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ARTICLE

Clinical pharmacokinetics of leriglitazone and a translational approach using PBPK modeling to guide the selection of the starting dose in children

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Abstract

Leriglitazone is a unique peroxisome proliferator-activated receptor-gamma (PPARγ) agonist that crosses the blood–brain barrier in humans and clinical trials have shown evidence of efficacy in neurodegenerative diseases. At clinical doses which are well-tolerated, leriglitazone reaches the target central nervous system (CNS) concentrations that are needed for PPARγ engagement and efficacy; PPARγ engagement is also supported by clinical and anti-inflammatory biomarker changes in the Cerebrospinal fluid in the CNS. Plasma pharmacokinetics (PK) of leriglitazone were determined in a phase 1 study in male healthy volunteers comprising a single ascending dose (SAD) and a multiple ascending dose (MAD) at oral doses of 30, 90, and 270 mg and 135 and 270 mg, respectively. Leriglitazone was rapidly absorbed with no food effect on overall exposure and showed a linear PK profile with dose-exposure correlation. A physiologically based pharmacokinetic (PBPK) model was developed for leriglitazone based on phase 1 data (SAD part) and incorporated CYP3A4 ($f_{mCYP3A4}$ = 24%) and CYP2C8-mediated ($f_{mCYP2C8}$ = 45%) metabolism, as well as biliary clearance (f_{eBIL} = 19.5%) derived from in vitro data, and was verified by comparing the observed versus predicted concentration-time profiles from the MAD part. The PBPK model was prospectively applied to predict the starting pediatric doses and was preliminarily verified with data from five pediatric patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Leriglitazone, a brain-penetrant PPAR gamma agonist, showed efficacy in preclinical models of X-ALD and FRDA and is being developed clinically for these indications.