



A Pharmacokinetic/Pharmacodynamic-Based Rationale for Dose Selection of the TPH Inhibitor Rodatristat Ethyl in ELEVATE 2 - a Phase 2b Study in Pulmonary Arterial Hypertension

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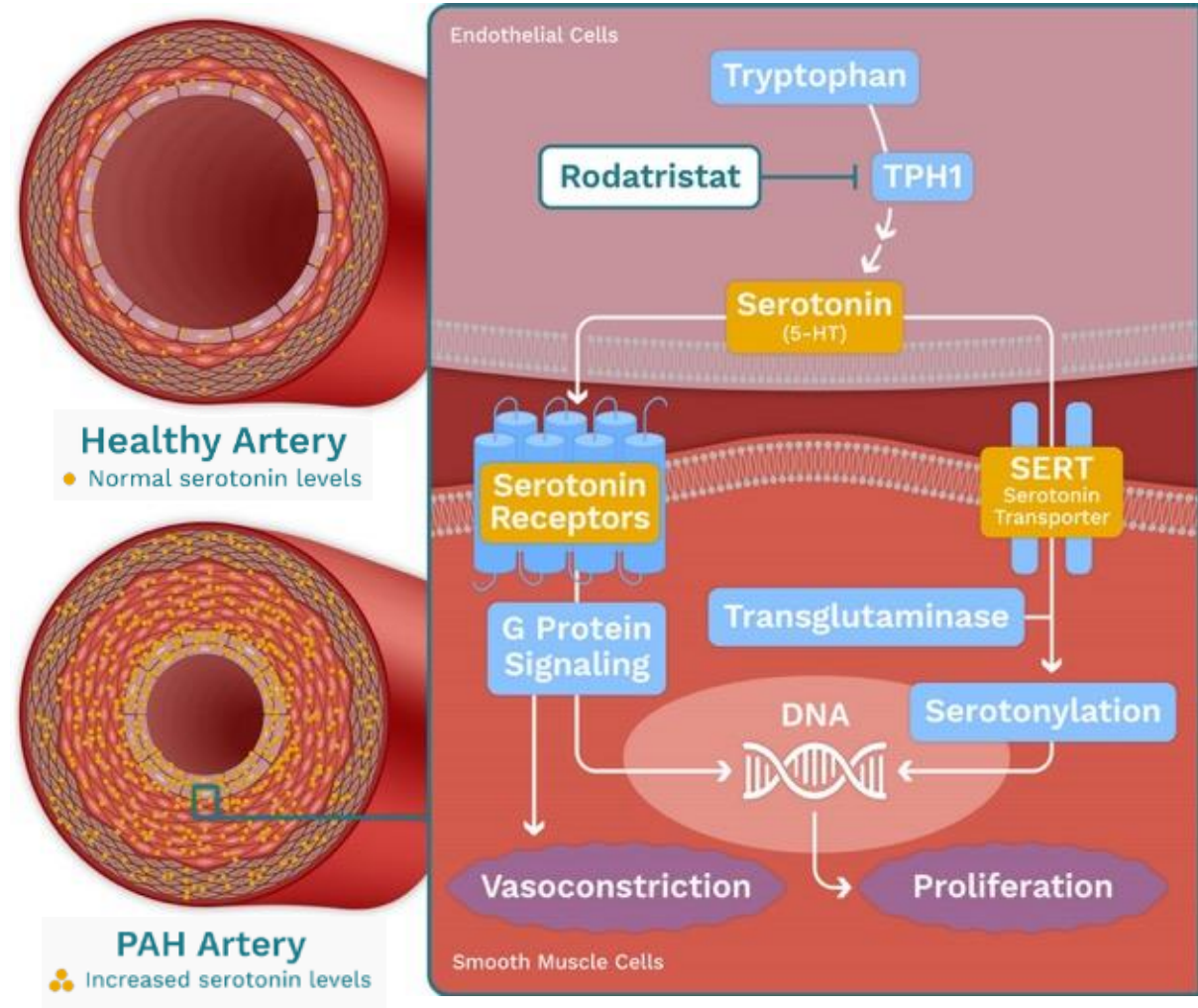
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Rodatrstat Ethyl

- Rodatrstat ethyl is a prodrug of rodatrstat, a peripheral inhibitor of tryptophan hydroxylase (TPH)¹, the rate-limiting enzyme in the production of serotonin²
- In pulmonary arterial hypertension (PAH), aberrant production of serotonin has been implicated in vascular remodeling, right-heart failure, and significant morbidity and mortality³
- This analysis further supports the 300 mg twice daily (BID) and 600 mg BID doses of rodatrstat ethyl being evaluated in an ongoing Phase 2b study in PAH: ELEVATE 2 (NCT04712669)

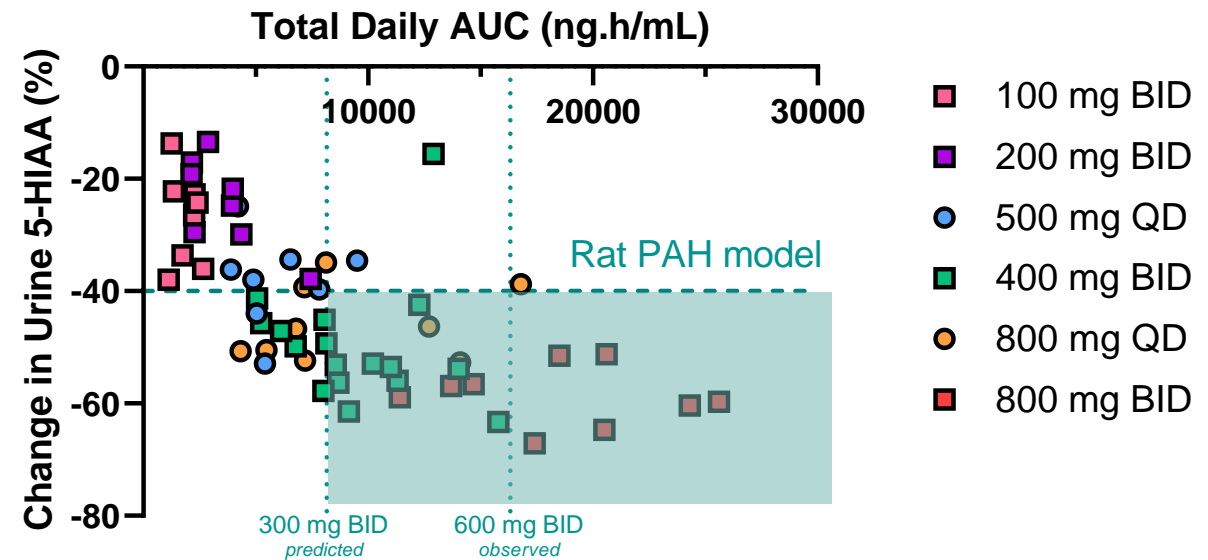
Putative mechanism of action of rodatrstat in PAH



Prior Animal and Human Data

- Disease-modifying effects of rodatristat ethyl have been demonstrated in the rat SU5416 hypoxia and monocrotaline models.¹ At the doses needed to observe these effects, a 40% reduction in serotonin biosynthesis was observed
- Clinical pharmacokinetic and urinary 5-HIAA* data, a metabolite and marker of serotonin biosynthesis, are available from 89 healthy subjects treated with rodatristat ethyl for 14 days²:
 - Placebo, 100 to 800 BID, 500 to 800 once-daily (QD)
- **Suggests high proportion of subjects should reach 40% reduction in urinary 5-HIAA at doses greater than 300 mg BID (figure)**

*normalized to urinary creatinine concentration

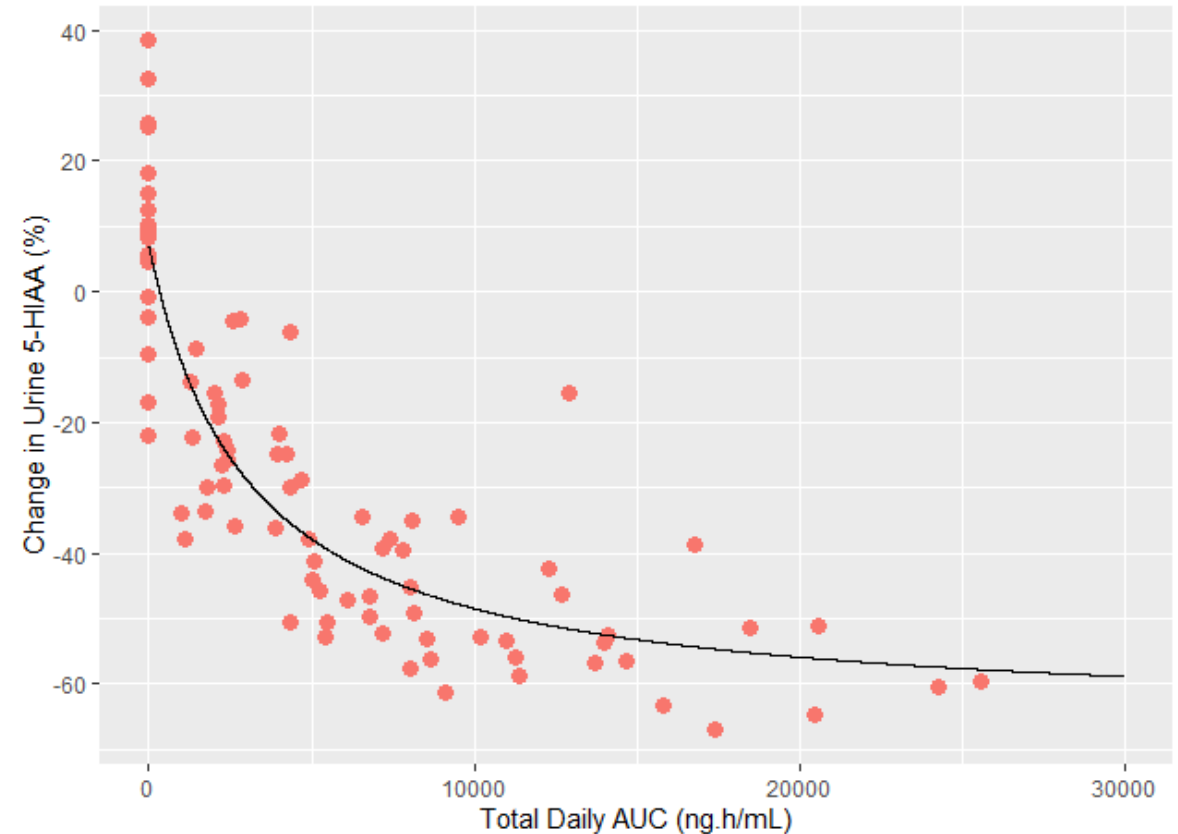


This analysis was conducted to characterize the PK/PD relationship of rodatristat with urinary 5-HIAA

PK/PD Model

- Relationship between the Day 14 total daily rodatristat AUC and the change from baseline 24 h urinary 5-HIAA excretion was described by an inhibitory Emax model (figure)
- Included placebo response, and all available data, providing the most conservative estimate of the between-subject variability in PD response

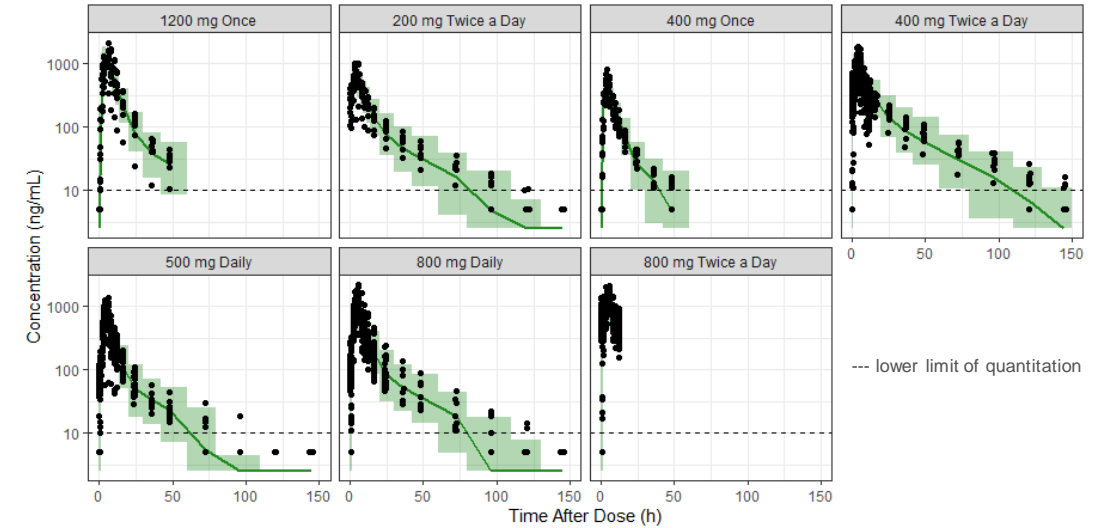
Observed (points) and fitted model (line) of relationship between steady-state change in daily 5-HIAA urinary output and total daily rodatristat AUC at Day 14



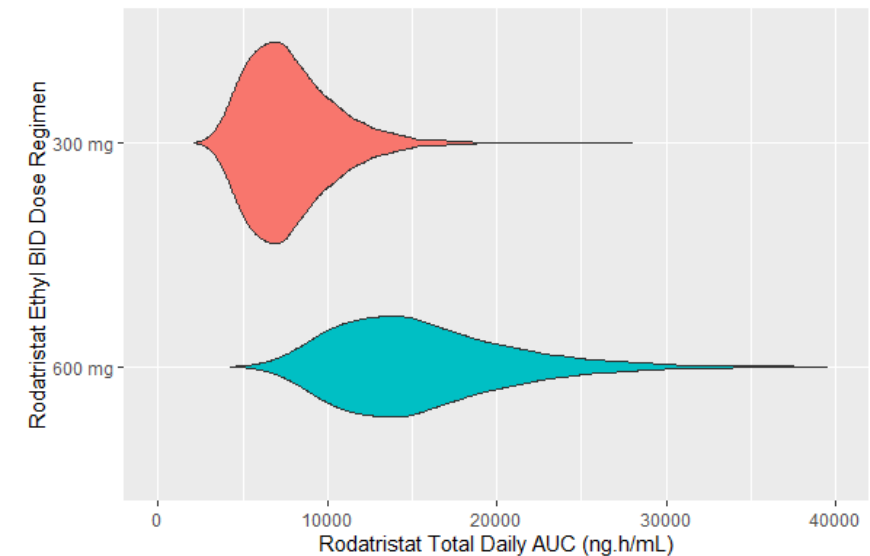
Population PK Model

- PK data from 46 subjects treated with the Phase 2b formulation were included in the analysis
 - 400 and 1200 mg single-dose, 400 and 800 BID for 14 days, 500 and 800 QD for 14 days
- Rodatristat plasma PK (based on dosing rodatristat ethyl) was well described by a 2-compartment model, including allometric effects of body weight on clearance and volume parameters (top figure)
- Rodatristat apparent oral clearance, its between subject variability, and a representative distribution of body-weight¹ were used to simulate the expected distribution of rodatristat total daily AUC
 - 10,000 virtual subjects were simulated following rodatristat ethyl 300 mg BID or 600 mg BID (bottom figure)

Rodatristat PK model: Observed data (points), median prediction (line), and 90% prediction interval (shaded area)



Simulated distributions of rodatristat total daily AUC for input into PK/PD Model

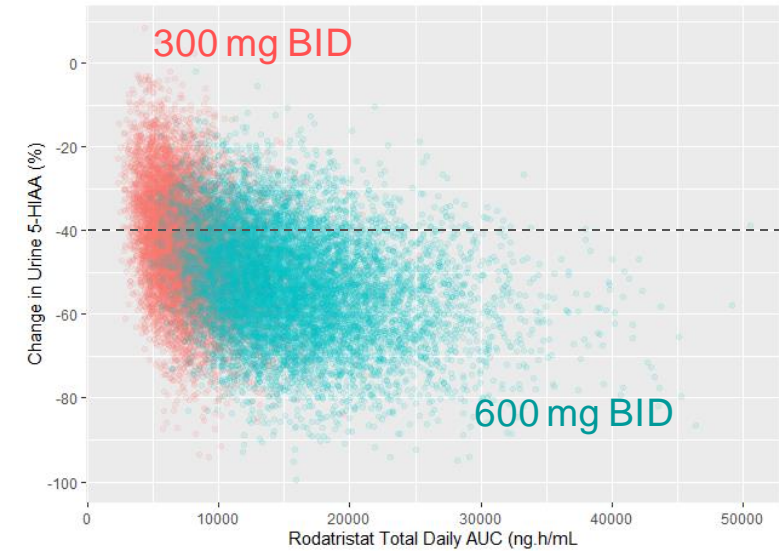


Simulations and Conclusion

- Based on the variability in expected AUC and the PK/PD relationship, PD response was estimated for each dose regimen (top figure)
- Empiric cumulative probability distribution was derived from simulated data (bottom figure)
- The probabilities of a 40% reduction in 5-HIAA after administration of twice daily rodatristat ethyl were **61% for 300 mg and 84% for 600 mg**

Simulations indicate that the 300 mg and 600 mg BID dose regimens may have a high probability of lowering serotonin biosynthesis to an extent that has the potential to lower pulmonary vascular resistance and improve exercise capacity over the 24-week treatment period of ELEVATE-2.

Simulated individual subject steady-state change in daily 5-HIAA urinary output and total daily rodatristat AUC



Cumulative frequency distribution of change in urinary 5-HIAA

