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POSTER COMMUNICATION – ABSTRACT

ADME PROPERTIES AND NON-CLINICAL PHARMACOKINETICS OF A NOVEL SELECTIVE σ2 RECEPTOR LIGAND WITH NEUROPROTECTIVE EFFECTS

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The sigma-2 receptor (S2R) has been investigated in the context of cancer treatment and imaging. However, a growing interest in the S2R as an innovative treatment in neurological diseases, particularly in Alzheimer's disease (AD) is evidenced. In the present study we evaluate the ADME-DMPK properties of ADV462, a novel selective S2R ligand with neuroprotective properties.

ADV462 is highly permeable (Papp > 100 nm/s) and no potential substrate of efflux transporters. Regardless of species, plasma protein binding is low (< 70%). In rat, plasma and brain tissue binding are similar. Metabolic stability in human liver microsomes and hepatocytes is higher than in preclinical species (rodents, dog, monkey and minipig). Metabolism occurs by hydroxylation and oxidation as observed *in vitro* and *in vivo*. Metabolites detected in human hepatocytes are also present in preclinical species.

ADV462 shows in rodents and dog a fast and extensive oral absorption (F > 58%), and a short half-life (< 3 h) related with a moderate to high clearance. In rats, ADV462 distributes fast into the brain with parallel brain and plasma kinetics.

No CYP induction was observed at concentrations ≤ 50 µM using mRNA levels as endpoint. The potential for CYP inhibition is low (IC_{50} > 100 µM). Efflux transporter-based inhibition was only observed for P-gp (IC_{50} = 11 µM). No BCRP inhibition was found at the concentration range of 2-200 µM.

In conclusion, ADV462 distributes into the brain, the target organ, and has appropriate ADME-DMPK properties that support its further development.