Critical Evaluation of the Pharmacokinetics of Verubecestat in Aged 5XFAD Mice

PR Territo1, SK Quinney1, C Biesdorf1, AR Masters1, KD Onos2, L Haynes2, KJ Keezer2, JA Meyer1, J Peters1, SC Persohn1, AA Bedwell1, K Eldridge1,

1Indiana University School of Medicine, Indianapolis, Indiana US; 2The Jackson Laboratory, Bar Harbor, Maine USA, 3University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

INTRODUCTION

The preclinical testing core (PTC) of the Model Organism Development for Late Onset Alzheimer’s Disease (MODEL-AD) consortium has established a streamlined preclinical drug screening pipeline including a primary screen to evaluate in vivo pharmacokinetics (PK) at disease-relevant ages in mouse models of Alzheimer’s disease (AD) in advance of chronic prophylactic treatment for preclinical efficacy assessment. In line with this tiered strategy, the PK profile of the BACE1 inhibitor verubecestat was initially evaluated to inform PK/PD modeling for pharmacodynamics assessments. The PTC strategy includes a primary screen to determine: 1) drug formulation; 2) drug stability; and 3) in vivo PK 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 as a pharmacodynamic (PD) readout matched to known disease pathology in the model. Compounds demonstrating positive PD effects in the secondary screen are further interrogated via a tertiary screen of functional assays that assess the compounds ability to normalize disease-related phenotypes in cognition and neurophysiological tests.

METHODS

• Verubecestat trifluoroacetate (MK-8931, synthesized by Selleckchem) was analyzed by LC/MS/MS to confirm dose and stability for all formulations. For chow studies, verubecestat was milled into LabDiet® 5LG4 (irradiated; TestDiet®, St. Louis, MO, USA).
• Five experiments were conducted in separate cohorts of 6 month aged male and female 5XFAD mice (B6.Cg-Tg(APPswe,Presen1*DeltaE9)6799Vas/Mmjax; #34848). 1. Acute 3, 10, 30 mg/kg (10ml/kg, PO) in Oµ-propyl-b-cyclodextrin 2. Sub-chronic (7 day) 3 or 30 mg/kg BID (10 ml/kg, PO) in 0.5% methylcellulose 3. Acute 1.5 or 15 mg/kg (10ml/kg, PO) in 0.5% methylcellulose 4. 30 mg/kg/day (180ppm) for ~ 2 wks milled in chow (pellets), group housed mice 5. Blood samples were obtained by tail bleed, processed to plasma and stored at -20C. Verubecestat was assessed in plasma by LC/MS/MS.
• Population PK modeling was performed using NONMEM 7.3 (ICON, Hanover, MD) utilizing the plasma concentration-time profiles from the oral gavage studies. Mean PK parameters were used to simulate various ad lib dosing scenarios and compared to observed plasma concentrations.

RESULTS

• Plasma concentrations of verubecestat following oral gavage administration fit a one-compartment first-order absorption model.
• Following oral gavage, verubecestat clearance was 0.24 L/h (15.7% RSE) and volume of distribution was 8.84 L (15.6% RSE), resulting in a terminal half-life of approximately 2.5 hrs (Figure 1). Verubecestat was not detected at time zero.
• Administration of verubecestat via oral gavage resulted in sexually dimorphic effects on clearance which was 23% greater in males than females (Figure 1).
• PK/PD modeling from oral gavage data indicated a requirement of dosing at least every 12 hours to minimize Cmin:Cmax (Figure 2).
• QC of chow revealed significant inter-pellet variability (31% CV) and intra-pellet variability (8-10% CV) for all components tested.
• Significant differences in verubecestat concentrations were observed for single vs. group housed, male vs. female, and time of day.
• Verubecestat concentrations were lower in male mice than in female mice. Inter-individual variability was greater in female mice than in male mice.
• Irrespective of whether chow was pulverized or in pellets, regardless of inter- and intra-pellet variability similar concentrations of verubecestat were observed (within individual subjects).
• PK/PD modeling supported selection of appropriate dose range (10-100 mg/kg/day) for chow formulation to cover pellet variability and sex differences in exposure levels for long term PD studies in progress. Consistent with previous reports, after ~ 4 weeks of chronic dosing in pelletized chow, coat color changes were observed. No other adverse events were observed.

ACKNOWLEDGEMENTS

MODEL-AD was established with funding from The National Institute on Aging (US4 AG054345-01), AMP-AD knowledge portal: ampadportal.org

1First author.
2Second author.
3Third author.

REFERENCES