AAT-730, A Cannabinoid CB2 Receptor Agonist

Irritable Bowel Syndrome / Chemotherapy-induced Peripheral Neuropathy

2026 January

AskAt Inc.

Non-confidential information

Executive Summary: AAT-730

- Mechanism of Action
  - Selective CB2 receptor agonist
- Target Indication
  - Visceral pain and diarrhea in irritable bowel syndrome (IBS)
  - Chemotherapy-induced peripheral neuropathy (CIPN)
- Non-Clinical Studies
  - Potent and selective full agonist at CB2 in human and rat
  - Demonstrated analgesic and anti-diarrheal effects in rat models of IBS, and anti-allodynia effect in chemotherapy-induced peripheral neuropathy in the rat.
  - Rapidly and well absorbed into blood following oral dosing, and the exposure proportional to dose in the rat and dog.
  - Having excellent safety profiles in toxicological studies in the rat and dog.
- Clinical Study
  - Phase 1 (Single ascending dose) was completed in the UK.
  - Well absorbed into blood following oral dosing, and all tested doses were well tolerated in human.
- IP status (as of January 28, 2026)
  - Substance (WO 2010/084767) filed on January 22, 2010
    - Granted: JP, US
  - Salt and crystal forms (WO 2022/102713) filed on November 11, 2021
    - Granted: AU, BR, CA, CN, EP, (UP, ES, GB, CH), IL, JP, KR, MX, NZ, US

Rationale of AAT-730 for IBS and neuropathic pain

- Expression and role CB2 receptor
  - Expressed in the immune system including the B and T lymphocytes, macrophages, monocytes, NK cells and polymorphonuclear cells
  - Regulating immune responses and inflammatory pathways
  - Upregulated in microglia during neuroinflammation, and increased expression in DRG and dorsal spinal cord synaptosomes after nerve injury
  - JWH-133 (CB2 agonist) significantly inhibited the amplitude of dorsal root–evoked glutamatergic excitatory postsynaptic currents in spinal dorsal horn neurons in spinal nerve ligation rats, but not in sham control rats.

- AAT-730 for IBS
  - AAT-730 exhibited significant analgesic effect on TNBS-induced visceral pain in the rat at the doses of 1 and 3 mg/kg, p.o..
  - AAT-730 showed significant reduction in fecal wet weight, dry weight, and water contents on stress-induced defecation in TNBS-treated rats at 3 and 10 mg/kg, p.o..
  - AAT-730 exhibited significant reduction in fecal wet weight at the doses of 10 and 30 mg/kg in rats under restraint stress.

- AAT-730 for neuropathic pain
  - AAT-730 showed significant analgesic effect in taxol-induced neuropathic pain in the rat.

Competitors of CB2-selective agonist

As of 2024 April by Biomedtracker
*: 2025 June by Clinical Trial Gov.

Drug	Lead company/ Partner	Indication	Route	Development stage	Status
FSD201	FSD Pharma Inc.	Inflammatory disorders	oral	P2	Terminated*
BTX-1503	Botanix Pharmaceuticals Limited	Acne	topical	P2	Completed*
NTRX-07	NeuroTherapia. Inc.	Alzheimer's disease	oral	P1	Completed*
JWH-133	Bellvitge University Hospital	Alzheimer's disease		Investigator initiated study	Ongoing
CS-NEURO-1	Cannabis Science. Inc.	Neurology	oral	Preclinical	Ongoing
CS-TATI-1	Cannabis Science. Inc.	Kaposi's sarcoma		Preclinical	Ongoing
SCI-160	SciSparc Ltd.	Pain indication		Preclinical	Ongoing
TA-A001	TALLC Corporation Inc./ IACTA Pharmaceutocals, Inc.	Postsurgical pain	iv	Preclinical	Ongoing
		Ocular pain and/or inflammation	iv	Preclinical	Ongoing
		Dry eye (Ophthalmology)	iv	Preclinical	Ongoing

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 Non-Clinical Safety Pharmacology
2. Non-Clinical Pharmacokinetics
3. Non-Clinical Toxicology
4. Clinical Study

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

Inhibition of forskolin-stimulated cAMP production in CB2 and CB1 transfectants

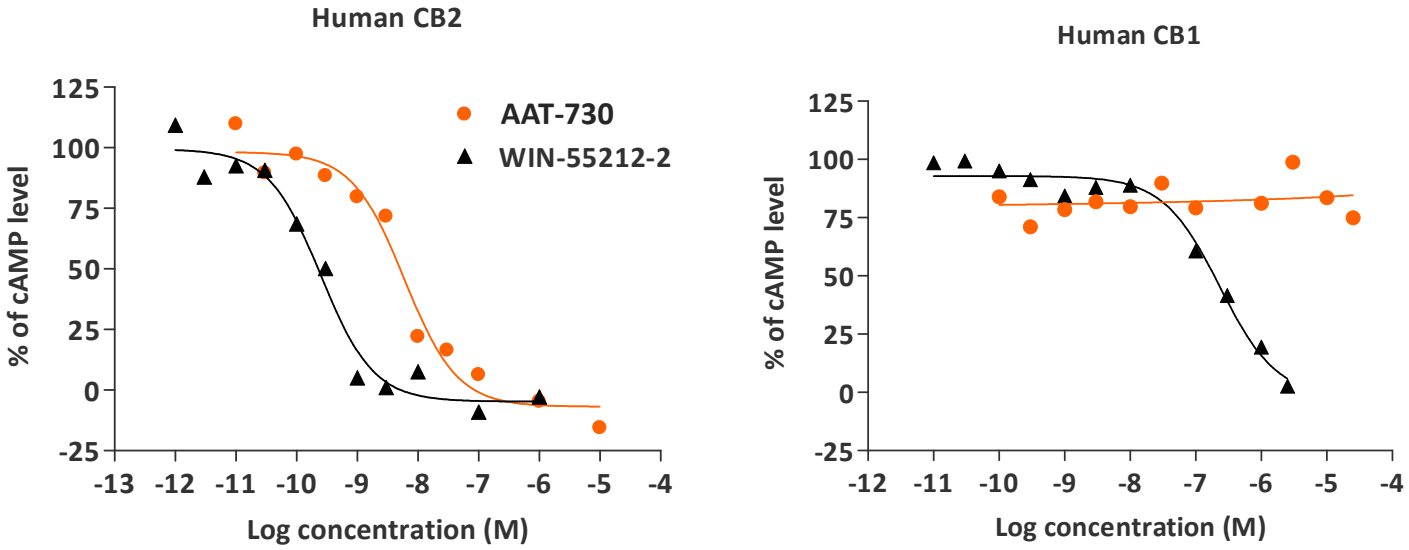
Receptor	EC_{50} (nM)	
	AAT-730	**WIN-55212-2**
Human CB2	5.57 (0.968, 32.0)	0.258 (0.0295, 2.25)
Human CB1	>22,200 (ND)	102 (82.4, 126)
Rat CB2	0.526 (0.423, 0.655)	0.236 (0.128, 0.437)
Rat CB1	2940 (219, 39300)	2.73 (1.22, 6.10)

CB2 and CB1 transfectants (human, rat) were made with CHO cells. Inhibition by AAT-730 of forskolin-stimulated cAMP production was determined. WIN-55212-2 was used as a reference compound.
Data were calculated from results of 3 experiments. EC_{50} values represent mean (95% confidence interval).

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

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

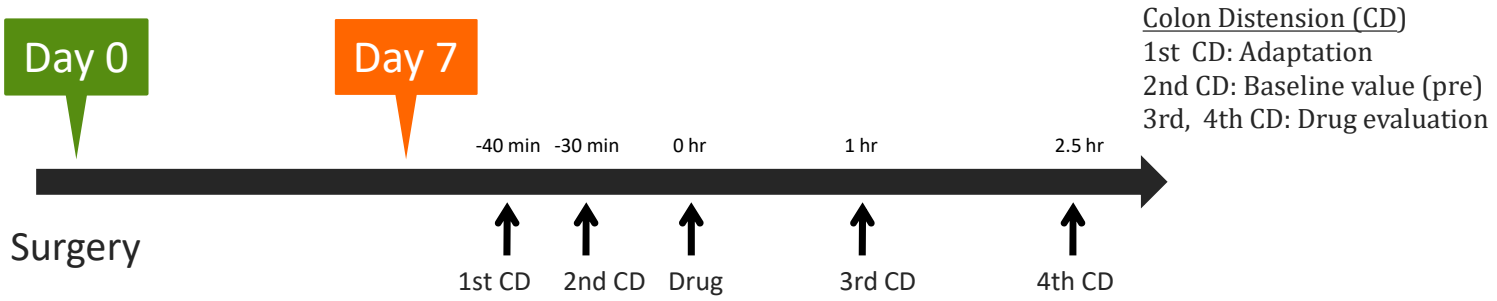
Effects of AAT-730 and WIN-55212-2 on forskolin-stimulated cAMP production in human CB2 and CB1 transfectants



Inhibition by AAT-730 of forskolin-stimulated cAMP production was determined in human CB2 and CB1 transfectants. WIN-55212-2 was used as a reference compound.

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

TNBS-Induced Visceral Pain Model in Rats [1)]



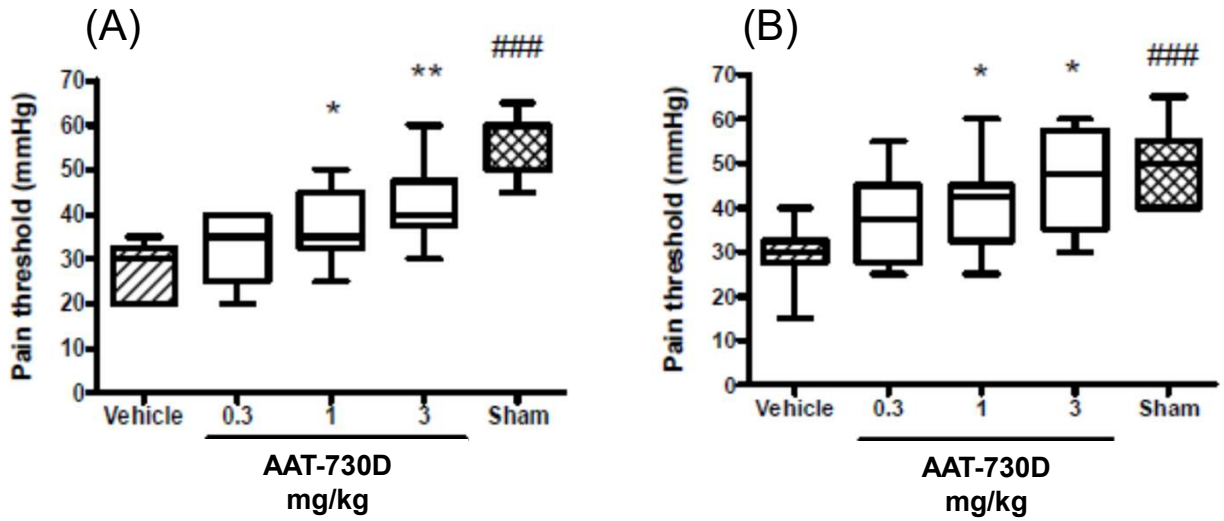
Surgery: Intra-colonic injection of TNBS (50 mg/kg, 30% EtOH) into the proximal colon
Colon distension: The balloon placed in the distal colon was progressively inflated from 0 to 70 mmHg

Model	Utilized as a model of chronic functional gut disorders characterized by visceral pain
Compound	AAT-730D (Di-hydrochloride of AAT-730)
Dose (Time point of Evaluation)	AAT-730D: 0.3, 1, 3 mg/kg, p.o. (1 and 2.5 hr post-dose)
Endpoint	Pain threshold: the pressure inducing the characteristic painful behavior (i.e., abdominal clamp)

1) TNBS: 2,4,6-Trinitrobenzene Sulfonic Acid

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

TNBS-Induced Visceral Pain Model in Rats

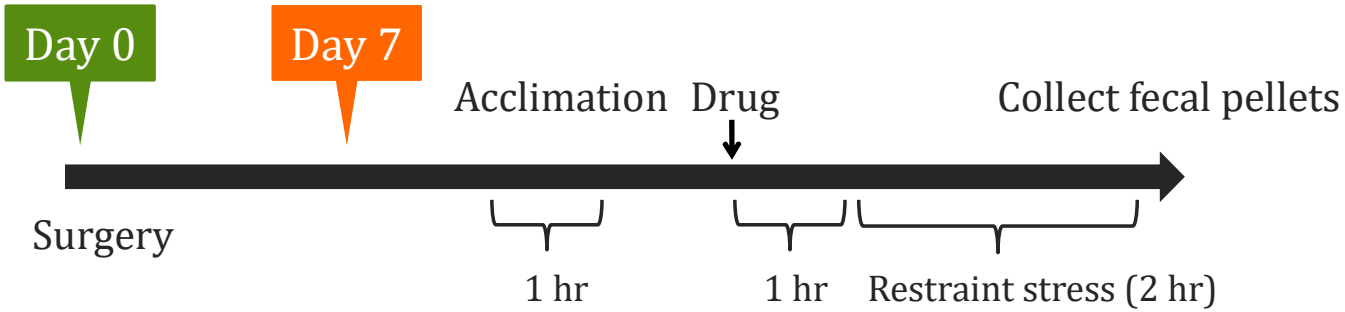


Data are expressed as median pressure threshold (mmHg) at 1 hr (A) and 2.5 hrs (B) after AAT 730D administration. The 1st and 3rd quartiles that indicate the range of median values, N=7-8
*p<0.05, **p<0.01, ###p<0.001, vs vehicle by Mann-Whitney U test

AAT-730 exhibited significant analgesic effect on TNBS-induced visceral pain at the doses of 1 and 3 mg/kg, p.o. in rats.

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

Restraint Stress Defecation in TNBS Treated Rats

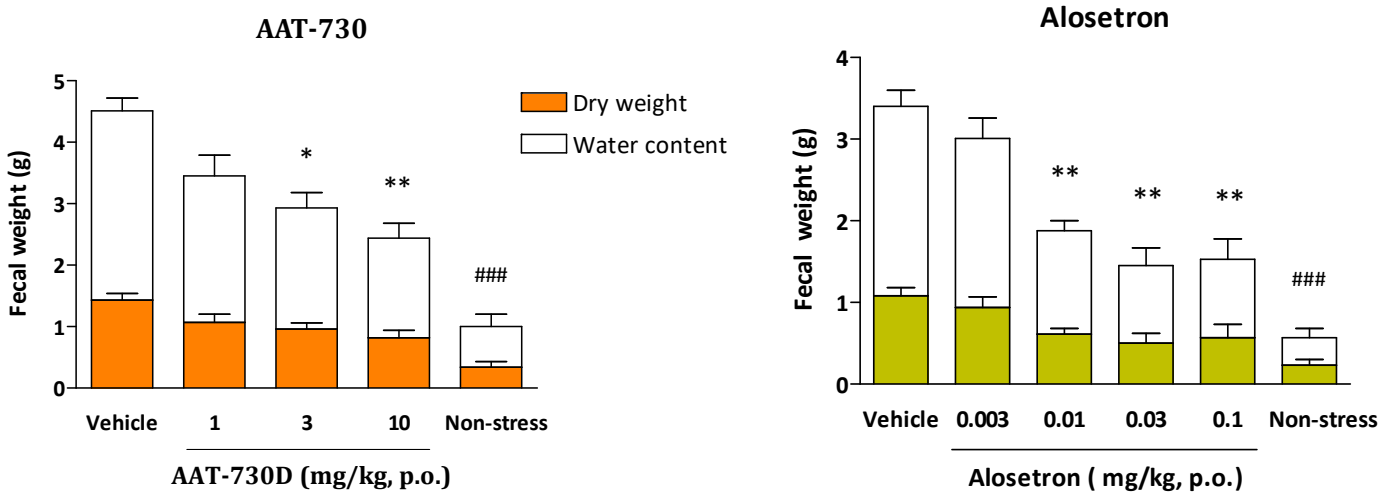


Restraint stress: Place animals in the individual wire-mesh cages (W50xL190xH55 mm)

Model	TNBS-treated rats were used for stress-induced defecation model
Compound	AAT-730D (Di-hydrochloride of AAT-730), Alosetron
Dose (Duration)	AAT=730D: 1, 3, and 10 mg/kg, p.o. (1 hr prior to restraint stress) Alosetron: 0.003, 0.01, 0.03 and 0.1 mg/kg, p.o. (1 hr prior to restraint stress)
Endpoint	Fecal weight (wet weight, dry weight, water content)

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

Restraint Stress Defecation in TNBS Treated Rats

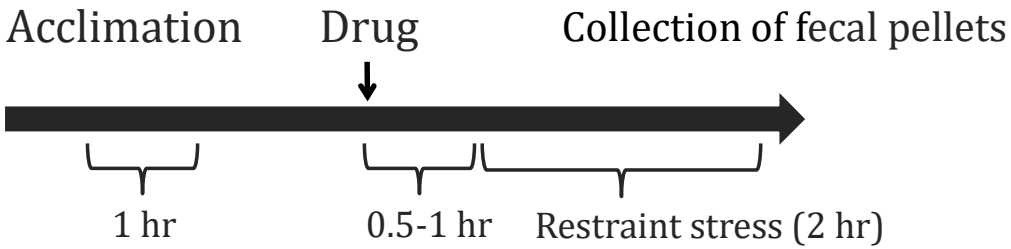


Data are expressed as mean + S.E.M., N=10-12
Filled bar; dry weight (g), Open bar; water content (g). Statistical significance was analyzed for the data of fecal weight.
*p<0.05, **p<0.01, 1-way ANOVA followed by Dunnett's test for drug-treated groups vs vehicle-treated group. ###p<0.001, vs vehicle-treated group by t-test.

AAT-730 showed significant reduction in fecal wet weight, dry weight, and water contents on stress-induced defecation in TNBS treated rats at 3 and 10 mg/kg, p.o..

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

Restraint Stress Defecation in Rats

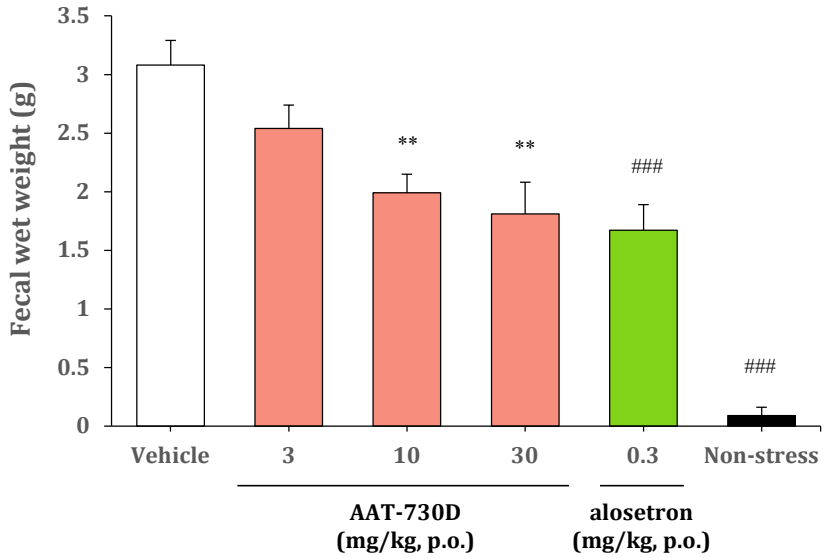


Restraint stress: Place animals in the individual wire-mesh cages (50x190x55 mm)

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-induced 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 in rats under restraint stress.

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

Paclitaxel-induced Peripheral Neuropathy in Rats

- Data will be disclosed under CDA.

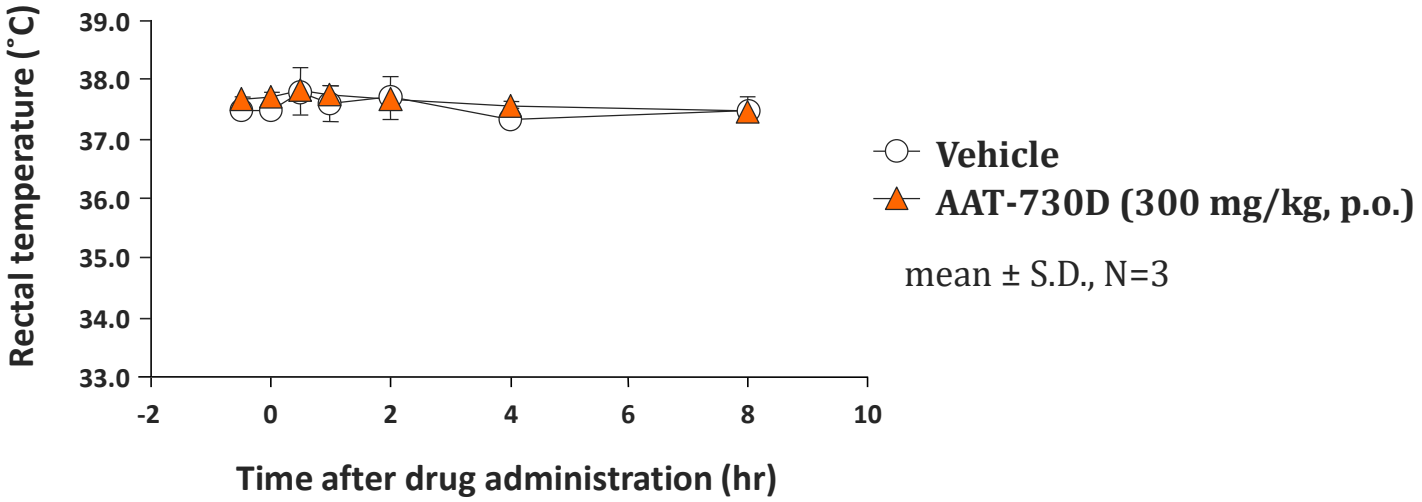
1.3 Non-Clinical Safety Pharmacology

List of Safety Pharmacology Studies

Model	Assay system, Species	Regulatory Compliance
In vitro hERG (HEK293)	*In vitro*	None
		GLP
Dofetilide binding to hERG (HEK293)	*In vitro*	None
Body temperature and behavior test	Rat	None
Ancillary pharmacology	*In vitro*	None
Respiratory, single oral	Rat	GLP
Cardiovascular and neurobehavioral	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 the rat.

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

4. Clinical Study

- Phase 1 study (single ascending dose) was completed in the UK.
- All tested doses were well tolerated with no abnormalities or SAEs observed.