AAT-009 for Mild Cognitive Impairment and Alzheimer's Disease

January 2026

AskAt Inc.

Non-Confidential Information

Executive Summary of AAT-009

- AAT-009 is a potent and selective serotonin receptor 4 (5-HT_4) partial agonist with high brain penetration
- AAT-009 demonstrated pharmacological properties for dementia and Alzheimer's Disease (AD) therapy
  - Increased hippocampal ACh levels specifically under cognitive engagement in the rat
  - Inhibited Aβ accumulation in the brain of Tg2576 mice
  - Exhibited efficacy superior to donepezil in animal models of cognitive impairment
- AAT-009 is safe in human as well as in animals
  - Well-tolerated at up to 20 mg BID for 14 days in Phase 1 clinical studies
  - No major safety issues, including CV and gastrointestinal, were observed in clinical and nonclinical (dogs and rats) safety studies
- Oral AAT-009 is efficacious for patients with gastroesophageal reflex disease (GERD) in Phase 2 study
  - Statistically significant effect on GERD symptoms was achieved at 5 mg QD for 14 days
- Predicted human efficacious dose for impaired cognition is 1~3 mg PO QD based on animal studies and human PK
- Intellectual Property
  - Use patent for dementia issued in the major country including the seven major markets (7MM)

Alzheimer's Disease and Mild Cognitive Impairment

- Alzheimer's Disease (AD)
  - There were 57 million cases of dementia worldwide in 2021, where AD accounted for 60-70 % of dementia cases[1)] and the cases will increase to 152.8 million in 2050
  - Characterized by lowered cognitive functions, memory and physical/mental activity
  - Loss of synapses and neurons, in particular cholinergic neurons, and accumulation of senile plaque, consisting of Aβ protein, and neurofibrillary tangles are observed for AD patients (page 7)
- Mild Cognitive Impairment (MCI)
  - Clinical diagnosis based on subjective cognitive decline, objective cognitive impairment and preserved activities of daily living
  - Transitioning stage between asymptomatic Preclinical and symptomatic Dementia (page 7)
  - A substantial portion (27-42 %) of MCI converts to dementia over time[2)] . The conversion rate is reportedly 10-20 % per year[3)]

1. WHO, Fact Sheets, Dementia, 2025. https://www.who.int/news-room/fact-sheets/detail/dementia
2. Alzheimer's Dement. 2025;17:e70074, https://doi.org/10.1002/dad2.70074
3. Frontiers in Neurology, 2025; 16:1596632, doi: 10.3389/fneur.2025.1596632

Unmet Medical Needs for MCI and AD Therapy

- A therapy to alleviate dementia symptoms in MCI and mild AD patients
  - Acetylcholinesterase (AChE) inhibitors and NMDA receptor antagonist are the main stay for the therapy of MCI and AD
  - These drugs alleviate the disease symptoms temporarily but the side effects and loss of efficacy over time discontinue their use
  - There is a strong demand for drugs that are safe and have long-lasting efficacy

- A disease-modifying therapy to delay the conversion of MCI to AD
  - Anti-Aβ monoclonal antibodies are currently marketed for patients with MCI and mild AD
  - Diagnosis (amyloid PET), side effects (brain bleeding and swelling) and drug price limit the use of the antibodies
  - There is still a strong need for innovative drugs that delay the conversion of MCI to AD without serious side effects at a lower price

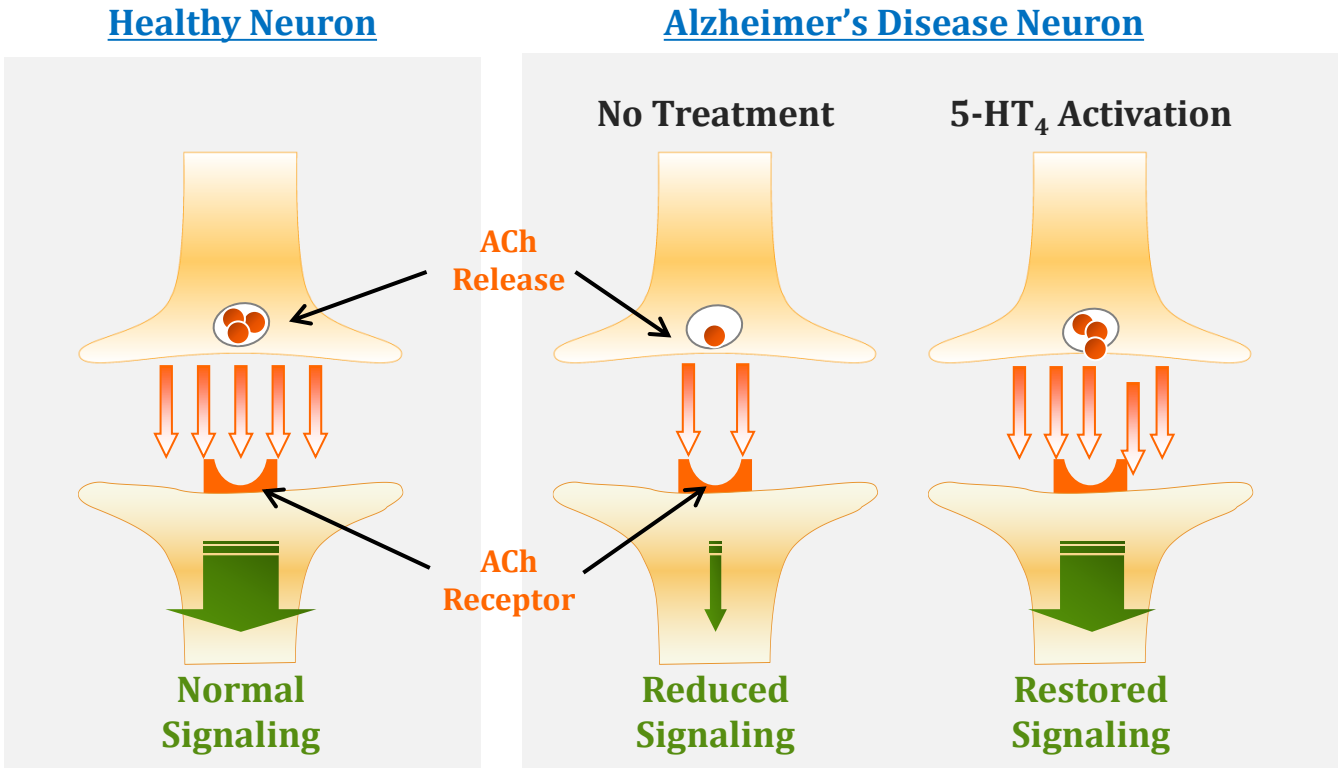
Rationale of 5-HT_4 Agonist for Ameliorating AD Symptoms

- AChE inhibitors such as donepezil increased brain ACh levels and showed therapeutic effects on the memory in animal models of AD
- 5-HT_4 agonists reportedly increased brain ACh levels and improved memory in animal models of AD
  - PRX-03140, a 5-HT_4 agonist, increased brain ACh and improved cognitive functions[2, 3)] in the rat
  - Prucalopride, a 5-HT_4 agonist, increased prefrontal cortex ACh and potentiated donepezil effect on ACh elevation in the rat[5)]
- PRX-03140 ameliorated dementia symptoms in a small Phase 2a study. Oral 150 mg for 14 days improved ADAS-cog score by 3.6 from baseline, while placebo worsened by 0.9 in AD patients[1)]
- Prucalopride at 1 mg PO for 6 days improved scopolamine-induced memory deficit in healthy human participants[4)]

1.Keystone Symposia, March 28, 2008; 2.Neuropharmacology, 2007, 53:563.; 3.Neuropharmacology, 2011, 61:69.; 4. Translational Psychiatry, 2021, 11:497 ; https://doi.org/10.1038/s41398-021-01568-4; 5. J. Pharmacol. Exp. Ther, 2012, 341: 681.

Mechanism of 5-HT_4 Agonist in Increased ACh in AD

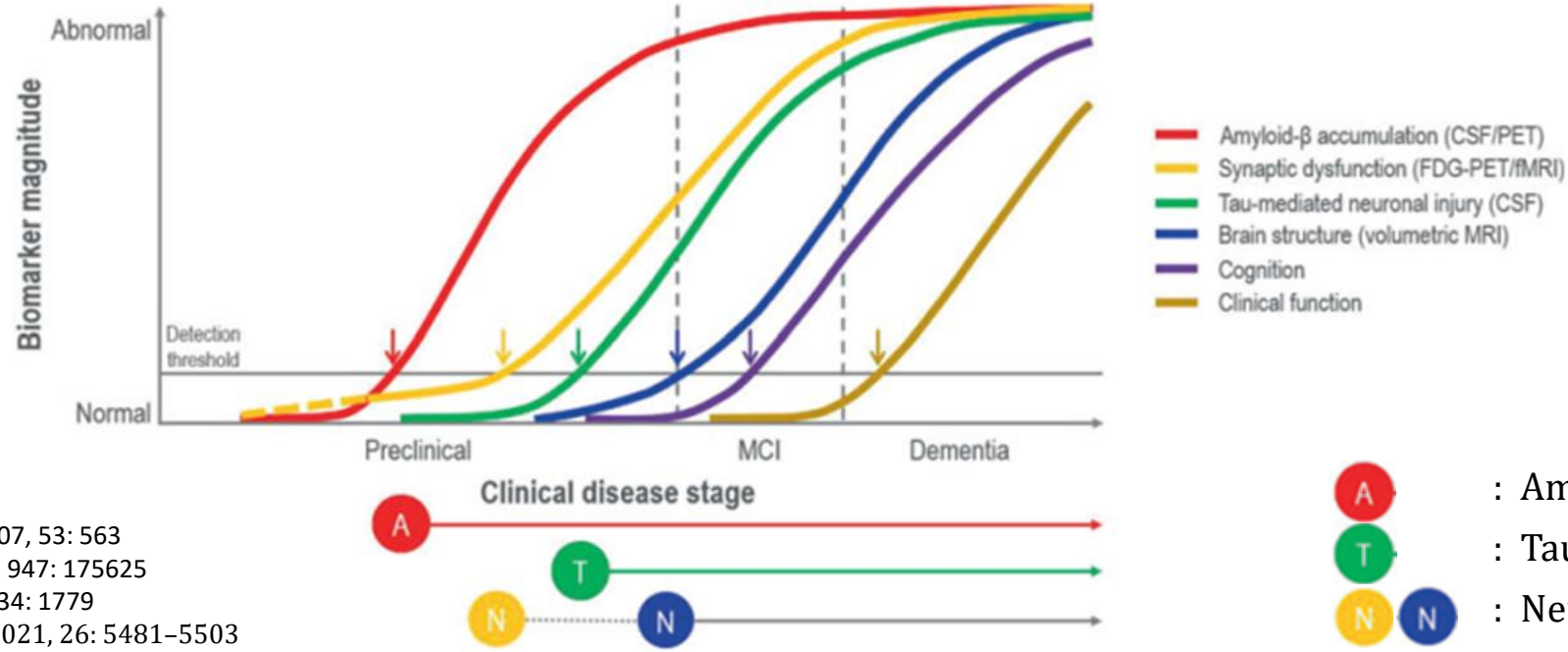
- Activation of 5-HT_4 functions by 5-HT_4 agonist increases brain ACh concentration with cognitive activity-dependent manner (page 13)[1]



1. Neuropharmacology, 2007, 53: 563-573

Rationale of 5-HT$_4$ Agonist for the Disease-modifying Therapy

- AAT-009 and other 5-HT$_4$ agonists decreased brain Aβ accumulation in AD model mice [1-3]
- Aβ accumulation, tau phosphorylation following synaptic dysfunction and neuronal loss begin at the late preclinical and continue during MCI stage which is more than 10 years before the AD onset [4]
- Suppressing Aβ accumulation during the MCI stage can delay the conversion of MCI to AD



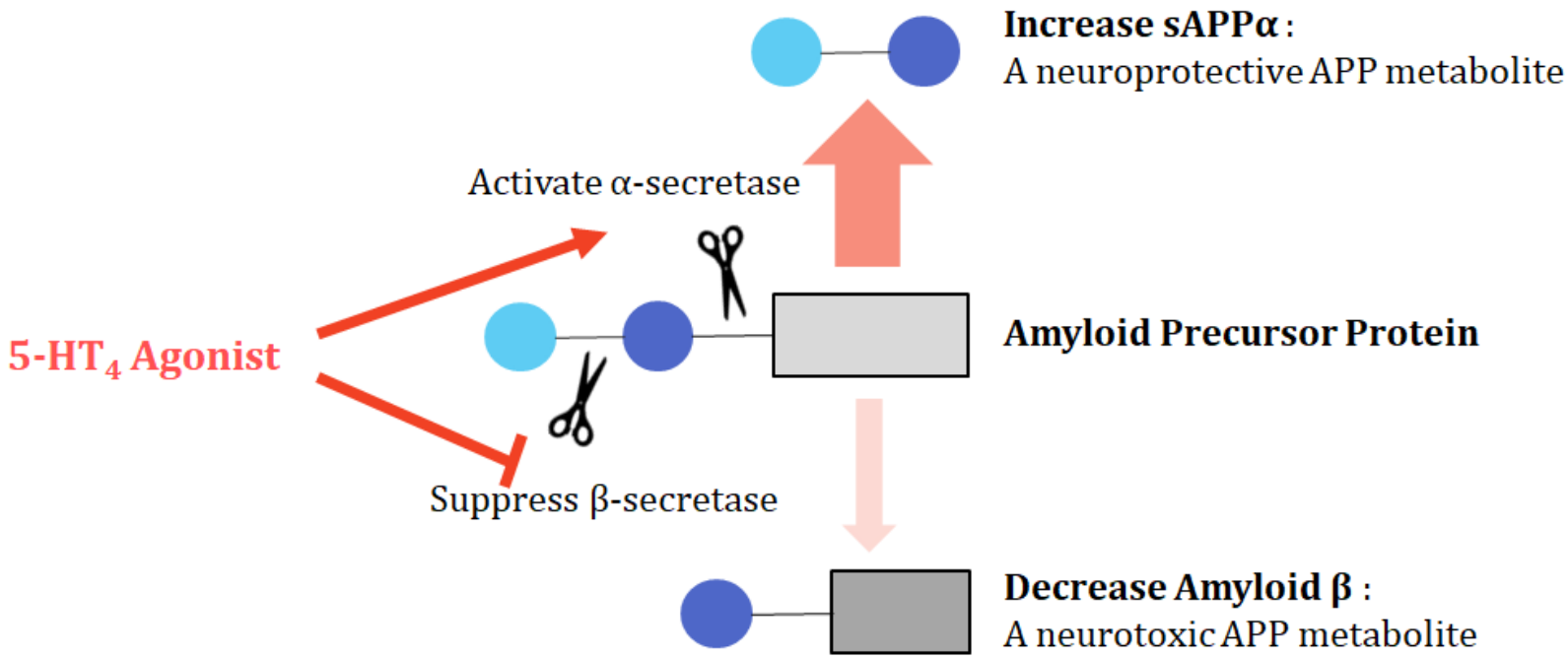
A : Amyloid Aβ

T : Tau protein

N N : Neuronal injury

1. Neuropharmacology, 2007, 53: 563
2. Eur. J. Pharmacol., 2023, 947: 175625
3. Neurobiol. Aging, 2013, 34: 1779
4. Molecular Psychiatry, 2021, 26: 5481–5503

Mechanism of 5-HT_4 Agonist in Reduced Aβ production



- Amyloid precursor protein (APP) is metabolized to a neuroprotective soluble amyloid precursor protein α (sAPPα) or neurotoxic Aβ by α- and β-secretase, respectively
- 5-HT_4 agonists increase sAPPα and decrease Aβ levels in the brain of mouse models of AD
- 5-HT_4 agonists regulate the APP metabolism from Aβ-dominant to sAPPα-dominant manner and produce neuroprotective and neurotrophic brain environment

AAT-009 Information

5-HT_4 Receptor Partial Agonist, AAT-009

1. Compound Information

- Compound code
  - AAT-009
- Modality
  - Small molecule
- Chemistry, manufacturing and control
  - Drug substance:
    - No major issue in the bulk campaign to provide ~1.8 kg
    - No stability issue (stable for 36 months at 25 ˚C/60% RH)
  - Drug product:
    - Highly soluble and permeable
    - Film coated tablets for clinical studies
    - No stability issue (stable for 24 months at 25 ˚C/60% RH)

2. Nonclinical Pharmacology

- Binding affinities to human 5-HT receptor subtypes

5-HT receptor	Ki (nM)	
	AAT-009	PRX-03140 [1]
5-HT_4	0.90*	31**
5-HT_{1A}	>4900	>5000
5-HT_{1B}	>5600	>5000$^{\$}$
5-HT_{1D}	>4300	>5000$^{\$\$}$
5-HT_{2A}	>5800	>5000
5-HT_3	1700***	>5000
5-HT_7	>4800	>5000

- 5-HT_{4d}, ** 5-HT_{4a}, *** 5-HT_{3A}, $ Rat, $$ Bovine

1) Neuropharmacology, 2007, 53: 563-573

AAT-009 has a highly selective and potent affinity to the human 5-HT_4 receptor

2. Nonclinical Pharmacology

- Functional activities against 5-HT_4 receptor

Assay		AAT-009		PRX-03140	
		EC_{50} (nM)	E_{max}* (%)	EC_{50} (nM)	E_{max} (%)
Human 5-HT_4 cAMP formation	5-HT_{4a} [1)]	0.092	86	15–93 [2)]	41–53 [2)]
	5-HT_{4b} [1)]	0.19	101	18–42 [2)]	39–59 [2)]
	5-HT_{4d}	1.3	70	NT**	NT
Rat TMM ***		2.0	77	NT	NT

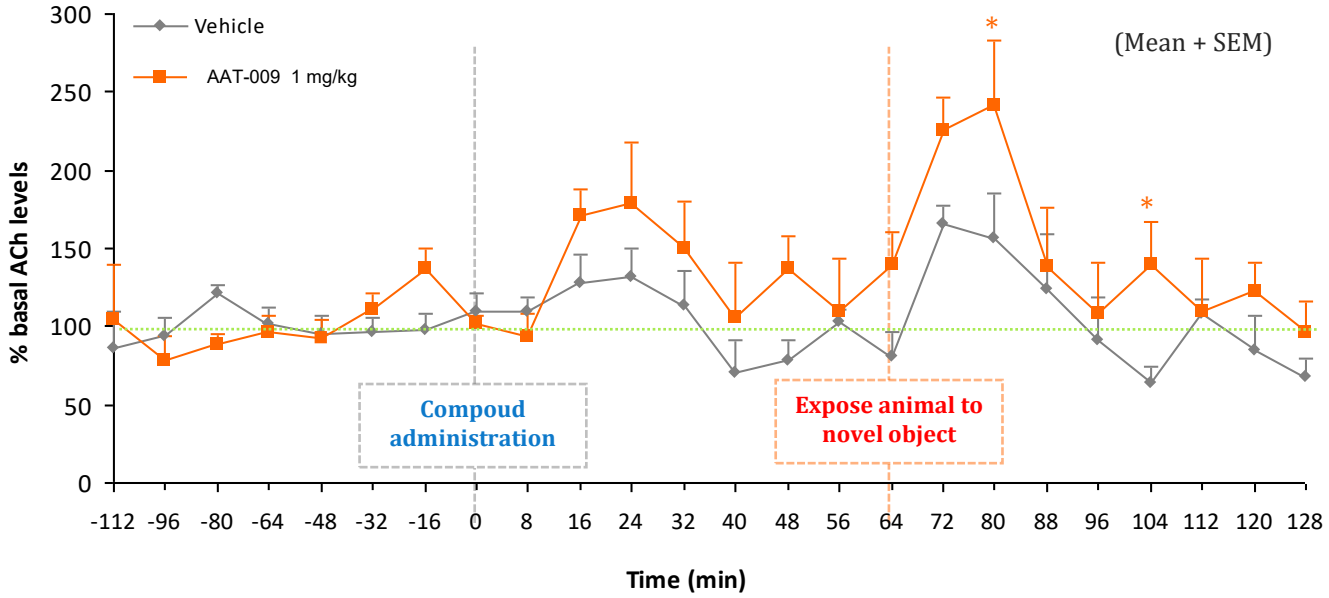
* E_{max}: % of 5-HT maximal response
** NT: Not tested
*** TMM: Tunica Muscularis Mucosae (relaxation of carbachol-induced contraction)

AAT-009 demonstrated a potent agonistic activity at the human and rat 5-HT_4 receptors and was >100-fold more potent than PRX-03140

1) Highly expressed in the brain
2) Neuropharmacology, 2007, 53: 563-573

2. Nonclinical Pharmacology

- Hippocampus ACh levels were determined in freely moving rats dosed with AAT-009 and exposed to a novel object

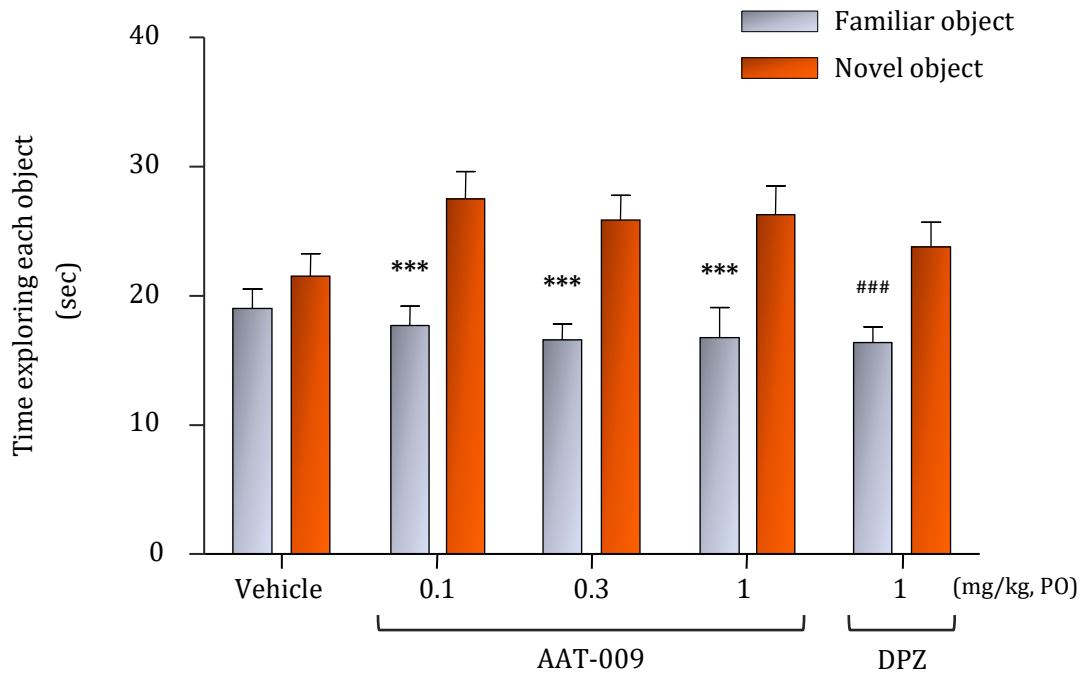


During the test periods, microdialysis probe-implanted SD rats (N = 9/group) were placed in the test arena. AAT-009 (1 mg/kg, PO) or vehicle was dosed at Time 0, and rats were exposed to a novel object from Time 64 to Time 128. *P<0.05; vs. vehicle (two-way ANOVA for repeated measurements followed by Student Newman Keuls post-hoc test)

AAT-009 significantly increased hippocampus ACh levels over placebo only during a novelty-seeking behavior

2. Nonclinical Pharmacology

- Effect of AAT-009 on time spent exploring the novel or familiar object in the rat



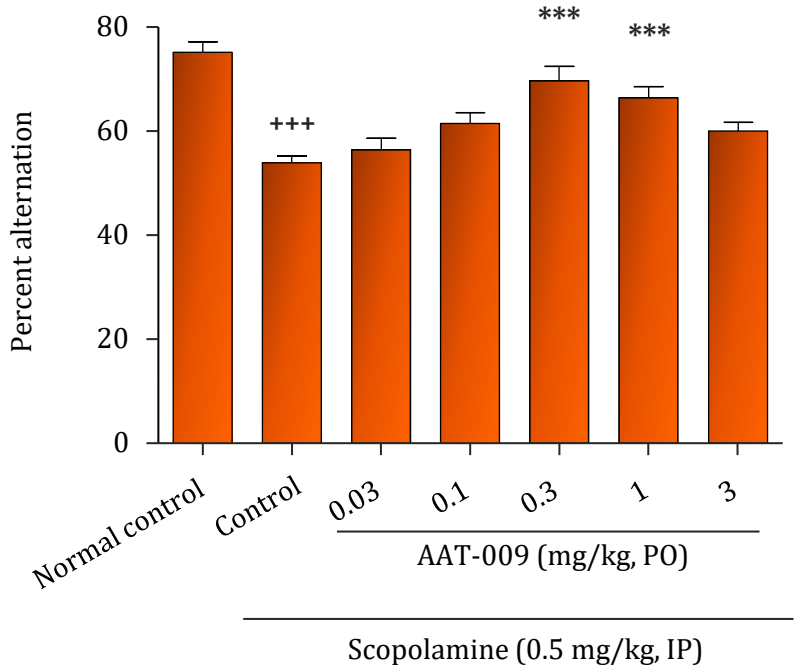
Each value represents the mean + SEM (N = 15)

AAT-009: two-way ANOVA followed by Tukey's multiple comparison test (***P<0.001; vs. novel object)
Donepezil (DPZ): paired t-test (###P<0.001; vs. novel object)

AAT-009 at 0.1 to 1 mg/kg and donepezil at 1 mg/kg increased time of exploring the novel object over time of exploring the familiar object

2. Nonclinical Pharmacology

- Effect of AAT-009 on spontaneous alteration in rats injected with scopolamine



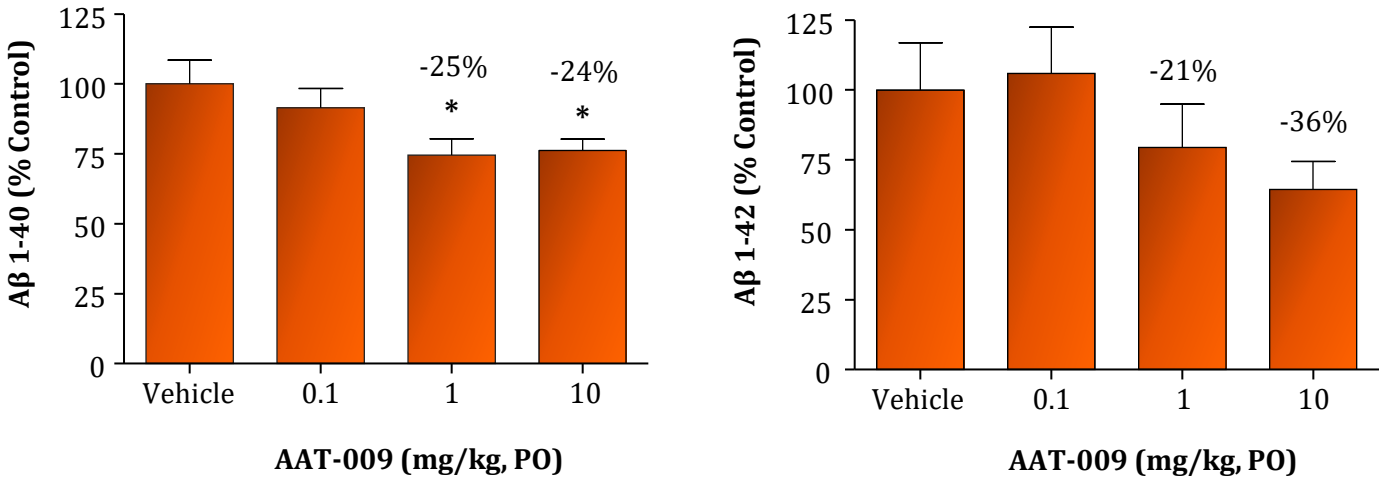
Each value represents the mean + SEM (N = 15). Alteration performance was measured by the number of arm entry of Y-maze. $^{+++}P<0.001$; vs. Normal control (Student's t-test), $^{***}P<0.001$; vs. Scopolamine control (Dunnett's test)

No significant change of total arm entry between each treatment group was observed.

AAT-009 significantly reversed scopolamine-induced decrease of alternation performance at 0.3 and 1 mg/kg, PO in rats

2. Nonclinical Pharmacology

- Effect of AAT-009 on brain Aβ levels in Tg2576 mice



Tg2576 mice (31-weeks old at the beginning of the experiment) were dosed orally twice a day with AAT-009 at doses of 0.1, 1 and 10 mg/kg for 3 weeks.

Each value represents the mean + SEM (N = 9–10).

*P<0.05; vs. vehicle control (one-way ANOVA followed by Dunnett's post-hoc analysis)

Cortical $A\beta_{1\text{-}40}$ significantly decreased by AAT-009 at 1 and 10 mg/kg PO
AAT-009 dose-dependently decreased $A\beta_{1\text{-}42}$ but without statistical significance

3. Nonclinical Pharmacokinetics

- Oral bioavailability
  - Rat: 19.9–27.9%, Dog: 44.1–63.4 %
- Brain penetration in rats
  - $AUC_{inf,brain}/AUC_{inf,plasma}$ = 8.84 (1 mg/kg, PO)
  - Higher brain penetration than PRX-03140 (1 hr after dosing)

Compounds (1 mg/kg SC)	Brain conc. (ng/g)	Brain/plasma ratio
AAT-009	175	3.24
PRX-03140	70.1	1.54

- Drug-drug interaction
  - IC_{50}: >30 μM against cytochrome P450 enzymes (1A2, 2C9, 2C19, 2D6, 3A4)
- Major clearance route
  - Hepatic metabolism: confirmed by rats

AAT-009 exhibited high brain penetration

3. Nonclinical Pharmacokinetics

- Pharmacokinetic Study List

Study Type and Description		Route of Administration	Species/Cell line (Method)
Absorption	Single dose	IV/PO	Rat, Dog
	Plasma conc. in tox study	PO	Rat, Dog (1-month tox)
		PO	Rabbit (Range finding study)
Distribution	Tissue distribution	PO	Rat (Radioactivity)
	Plasma protein binding	-	Rat, Dog, Human (Radioactivity)
	Red blood cell partitioning (blood/plasma ratio)	-	Rat, Dog, Monkey, Human
	Permeability, mechanism, P-glycoprotein substrate properties	-	Caco-2
	Brain penetration	PO/SC	Rat

3. Nonclinical Pharmacokinetics

- Pharmacokinetic Study List

Study Type and Description		Route of Administration	Species/Cell line (Method)
Metabolism	*In vitro* metabolism in liver microsomes	-	Rat, Dog, Monkey, Human
	In vitro metabolism in hepatocytes	-	Rat, Dog, Human
	In vivo metabolism to identify CYP	-	Human
	Isolation and identification of the metabolite	-	Rat, Dog, Human liver microsomes and recombinant CYPs
		PO	Rat, Dog (Radioactivity)
	Inhibition of drug metabolizing enzymes (DDI)	-	Human
Excretion	Excretion	PO	Rat, Dog (Radioactivity)
	Urine excretion	IV	Rat, Dog (LCMS)
	Biliary excretion	IV	Rat (Radioactivity)

4. Nonclinical Safety

- Genotoxicity
  - Negative in all core-battery studies (Ames, HLA* and *in vivo* micronucleus)

- Cardiovascular Toxicity
  - No significant effects observed in dog Purkinje assay
  - No QT changes observed in dog at a dose up to 5 mg/kg
  - IC_{50} values for AAT-009 and PRX-03140 in hERG** assay were 8.64 µM and 1.59 µM, respectively

- General Toxicity (1 month)
  - NOAEL***: 10 mg/kg, PO in rats, and 6 mg/kg, PO in dogs

* HLA: human lymphocyte aberrations, ** hERG: human ether-a-go-go related gene (ERG)

*** NOAEL: no observed adverse effect level

4. Nonclinical Safety

- Toxicology Study List

Study Type and Duration		Route of Administration	Species/Cell line
Acute		PO	Rat
Multiple	7-Day range-finding	PO	Rat
	2-Week range-finding	PO	Rat, Dog
	1-Month	PO	Rat, Dog
Genotoxicity	Ames	-	Microbial
	In vitro cytogenetic	-	Human lymphocytes
	In vivo cytogenetic	PO	Rat
Reproductive*	Range-finding for teratology	PO	Rat
	Range-finding for teratology	PO	Rabbit

* This is not anticipated to be critical for AD therapy

4. Nonclinical Safety

- Safety Pharmacology List

Study Type and Description		Route of Administration	Species/Cell line
Cardiovascular system	Hemodynamics Electrocardiograph	PO	Dog
	Purkinje fiber	-	Dog
	Human ERG assay	-	Human ERG
Central nervous system	Rotarod Locomotor activity	PO	Rat
Respiratory system	Plethysmography	PO	Rat
Renal/urinary system	Excretion of fluid and electrolytes	PO	Rat
Gastrointestinal system	Propulsive activity	PO	Rat
Metabolites/isomers/ finished products	5-HT_3 antagonistic activity of the metabolite	-	Human/ HEK293
	Effect of the metabolite on the Bezold-Jarisch reflex	IV	Rat

5. Clinical Studies

- Clinical Study List

Stage	Study	Participants (N)
Phase 1	Single dose/Safety, Tolerability, PK, Biomarker	Healthy participants (37)
	Single dose/Esophageal Parameters	Healthy participants (30)
	Single dose/Biomarker	Healthy participants (12)
	Multiple dose/Safety, Tolerability, PK	Healthy participants (24)
Phase 2a	Multiple dose/GERD	Patients with GERD (24)

5. Clinical Studies

- Phase 1 study
  - Four studies conducted in healthy participants
    - » Single dose: 0.1 ~ 80 mg
    - » Multiple dose: 10, 20 mg QD, and 20 mg BID for 14 days
  - Oral PK profile
    - » AUC = 174 ng·h/mL, Cmax = 9.5 ng/mL, $T_{½}$ = 22.6 h (6 mg single dose)
  - No serious adverse events observed
- Phase 2a study (Indication: Gastroesophageal reflux disease [GERD])
  - One study was conducted in GERD patients
    - » 5 mg QD and 20 mg BID for 7 days
  - Tolerability confirmed, no serious adverse event observed
  - Statistically significant reduction in the mean number of acid reflux events in patients dosed with AAT-009 at 5 mg QD
  - No clinically-relevant changes in any of the safety parameters

6. Predicted Efficacious Dose for Dementia

	Novel Object Recognition/ Spontaneous Alternation Test in rats	ACh release during novel object recognition test in rats
Rat MED* (mg/kg, PO)	0.3	1
Efficacious plasma conc. in rats (ng/mL)	2.77	11.2
Predicted efficacious plasma conc. in human (ng/mL)	0.453	1.82
Predicted efficacious dose in human (mg QD)	**1**	**3**

Rat and human functional efficacy data, and plasma protein binding data were used for the calculation.
Values in parentheses denote the free exposure levels. * MED: minimum effective dose.

Predicted efficacious dose of AAT-009 is 1~3 mg PO, QD

7. Safety Margin in Human

- Phase 1
  - Single-dose study: well tolerated at doses of 0.1 ~ 80 mg QD
  - 14-day multiple-dose study: well tolerated at doses of 10 mg QD, 20 mg QD, 20 mg BID
  - Long half-life in plasma ($T_{½}$ = 22.5 ~ 47.1 hrs) enables QD dosing
- Phase 2a
  - Efficacy achieved for GERD following 7-day treatment with AT-009 at 5 mg QD
  - No serious adverse event observed
  - No clinically-relevant changes in any of the safety parameters
- A projected efficacy dose for AD therapy is 1~3 mg QD

Based on currently available nonclinical and clinical data,
sufficient safety margin is feasible in AD therapy

8. Intellectual Properties

Patent	Int'l. Publication No. (Int'l. Application No.)	Int'l. Filing Date (Normal Expiration Date)	Status as of January 28, 2026
AAT-009 for Dementia Use	WO 2011/099305 (PCT/JP2011/000793)	February 14, 2011 (February 14, 2031)	Granted: BR, CA, EP (FR, DE, GB, IT, ES), JP, KR, MX, RU, US