RODENT PHARMACOKINETICS AND *IN VITRO* ADME PROPERTIES OF IV3086: AN ORALLY AVAILABLE AND BRAIN PENETRANT NURR1/RXR ACTIVATOR

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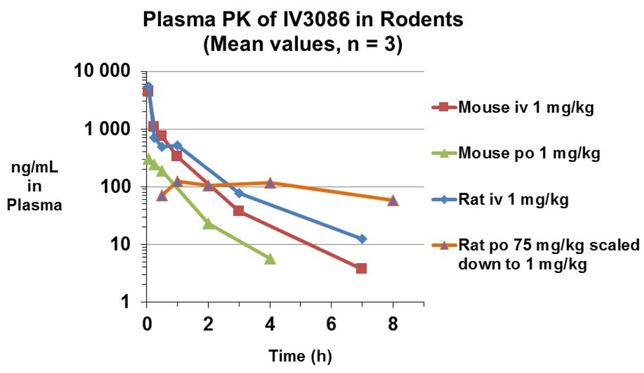
1. INTRODUCTION

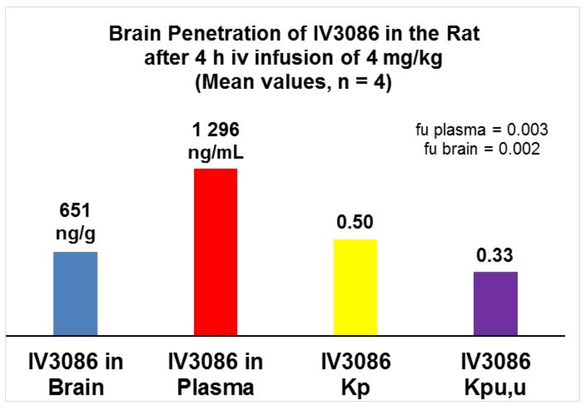
IV3086 is a Nurr1/RXR activator developed by INVENTIVA as disease modifier approach to treat Parkinson's Disease. IV3086 was shown to be significantly neuroprotective at low oral doses in the mouse MPTP model. Early *in vitro* ADME and *in vivo* pharmacokinetics of IV3086 in mouse and rat are presented.

2. MATERIAL AND METHODS

Male Wistar or Sprague Dawley rats and C57BL/6JRj mice were administered with IV3086 in 1% methylcellulose / 0.1% Poloxamer 188 (oral suspension) or in saline containing 2% Cremophor EL (3 min IV infusion). A 4h constant rate IV infusion was performed in jugular vein cannulated rats with blood and brain collection to determine Kp (brain/plasma concentration ratio). Rats were also placed in metabolic cages to collect urine and feces. Protein binding was assessed by equilibrium dialysis using rat plasma and brain homogenate. Metabolic stability was assessed in mouse and human liver microsomes. CYP inhibition was performed by co-incubation of IV3086 with two cocktails of probe substrates. CYP induction was evaluated using plated human hepatocytes incubated for two days. Permeability was studied on PAMPA (hexadecane, pH 7.4), Caco-2, MDCK hMDR1 and MDCK WT cells mono-layers. *In vitro* and *in vivo* samples were analyzed by LC-MS/MS and PK parameters were determined with Phoenix WinNonLin software.

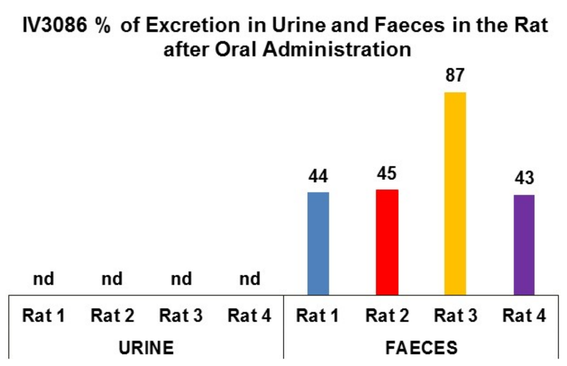
3. IN VIVO RESULTS





IV3086 PK PARAMETERS		IV 1 mg/kg Single Dose		PO 1 mg/kg* Single Dose	
Parameter	Unit	Mouse	Rat	Mouse	Rat
Cmax	ng/mL	4 353	5 422	304	125
Tmax	h	-	-	0.25	1.0
AUClast	h.ng/mL	1 602	2 048	485	1 228
Half-Life	h	0.8	3.8	1.2	-
AUCinf	h.ng/mL	1 607	2 054	495	1 228
CL	L/h/kg	0.7	0.5	-	-
CL	% LBF**	14	12	-	-
Vz	L/kg	0.9	2.7	-	-
Vss	L/kg	0.5	0.7	-	-
Oral F	%	-	-	31	60

* Rat: 75 mg/kg dose normalized to 1 mg/kg for comparison
** % of liver blood flow, assuming blood/plasma ratio = 1



IV3086 per os PK Linearity in the mouse

Dose (mg/kg)	Cmax (ng/mL)	Cmax ratio	AUClast (h.ng/mL)	AUC Ratio
1	304	1	485	1
3	1 118	4	2 294	5
10	7 317	24	14 745	30
30	21 053	69	79 799	164

Clearance is low in both species.

Half-life is short in mouse and moderate in rat.

Oral absorption is very quick in the mouse, much slower in rat.

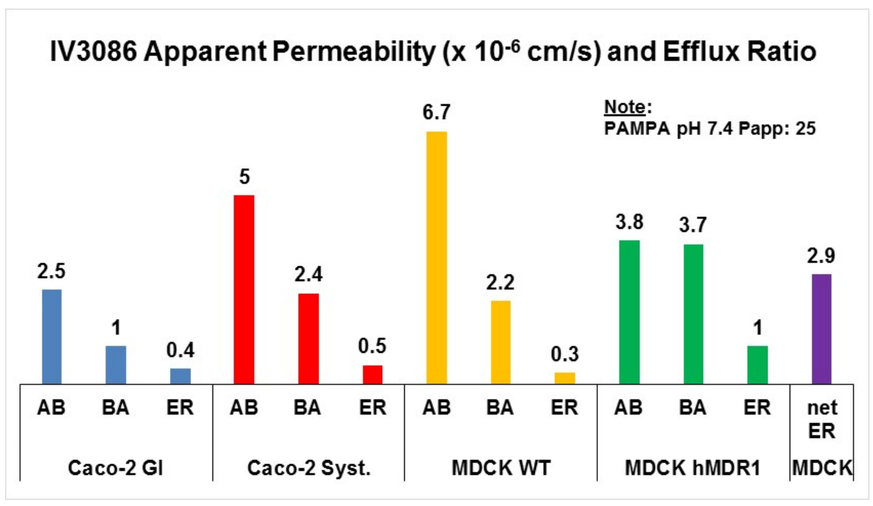
Oral bioavailabilty is moderate in mouse and good in rat.

Brain penetration is good. Free fraction is very low both in brain and plasma.

Excretion is via faeces mainly as unchanged compound.

Low dose oral PK is not linear in mouse. Linearity was observed in the rat at higher oral doses (not shown)

4. IN VITRO RESULTS



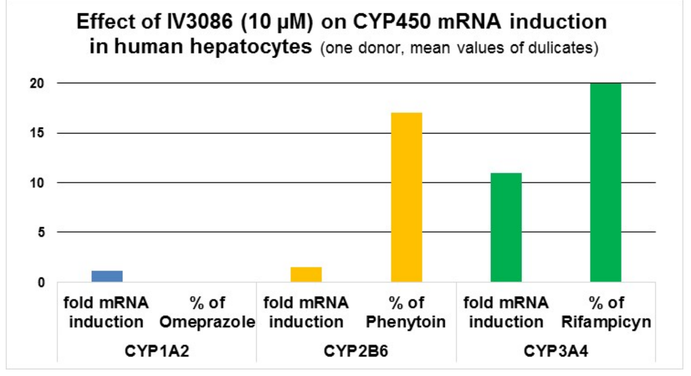
IV3086 10 µM. Apical and basolateral buffer: HBSS Hepes pH 7.4 with 1% BSA, except apical Caco-2 GI (gastro intestinal): FaSSiF buffer. Syst.: systemic. Net ER = ER hMDR1/ER WT (wild type).

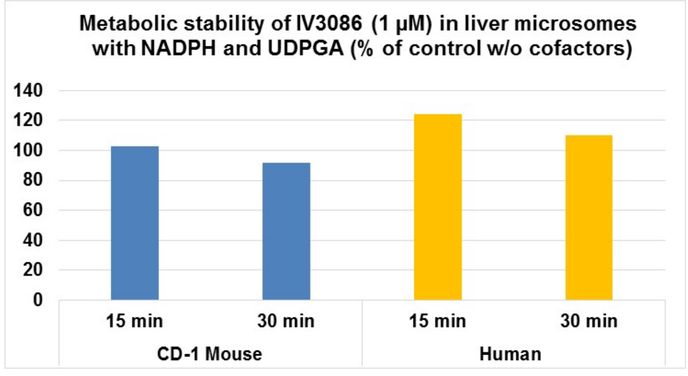
High PAMPA permeability. Moderate cellular permeability with possible uptake and no significant P-gp involvement.
No CYP450 inhibition except on CYP2C8 with IC_{50} > 1 µM.
No induction of CYP1A2 and 2B6. Slight induction of CYP3A4 mRNA.
Stable in human and mouse liver microsomes.

CYP450 inhibition by IV3086 in human liver microsomes

(0.5 mg protein/mL, 15 or 30 min co-incubation with NADPH. Mean values n = 2)

	CYP450:	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4/5
	Probe substrate:	Ethoxy-comarine	Coumarine	Bupropion	Paclitaxel	Tolbutamide	Mephenytoin	Bufuralol	Chlorzoxazone	Midazolam
IV3086 Concentration	1 µM	-14	-14	-7	27	-5	-8	-18	-18	-18
	10 µM	-16	13	20	74	37	20	3	9	5





5. CONCLUSION

In vivo rodent PK of IV3086 showed good oral bioavailability, low clearance and good brain penetration.
in vitro permeability and microsomal stability of IV3086 were good, while free fraction in plasma and brain homogenate was very low.
IV3086 displayed low risk of drug-drug interaction: weak CYP3A4 induction potential as well as moderate CYP2C8 inhibition and no P-gp involvement.