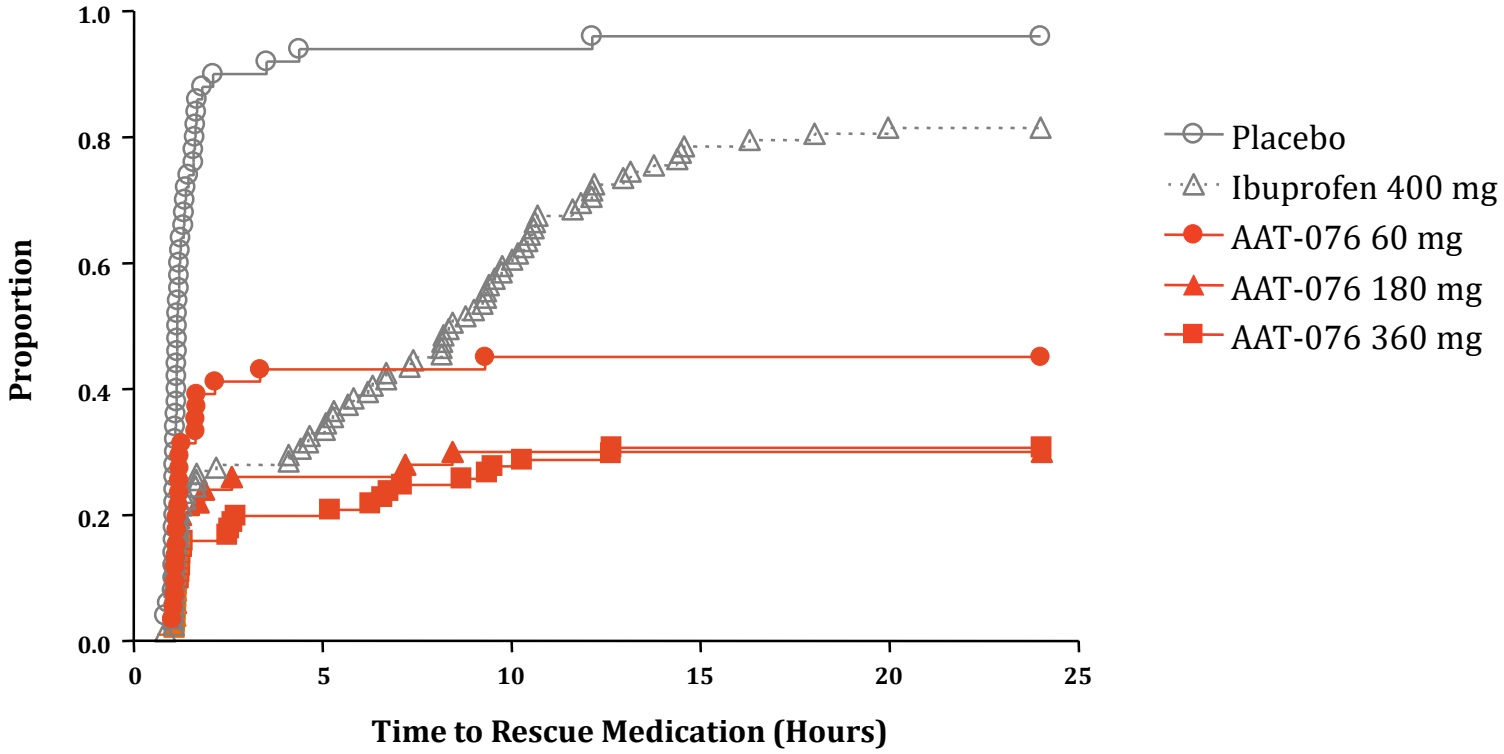
- Time to Onset of Analgesia
  - Significantly faster in the 360 mg AAT-076 treatment group (00:20 min) compared with 400 mg ibuprofen (00:28 min), 60 mg AAT-076 (00:55 min), and placebo treatment group (>24 hours)
  - A clear dose response was observed in onset of analgesia for AAT-076-treated subjects

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.

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



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	• 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 – Effect of stomach pH – Bioavailability of the prototype tablet formulations with the solution formulation	• 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	• 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	• 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) – Superior overall analgesic efficacy at a single oral dose of 60 mg compared with placebo • Safe and well tolerated; no dose-related safety findings

Appendix

"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

“PRECISION” Study Design-2

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 ± 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)