AAT-730
A Cannabinoid Receptor 2 Agonist for Stress-induced Diarrhea Therapy in Dogs and Cats

Animal Health

AskAt Inc.

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Non-confidential Information

Executive Summary-1

Compound

AAT-730, a selective CB2 agonist

Background Information

- AAT-730 was licensed to Oxford Cannabinoid Technologies (OCT) in 2019 for human use (WW except Japan).
- Phase 1 FIH study (SAD only) of AAT-730 was completed by OCT, and all doses were well tolerated with no abnormalities or SAEs observed.

Indication

- Stress-induced diarrhea in dogs and cats

Pharmacological Effect

- AAT-730 reduced an increase of fecal weight induced by restraint stress in rats with an MED of 10 mg/kg, p.o..

Safety Pharmacology and Toxicology Studies

- No adverse effects were observed in the respiratory functions (rats) at up to 500 mg/kg, and the cardiovascular and neurobehavioral functions (dogs) at up to 100 mg/kg, p.o..
- NOAEL in dogs was 100 mg/kg, p.o. in 1-month general toxicology study.

CMC

- ~2 kg of GMP API is available

Executive Summary-2

IP Status

- Substance: WO 2010/084767 (PCT/JP2010/000377), filed on January 22, 2010, (US and JP)
- Salt & crystal forms: WO 2022/102713 (PCT/JP2021/041552), filed on November 11, 2021
- Opportunity to file new patents for animal health use.

Studies for NADA Submission

- A pilot POC study on stress-induced diarrhea in laboratory or client-owned dogs/cats
  - Estimated efficacious dose range is 2 ~ 21 mg/kg QD, p.o..
  - Wide safety margin (5 to 50-fold) is expected in dogs based on the results of 1-month repeated oral dose toxicity study.
- Pivotal field efficacy study and target animal safety study with final formulation using client-owned stress-induced diarrhea dogs/cats

Compound Attributes of AAT-730

1. Non-Clinical Pharmacology
   - 1.1 Non-Clinical Efficacy Pharmacology (*In Vitro*)
   - 1.2 Non-Clinical Efficacy Pharmacology (*In Vivo*)
   - 1.3 List of Non-Clinical Safety Pharmacology
2. List of Non-Clinical Pharmacokinetics
3. List of Non-Clinical Toxicology

1.1 Non-Clinical Efficacy Pharmacology (*In Vitro*)

Functional Activity against Forskolin-stimulated cAMP Production in CB1, CB2 Transfectants

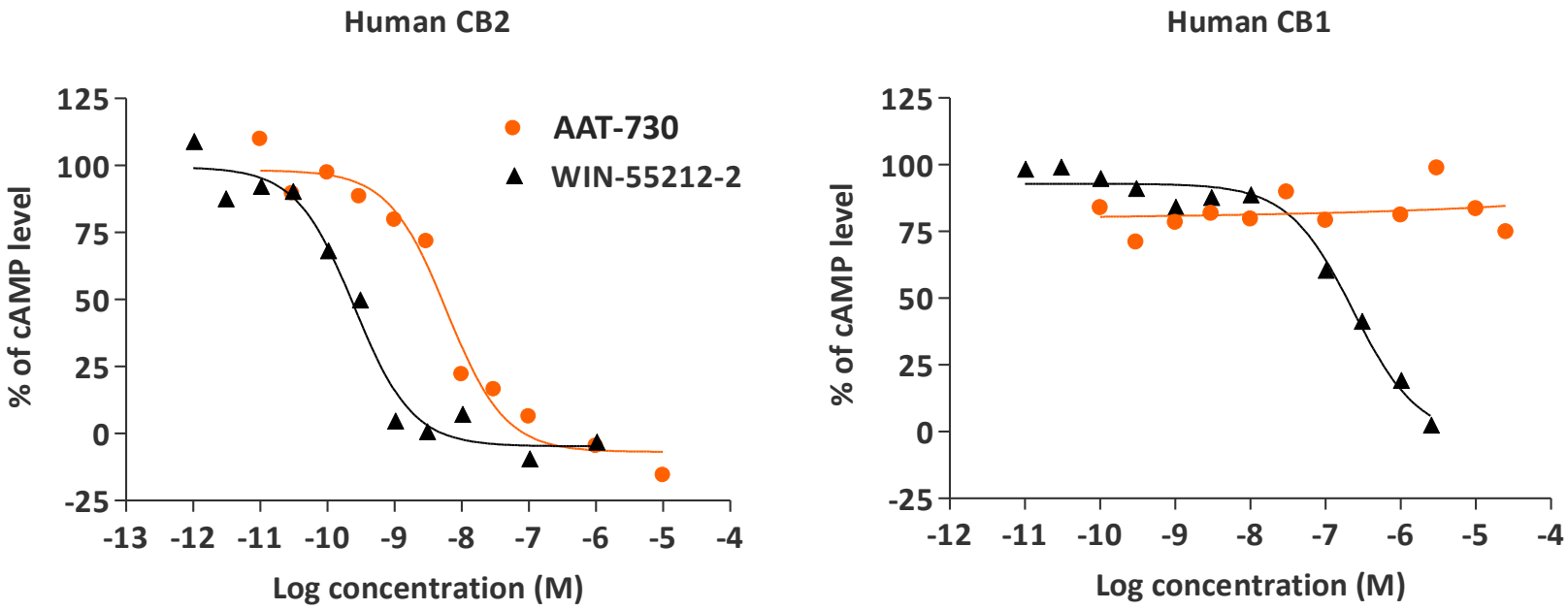
Receptor	EC_{50} (nM)	
	AAT-730	**WIN-55212-2**
Human CB2	5.57 (0.968, 32.0)	0.258 (0.0295, 2.25)
Human CB1	>22,200 (ND)	102 (82.4, 126)
Rat CB2	0.526 (0.423, 0.655)	0.236 (0.128, 0.437)
Rat CB1	2940 (219, 39300)	2.73 (1.22, 6.10)

The potency of AAT-730 for human and rat was assessed by inhibition level of forskolin-stimulated cAMP production in CHO cells expressing CB2 and CB1 receptors. WIN-55212-2 was used as a reference compound.
Data were calculated from 3 experiments. EC_{50} values represent mean (95% confidence interval).

AAT-730 is a potent agonist at human and rat CB2, and >3000 selective for CB2 over CB1.

1.1 Non-Clinical Efficacy Pharmacology (*In Vitro*)

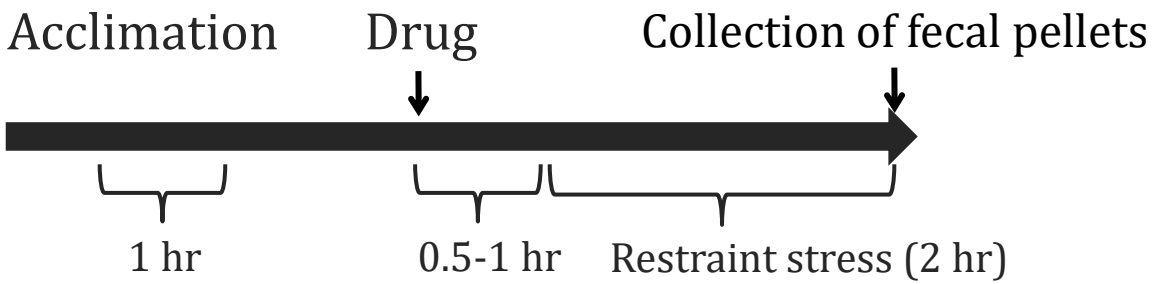
Functional Activity against Forskolin-stimulated cAMP Production in Human CB1, CB2 Transfectants



AAT-730 was assessed by inhibition of forskolin-stimulated cAMP production in CHO cells expressing human CB2 and CB1 receptors. WIN-55212-2 was used as a reference compound.

1.2 Non-Clinical Efficacy Pharmacology (*In Vivo*)

Restraint Stress Defecation in Rats

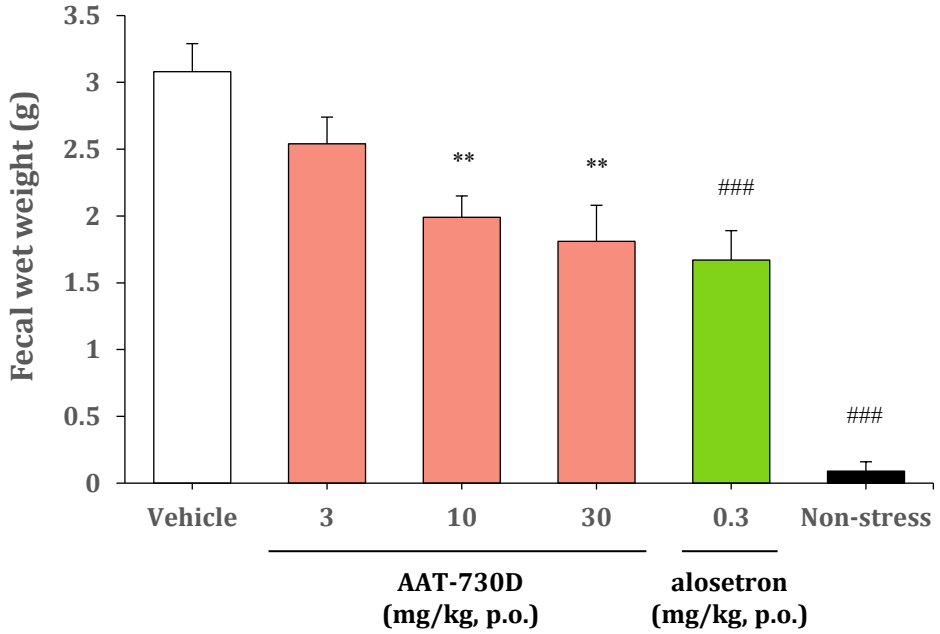


Restraint stress: Animals were placed in the individual wire-mesh cages (50x190x55 mm)

Model	Stress-induced defecation model is widely used for the evaluation of anti-IBS agents
Compound	AAT-730D (Di-hydrochloride of AAT-730), Alosetron
Dose (Duration)	AAT-730D: 3, 10 and 30 mg/kg, p.o. (1 hr prior to restraint stress) Alosetron: 0.3 mg/kg, p.o. (0.5 hr prior to restraint stress)
Endpoint	Fecal weight (wet weight)

1.2 Non-Clinical Efficacy Pharmacology (*In Vivo*)

Restraint Stress Defecation in Rats



Data are expressed as mean+SEM, N=12
*p<0.05, **p<0.01, 1-way ANOVA followed by Dunnett's test for drug treated groups vs vehicle.
###p<0.001, vs vehicle by t-test.

AAT-730 exhibited dose-dependent reduction in fecal wet weight with statistical significance at the doses of 10 and 30 mg/kg under restraint stress in rats.

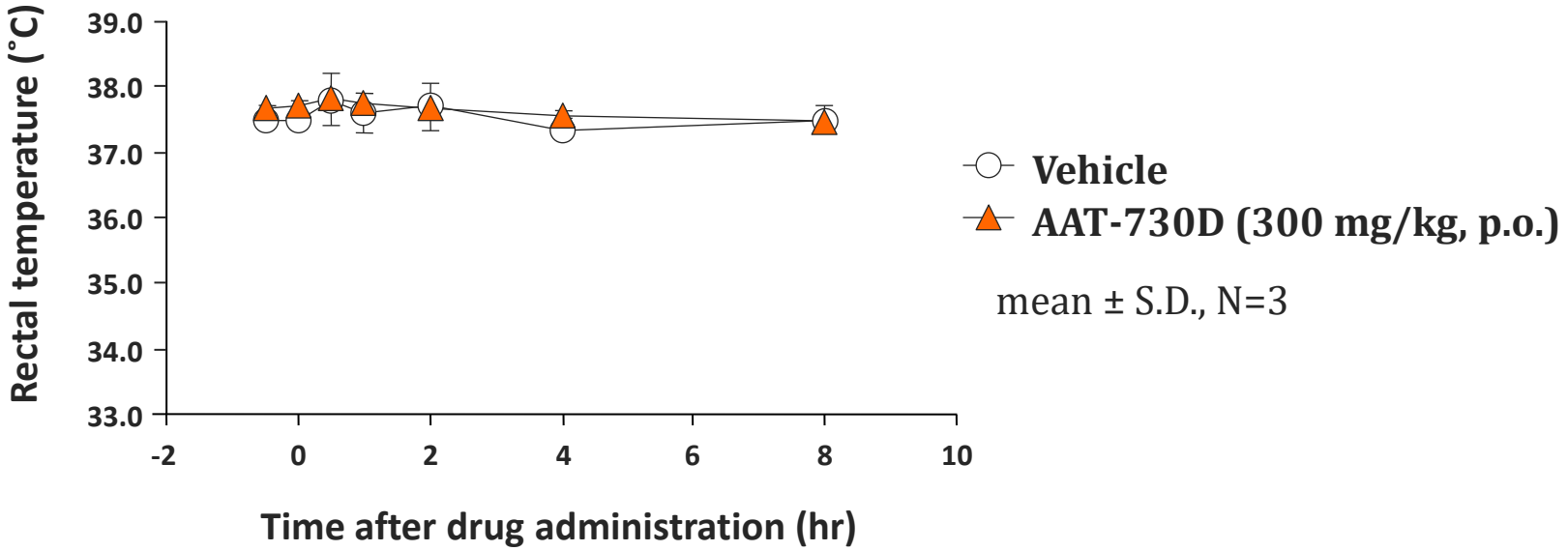
1.3 Non-Clinical Safety Pharmacology

List of Safety Pharmacology Studies

Model	Assay system, Species	Regulatory Compliance
In vitro hERG, HEK293 cells	*In vitro*	None
		GLP
Dofetilide binding	*In vitro*	None
Body temperature and behavior test	Rat	None
Ancillary pharmacology	*In vitro*	None
Respiratory, single oral	Rat	GLP
Cardiovascular and neurobehavioural	Dog	GLP

1.3 Non-Clinical Safety Pharmacology

Body Temperature and Behavior Test in Rats



- No observable abnormal behavior at 300 mg/kg
- C_{max} = 18 μg/mL

No change of body temperature and no abnormal behavior were observed after a single oral dose of AAT-730 at 300 mg/kg in rats.

2. Non-Clinical Pharmacokinetics

List of Pharmacokinetic Studies

Study Type		Route of Administration, Assay system	Species / Cell Line
Absorption	Single Dose	iv, po	Rat, dog
	Repeated Dose	po	Rat, dog
Distribution	Plasma protein binding	*in vitro*	Rat, dog, human
		in vitro	Rat, dog, human; equilibrium dialysis
	CNS Penetration	po	Rat
	Brain Penetration	PO	Mouse, rat
Metabolism	In vitro metabolic stability	*in vitro*	Rat, dog, human liver microsomes
		in vitro	Human, rat, dog, monkey hepatocyte
	CYP phenotyping	*in vitro*	-
	In vitro drug-drug interaction	*in vitro*	Human liver microsomes
	CYP inhibition/TDI	*in vitro*	Human liver microsomes
	Nuclear receptor activation (PXR, AhR)	*in vitro*	Human, rat, dog
	Reactive metabolite formation	*in vitro*	Human liver microsomes
	In vitro metabolic profiling	*in vitro*	Rat, dog, human cryopreserved hepatocytes
Others	Caco-2 permeability	*in vitro*	Caco-2 cells
	P-gp, BCRP substrate	*in vitro*	MDCK-MDR1 cell monolayers
	P-gp, BCRP, BSEP inhibition	*in vitro*	MDCK-MDR1 cells, Caco-2 cells, HEK293-BSEP membrane vesicles

3. Non-Clinical Toxicology

List of Toxicology Studies

Study Type and Duration		Species, Assay system	Regulatory Compliance
Repeated-Dose Toxicity	3-day exploratory oral dose	Dog	None
	7-day oral DRF, rats	Rat, dog	None
	28-day pivotal oral with a 14-day recovery	Rat, dog	GLP
Genetic Toxicity	Screening AMES	*In vitro*	None
	Pivotal AMES	*In vitro*	GLP
	Screening *in vitro* micronucleus	*In vitro*	None
	Pivotal *in vitro* micronucleus, human peripheral lymphocytes	Human	GLP
	AMES for impurity	In vitro	None
Phototoxicity	UV-VIS spectrophotometric analysis	-	None
	In vitro phototoxicity, 3T3 NRU assay	*In vitro*	GLP
Other *in vitro* studies	3D hepatotoxicity assay using HepaRG spheroids	*In vitro*	None
	Functional mitochondrial toxicity assay, seahorse mitochondrial profiling	*In vitro*	None
	Mitochondrial toxicity (ATP), HepG2 cells (galactose and/or glucose)	*In vitro*	None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