Tissue Distribution And Biomarker Data For Rodatristat, A Novel Serotonin (5-HT) Synthesis Inhibitor For PAH, Demonstrate Negligible Blood-brain Barrier Penetration And Pharmacologically Meaningful Exposure In Lung

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Rodatristat is peripherally restricted and is ***low-risk for secondary CNS effects***

BACKGROUND

- Current pulmonary arterial hypertension (PAH) meds do not treat the underlying cause of PAH
- Excess **serotonin** (**5-HT**) has been **implicated in the pathology of PAH**[1]
- **Tryptophan hydroxylase (TPH)** is the rate-limiting enzyme for 5-HT biosynthesis and is upregulated in PAH[2]
- A TPH inhibitor for PAH should **lower peripheral 5-HT but not CNS 5-HT**
- Rodatristat lowers peripheral 5-HT
- Rodatristat ethyl currently is in **Phase 2 clinical development** for PAH

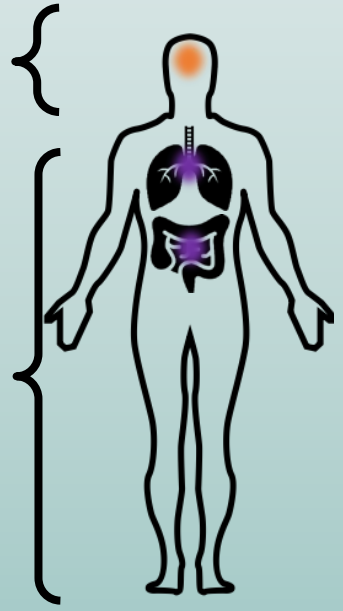
ALTAVANT SCIENCES

Two Separate 5-HT Systems: Central & Peripheral

CNS: 5-HT is a neurotransmitter produced by **TPH2**

Periphery: 5-HT is an autacoid produced by **TPH1**

TPH1 is upregulated in the lungs of PAH patients



5-HT does not cross the blood-brain barrier and lowering brain 5-HT could impact mood

Rodatristat distributes to rat lung but not CNS tissues as determined by QWBA

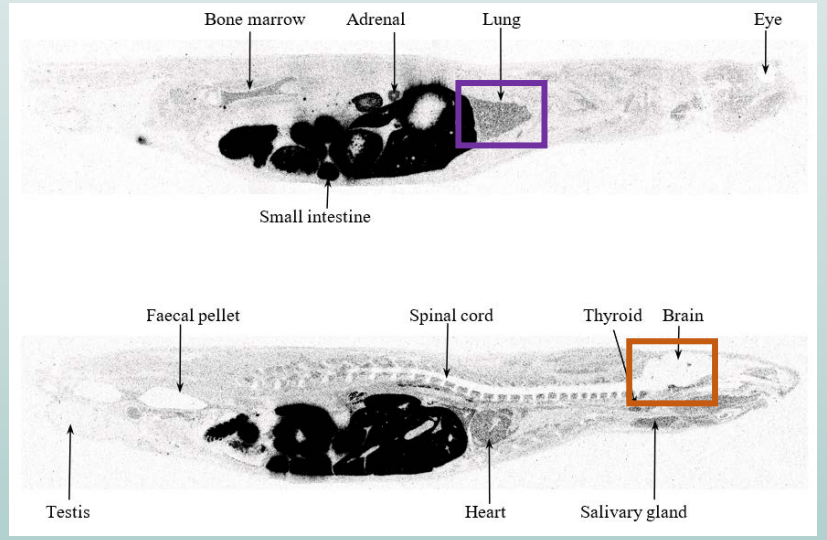


Fig 1. Healthy rats received ^{14}C-rodatristat ethyl (12 mg/kg) for clinically relevant exposure. The brain:blood ratio was ~0.1 and lung:blood ratio was ~5 (2 hours shown).

The NOAEL in the functional observational battery (Irwin) study in rats was 1000 mg/kg/day (at least 3X Cmax for highest envisaged clinical dose for PAH)

Rodatristat treatment lowers lung, but not brain, serotonin

Fig 2

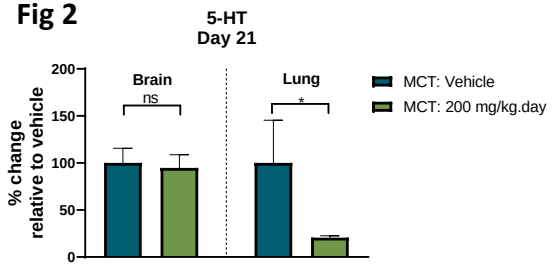


Fig 2. A monocrotaline (MCT)-induced rat PAH model was used, and animals were administered 200 mg/kg/day of Rodatristat ethyl for 21 days. Brain and lung homogenates were analyzed for 5-HT levels and data presented relative to vehicle. Data are expressed as means ± SD, Welch's t-test (*p<0.05).

Rodatristat treatment achieves pharmacologically meaningful levels in lungs but not brain

Fig 3A

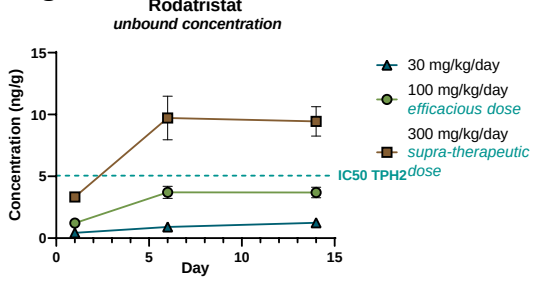


Fig 3B

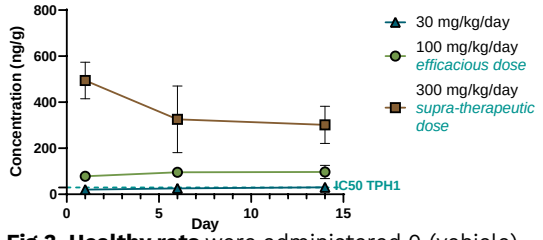


Fig 3. Healthy rats were administered 0 (vehicle), 30, 100, or 300 mg/kg/day of Rodatristat ethyl for 1, 5, or 13 days. **(A)** Brain or **(B)** lung homogenates were analyzed for Rodatristat levels (24 hours post last dose). Data are expressed as means ± SD.

[1] MacLean, M.R. 2018. The serotonin hypothesis in pulmonary hypertension revisited: targets for novel therapies. PulmCirc. 8 (2). 1-9.
[2] Eddahibi, S., et al. (2006). Cross talk between endothelial and smooth muscle cells in pulmonary hypertension: critical role for serotonin-induced smooth muscle hyperplasia. Circulation 113, 1857-18642.