The MODEL-AD consortium preclinical testing pipeline: pharmacokinetics and pharmacodynamics of prophylactic treatment with levetiracetam on the 5XFAD mouse model of Alzheimer’s Disease

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INTRODUCTION

IN VIVO PK AND PK/PD MODELING

The PTC strategy includes a primary screen to determine: 1) drug formulation and qualification of the active pharmaceutical ingredient (API); 2) drug stability in the intended formulation; and 3) in vivo pharmacokinetics and target tissue concentrations in models at disease-relevant ages. A secondary screen evaluates target engagement and disease modifying activity utilizing non-invasive PET/MRI imaging. 

Prior to in vivo PK and PD studies, lot-to-lot variability and formulation stability for LEV were assessed. Data indicate <5% variation across LEV lots and LEV was stable in 0.9% NaCl at 4°C for up to 9 days. A total N=73 6mo old 5XFAD mice were imaged (n=32 female; n=41 male; N=7-11 per sex per dose level) with 56 brain regions per subject (N=4088 total regions; 1792 females, 2296 males) extracted from co-registered to Paxinos-Franklin atlas using semi-automated methods.

18F-AV45 PET/MRI/AUTORADIOGRAPHY

Simulations of twice daily dosing minimized the C_\text{max}:C_{\text{min}} ratio and would produce the same AUC while providing a more consistent steady state level with C_{\text{min}} concentrations within the therapeutic range.

METHODS & MATERIALS

For PK studies, LEV was administered acutely p.o. to 6 mo aged female and male 5XFAD mice in which AD-relevant pharmacokinetic, metabolism, and amyloid deposition have been reported. From serial blood samples (0.5, 1, 2, 4, 8, h and terminal) plasma and brain tissue were evaluated for exposure levels. A second independent PK study was conducted to refine the optimal dose range and dosing frequency. All samples were frozen and stored at -80°C until analysis. Biocatalysis analysis was performed by LC-MS/MS for the parent and primary metabolite (levetiracetam). To determine the initial pharmacokinetics for LEV, non-compartmental analysis (NCA) was performed for both the parent and primary metabolite in female and male mice. Provided the NCA rate constants, a 1-tissue compartment model was fit to the population data using Phoenix WinNonlin. The resultant rate constants for absorption (Ka), elimination (Kel), and volumes of distribution (Vd) were then used to generate simulations for once (QD) and twice (BID) daily dosing.

In line with the PTC's prophylactic dosing strategy for PK studies, BID chronic administration of LEV (10, 30, and 56 mg/kg, p.o.) began at 3 mo of age with all PD endpoints including functional behavioral measures, 18F-FDG (experiment in progress) and 18F-AV45 PET/MRI measured at 6 mo of age. The behavioral testing battery included assessments of exploratory and locomotor activity in the open field, hippocampal working memory as measured by spontaneous alternation in a y-maze, and rotarod motor coordination (see Sukoff Rizzo et al 2018 Current Protocols in Mouse Biology for SOPs). Behavioral tests were separated by a one day inter-test interval. All PET scanning (75 minutes) was performed on the in vivo PET/autoradiography system and post mortem brains were extracted and frozen for autoradiography (Automat) MRI were acquired (1 mm, 3D T1 Prisma scanner outfitted with a 4 channel phased array head coil). PET/MRI images were co-registered to Paxinos-Franklin atlas and 27 average brain (56 total for left and right hemispheres) targets were extracted. LEV was typically administered every other day (7am and 7:30pm). On the day of the PD measures, with the exception of 18F-AV45, subjects were administrated LEV as a 30 or 60 mg/kg oral dose. For Autoradiography, frozen brains were sectioned at 20 um in sagittal at 3 brain regions which have been mapped to PET/MRI data. 

18F-AV45 PET / MRI / AUTORADIOGRAPHY

Prophylactic treatment with LEV (10, 30, or 56 mg/kg; p.o., BID, initiated at 3 months of age) in female and male 5XFAD mice for glucose metabolism at 6 months of age as measured by 18F-FDG PET/MRI and Autoradiography are ongoing and preliminary results are shown below.

BEHAVIORAL EFFECTS OF CHRONIC ADMINISTRATION OF LEV

Male and female 5XFAD mice were treated with LEV (10, 30, or 56 mg/kg; p.o., BID, initiated at 3 months of age) or vehicle control. Male and female WT littermates were treated with vehicle control (10 ml/kg; p.o.; BID, initiated at 3 months of age). At 6 months of age, subjects were pre-treated with LEV or vehicle 30 min prior to being placed into the open field for a 60 min period or evaluated for motor coordination on an accelerating rotarod (4-40 rpm over 5 min). Significant differences were found in the rotarod task between vehicle and LEV treatment groups but this was not dose dependent.

Model-AD: www.modelad.org
JAX AD models: https://www.jax.org/alzheimers
AlzForum research models: http://www.alzforum.org/research-models

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