Translational analysis of RVT-1201 Nonclinical and clinical pharmacokinetic and pharmacodynamic biomarker data to predict clinical dose of a novel tph inhibitor for treatment of pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a progressive disorder associated with increased pulmonary vascular resistance, remodeling and occlusion. While etiology is unknown, nonclinical and clinical data implicate a causative role for serotonin. RVT-1201 (previously KAR5585), is an oral prodrug for KAR5417 - a potent inhibitor of tryptophan hydroxylase 1, the rate-limiting enzyme in the peripheral biosynthesis of serotonin. Here we report translation of PK/PD relationships for KAR5417 exposure and serotonin biomarker pharmacodynamics, to a human dose for treatment of PAH. In rat, oral RVT-1201 at the median effective dose (100mg/kg/day; KAR5417 $AUC_{0\text{-}24}$ 15,300ng.h/mL) blocks or ameliorates PAH in both a monocrotaline prevention model and a SUGEN-hypoxia treatment model for established PAH. RVT-1201 (30 to 300mg/kg/day) yielded a dose-dependent reduction in rat serum serotonin (-27% to -96%) and 24h urinary output of 5-HIAA (-45% to -56%) - the metabolite that reflects total serotonin biosynthesis. Divided dose studies in rats given 75mg/kg/day (~65% serotonin reduction) demonstrated KAR5417 $AUC_{0\text{-}24}$, rather than C_{max} or C_{trough}, correlated with lowered serotonin biomarkers. Once daily administration was comparable to BID or TID regimens. Healthy human subjects (*n*=~*120*) have received RVT-1201 across 2 studies. Treatment emergent adverse events resolved, none were serious, nor considered a dose limiting toxicity. With standard meals, AUC following single doses appeared proportional to dose (200-1200mg). At 400mg BID changes in 5-HIAA were comparable across studies. Mean change in plasma 5-HIAA was −53% from Day 1 to Day 14, whereas placebo was +26%. Change in urine 5-HIAA was −53% and placebo was +12%. Interpolation of KAR5417 AUC between 400mg and 800mg BID regimens predicts 500-600mg BID in humans will achieve the target exposure associated with efficacy in rat models. In summary, RVT-1201 was generally well tolerated in healthy subjects at doses required to achieve clinically-relevant AUC and lowering of serotonin biomarkers for treatment of PAH.

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