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# ADME properties and non-clinical pharmacokinetics of a novel selective σ2 receptor ligand with neuroprotective effects

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## INTRODUCTION

ADV462 is a novel small molecule resulting from a rational hit to candidate process focused on selective sigma-2 receptor ligands with neuroprotective properties.[1] In this study, we show the experiments done in our laboratory to characterize the ADME-DMPK profile of ADV462, as part of the decision-making process for its development as neuroprotective oral drug.

## EXPERIMENTAL METHODS AND RESULTS

The assessment of ADME-DMPK properties of ADV462 included *in vitro* ADME, non-clinical DMPK and drug interactions; all performed using standard methods. Bioanalysis was done by UPLC-MS/MS.

**In vitro ADME**
- Bidirectional permeability in Caco-2 cells
- Metabolitc stability in liver microsomes
- Metabolic stability in hepatocytes
- Metabolic stability in plasma
- Plasma protein binding
- Brain tissue binding
- Metabolite profiling

**Non-clinical DMPK**
- Pharmacokinetics in rodents
- Pharmacokinetics in dogs
- Brain kinetics in rats
- Renal excretion in rats
- Metabolite profiling

**Drug interactions**
- Metabolism-based drug interactions
  - CYP inhibition
  - CYP induction
- Efflux transporter-based drug interactions
  - P-gp inhibition
  - BCRP inhibition

## *In vitro* ADME

### Permeability (Caco-2 cells)

- Highly permeable (Papp = 177 nm/s)
- No potential efflux transporter substrate (Efflux ratio = 1.2)

### Metabolic stability

- Plasma: stable in rodent and human plasma
- Liver microsomes and hepatocytes: higher metabolic stability in humans vs. other species
- Hepatocytes: *In vitro-in vivo* clearance correlation in rats using the *well-stirred* model

| Cl int | Human | Rat | Mouse | Dog | Monkey | Minipig |
|---|---|---|---|---|---|---|
| **Liver microsomes** (µl/min/mg protein) | 1.6 | 1.5 | 2.8 | 4.5 | 79.9 | 28.5 |
| **Hepatocytes** (µl/min/million cells) | 1.9 | 28.5 | - | 5.1 | 66.4 | 7.1 |

### Plasma and brain tissue binding

- Method: rapid equilibrium dialysis (RED)
- Low plasma protein binding in humans and rodents (< 67%)
- Low brain tissue binding (rat, 58%)

### Metabolite profiling: hepatocytes

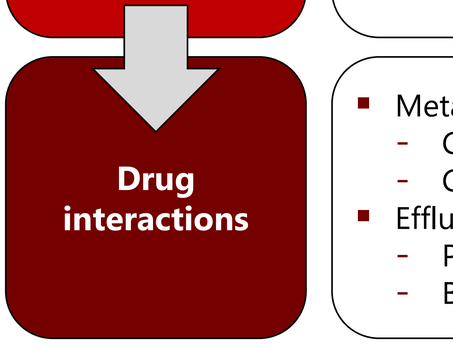
- Metabolism routes: hydroxylation and oxidation
- Metabolites found in human hepatocyte also present in preclinical species

## Non-clinical DMPK

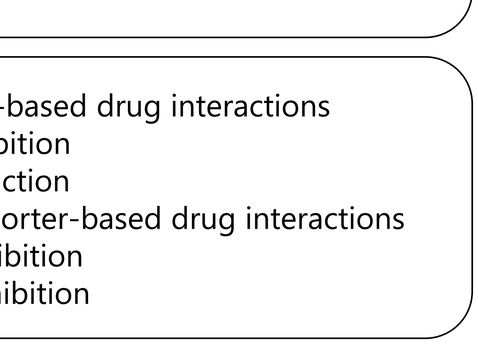
### Pharmacokinetics: oral (10 mg/kg) and intravenous (1 mg/kg)

- Fast oral absorption and good bioavailability (F >60%)
- Moderate to high plasma clearance (>40% liver blood flow)

Oral pharmacokinetics in rodents and dog




Brain Kinetics in rats




| Species | $t_{1/2}$ (h) | $C_{max}$ (ng/ml) | $t_{max}$ (h) | Cl (l/h/kg) | Vss (l/kg) | F (%) | $AUC_{brain}/AUC_{plasma}$ |
|---|---|---|---|---|---|---|---|
| **Mouse** | 2.6 | 2022 | 0.3 | 2.4 | 1.1 | 60 | - |
| **Rat** | 2.4 | 900 | 0.8 | 2.1 | 1.4 | 58 | 0.4 |
| **Dog** | 1.0 | 3424 | 0.3 | 2.9 | 2.3 | 89 | - |

### Brain kinetics: oral (10 mg/kg p.o., rat)

- Brain distribution is fast with a peak concentration of 250 ng/g
- Brain concentration-time profile parallel to plasma

### Renal excretion: oral (10 mg/kg, rat)

- 21% excreted in the urine as unchanged compound
- Renal excretion is one route of elimination

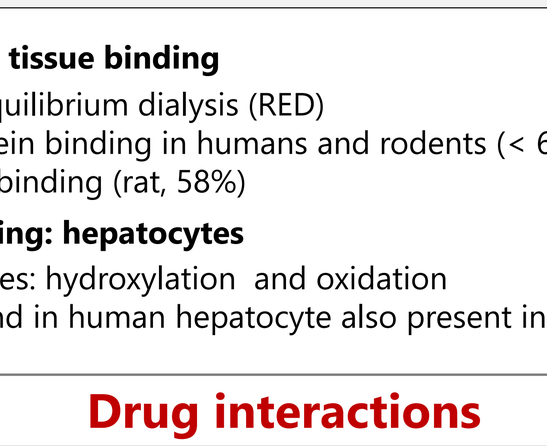
### Metabolite profiling: plasma (rodents and dog), urine (rat)

- Metabolites detected *in vivo* also present *in vitro*
- Metabolites formed by hydroxylation and oxidation
- Most metabolites detected in rat urine also present in plasma

## Drug interactions

### Metabolism-based interactions

- No CYP induction (1A2, 2B6, 3A4) in the concentration range of 1-50 µM (mRNA levels as endopoint)
- Low potential for CYP inhibition using human liver microsomes ($IC_{50}$> 100 µM)




### Efflux transporter-based interactions

- BCRP inhibiiton (Caco-2 cells): no inhibition in the concentration range of 2-200 µM
- P-gp inhibition (Caco-2 cells): inhibition in the concentration range of 2-200 µM ($IC_{50}$ = 11 µM)

## CONCLUSIONS

- **ADV462 distributes to the target organ in rats**
- **ADV462 has appropriate ADME-DMPK properties in preclinical studies supporting its further development**

1. Christmann et al. J. Med. Chem. 2023, 10.1021/acs.jmedchem.3c01060