In vivo PK/PD profile of Compound A, a brain penetrant, orally available potent and selective LRRK2 inhibitor, in rodent and non-rodent species

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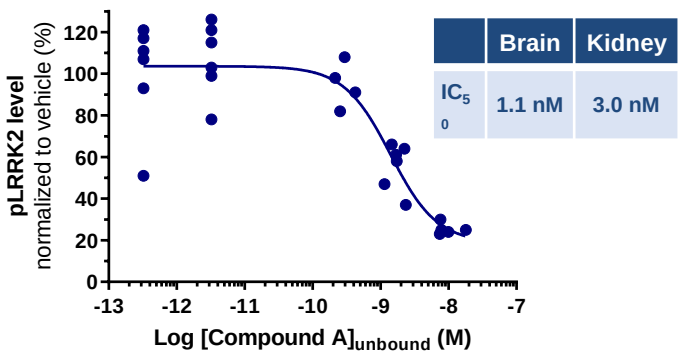
OBJECTIVES

Mutations in Leucine-Rich Repeat Kinase 2 (LRRK2) are the most common genetic cause of Parkinson's disease, leading to the development of LRRK2 inhibitors as potential therapeutic approach. Among them, Compound A has recently been selected as a potent, selective and brain-penetrant LRRK2 inhibitor. In order to confirm its *in vivo* target engagement and equipotency on wild type and G2019S LRRK2 mutants, several Pharmacokinetic/Pharmacodynamic (PK/PD) studies were performed in rodent and non-rodent species. Please see the accompanying poster for the *in vitro* profile of Compound A.

Potent LRRK2 inhibition in rat brain

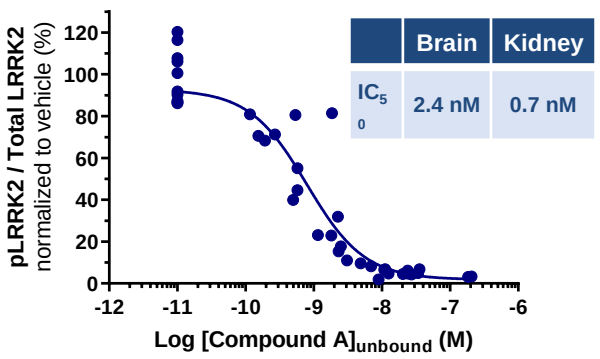
Brain, Rat



	Brain	Kidney
IC_{50}	1.1 nM	3.0 nM

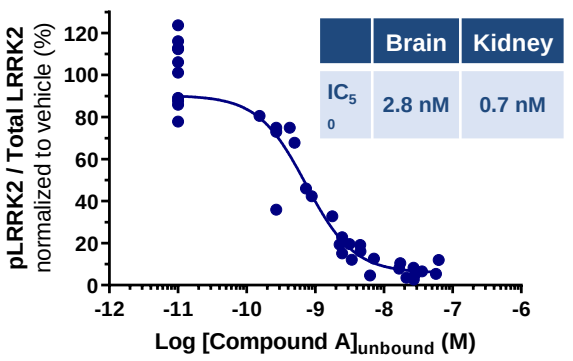
Equipotency in wild type and G2019S mice

Brain, wild type mice



	Brain	Kidney
IC_{50}	2.4 nM	0.7 nM

Brain, G2019S mice



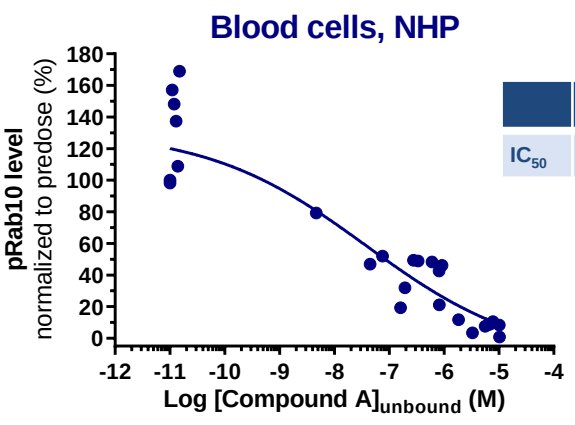
	Brain	Kidney
IC_{50}	2.8 nM	0.7 nM

Rodent studies :
Measurement of Ser935-LRRK2 phosphorylation or pSer935 LRRK2/total LRRK2 ratio in brain and kidney by ELISA, 90 min after administration of Compound A (rats: 0, 0.3, 1, 3 and 10 mg/kg PO, n=6/dose and mice: 0, 0.1, 0.3, 1, 3 and 10 mg/kg PO, n=11/dose). Determination of brain and kidney concentrations of Compound A by Liquid Chromatography-Tandem mass spectrometric detection (LC-MS/MS). Determination of the unbound brain and kidney concentrations of Compound A required to give 50% inhibition (IC_{50}), using free-drug concentrations

Highly potent LRRK2 inhibition confirmed in non-human primate (NHP) blood cells

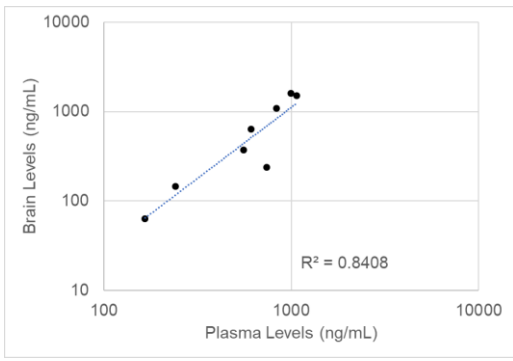
The first study was performed using blood cells and assessing pSer935-LRRK2 for target engagement and pThr73-Rab10, its physiological substrate, for pathway engagement/proof of mechanism. Both biomarkers were determined by ELISA 90 min after compound A administration (0, 1, 3, 10 and 30 mg/Kg PO, n=4/dose).
Using free-drug concentrations, the unbound concentrations of Compound A required to give 50% inhibition (IC_{50}) were calculated.

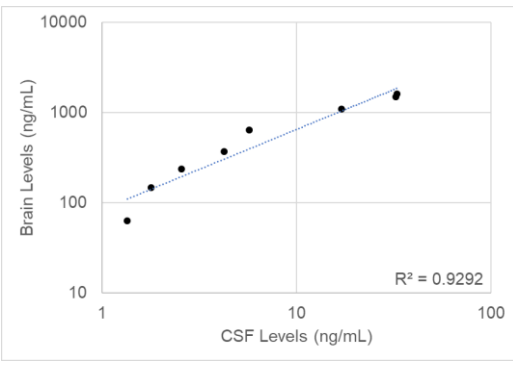
Blood cells, NHP



	pLRRK2	pRab10
IC_{50}	6 nM	0.1 nM

Good brain penetration in NHP

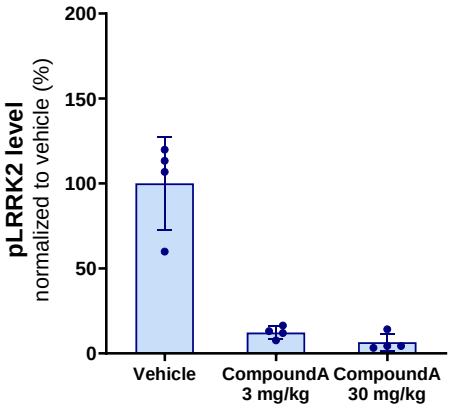




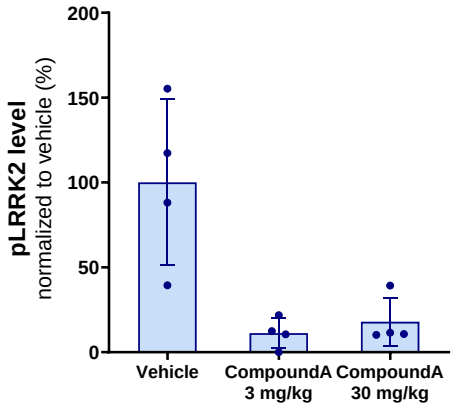
An additional PK/PD study was performed at 3 and 30 mg/kg PO (n=4/dose) assessing pSer935-LRRK2 and pThr73-Rab1 by ELISA in brain and blood cells 150 min after administration. The concentrations of Compound A in plasma, CSF and brain were determined by LC-MSMS.

Comparable inhibition of LRRK2 in NHP brain and blood cells

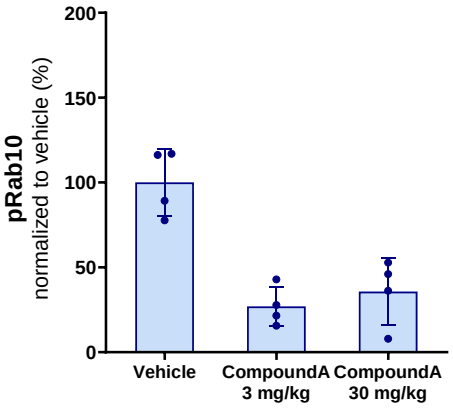
Brain, pLRRK2



Blood cells, pLRRK2



Blood cells, pRab10



CONCLUSION

Compound A is a highly potent LRRK2 inhibitor with Central Nervous System (CNS) activity.

- **All PK/PD studies demonstrated the ability of Compound A to engage and to inhibit brain LRRK2 kinase *in vivo* within a similar nM range of activity as those observed *in vitro* on rodent and human cells (see accompanying poster).**
- **Compound A inhibits LRRK2 with the same potency in the brains of wild type and G2019S mutant transgenic mice.**
- **NHP PK/PD studies confirmed the good penetration of the compound into the brain, with a correlation between drug levels in the brain and the plasma and the cerebrospinal fluid (CSF), as well as comparable biomarkers inhibition in brain and blood cells.**

Compound A therefore has a very promising therapeutic potential for the treatment of Parkinson's disease.