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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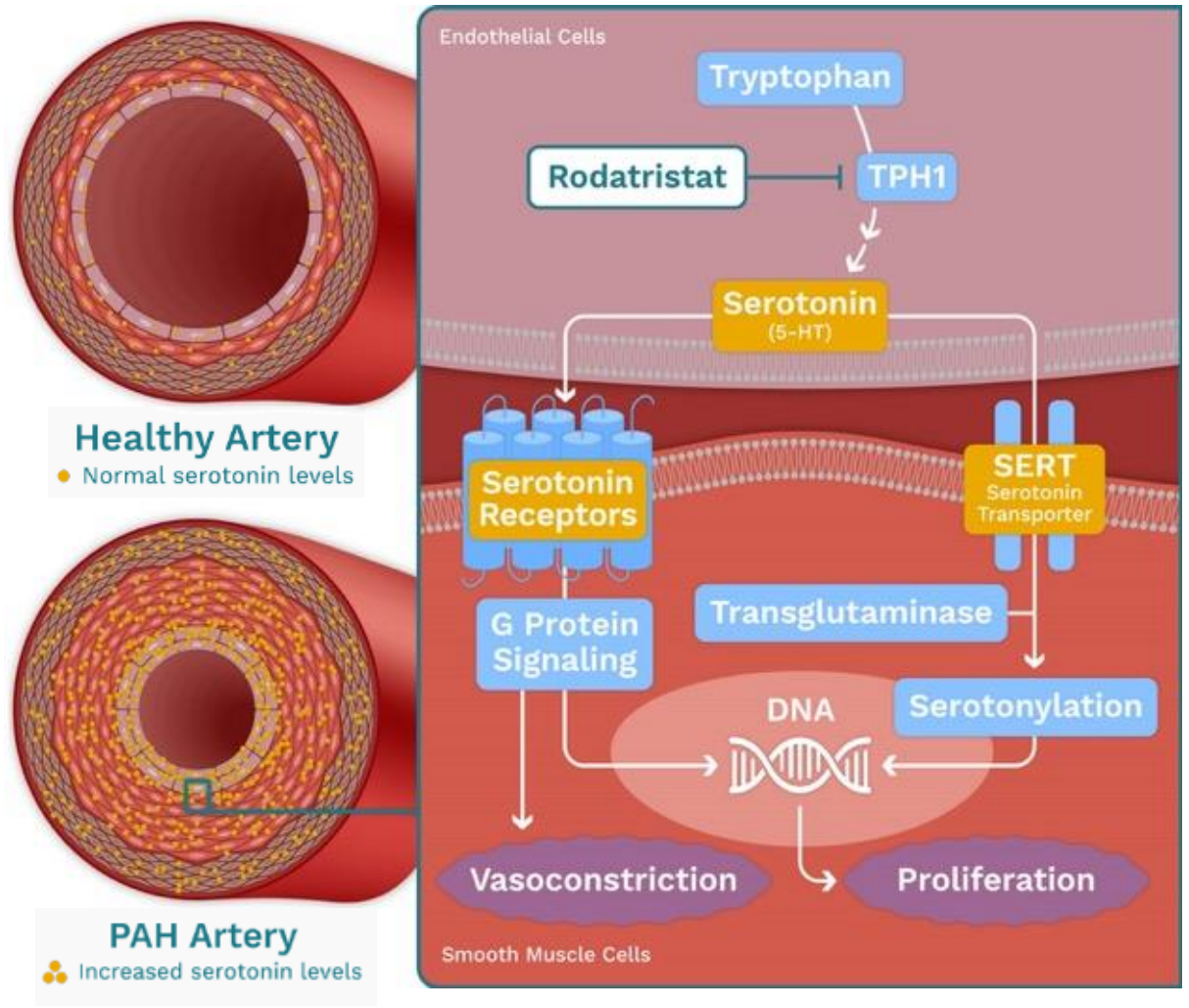
Rodatristat Ethyl

- Rodatristat ethyl is a prodrug of rodatristat, a peripheral inhibitor of tryptophan hydroxylase (TPH)[1], the rate-limiting enzyme in the production of serotonin[2]
- In pulmonary arterial hypertension (PAH), aberrant production of serotonin has been implicated in vascular remodeling, right-heart failure, and significant morbidity and mortality[3]
- This analysis further supports the 300 mg twice daily (BID) and 600 mg BID doses of rodatristat ethyl being evaluated in an ongoing Phase 2b study in PAH: ELEVATE 2 (NCT04712669)

Putative mechanism of action of rodatristat in PAH

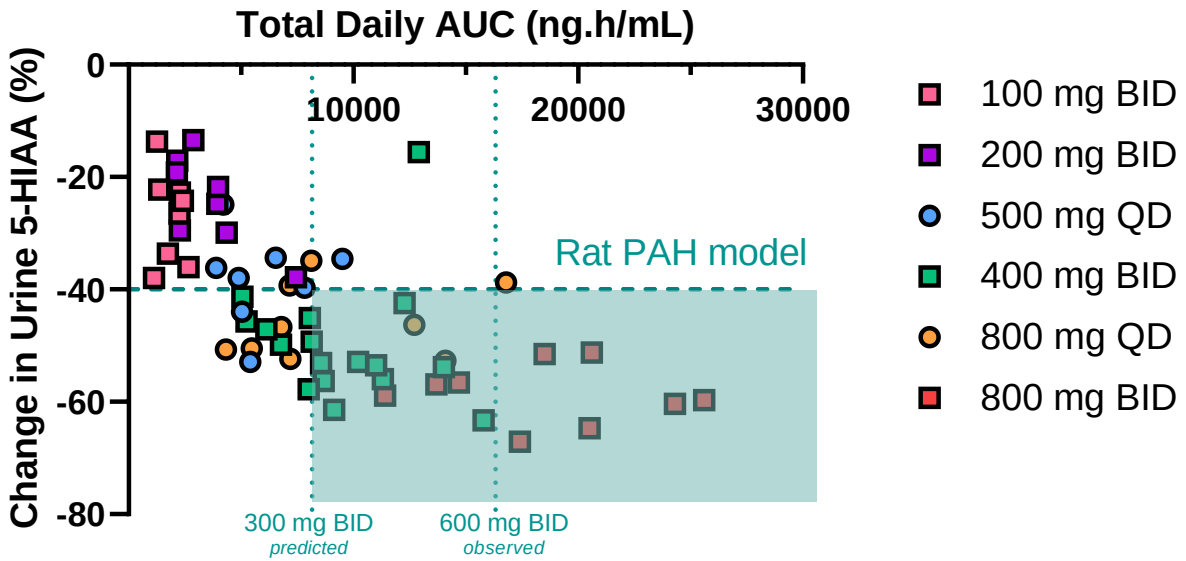


1. Wring et al., American Thoracic Society Annual Meeting, 2020.
2. Mathes and Bader, Trends Pharmacol Sci 2018; 39: 560-572.
3. Thomas et al., Pharmacol Ther 2013; 139:409-417.

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 days[2]:
  - 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

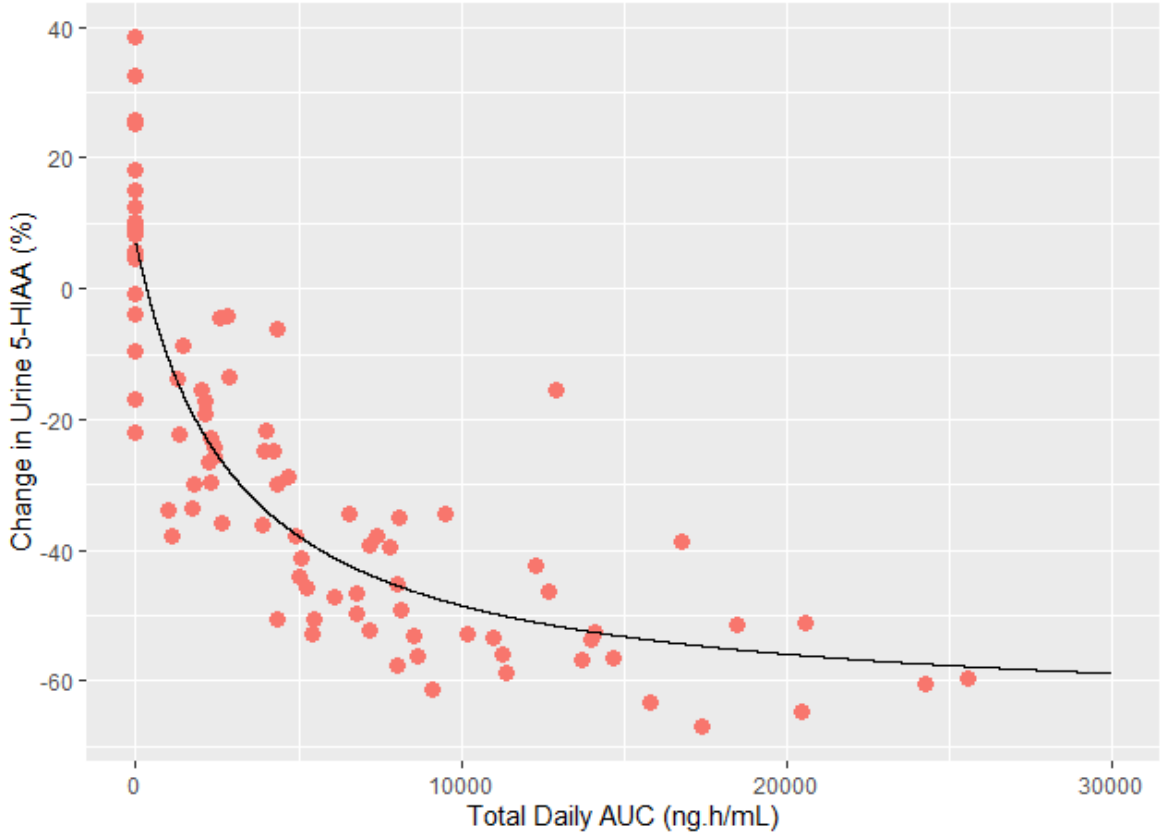
Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; AUC. area under the plasma concentration-time curve

1. Aiello et al., J Pharmacol Exp Ther 2017; 360:267-279
2. Wring et al., European Respiratory Society International Congress, 2019

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

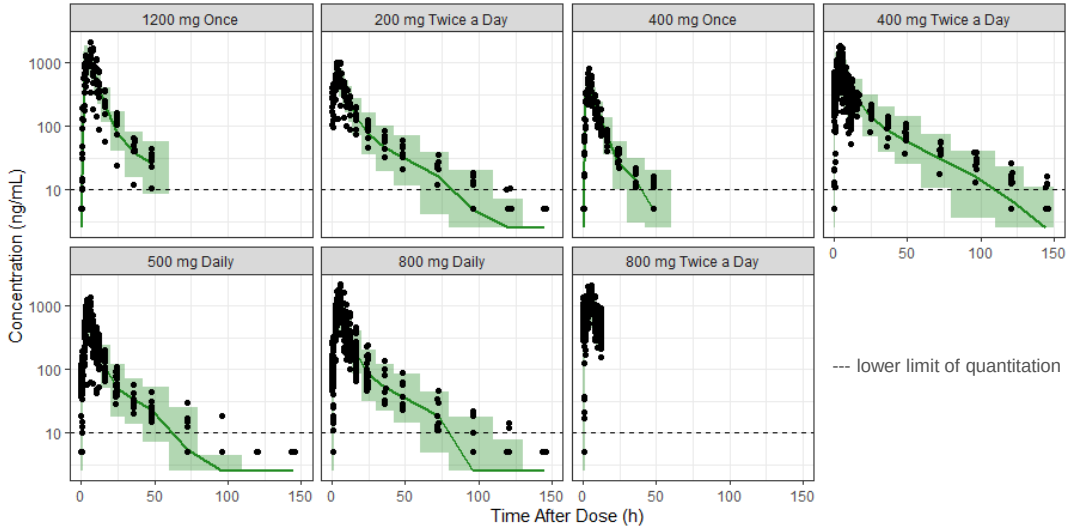


Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic

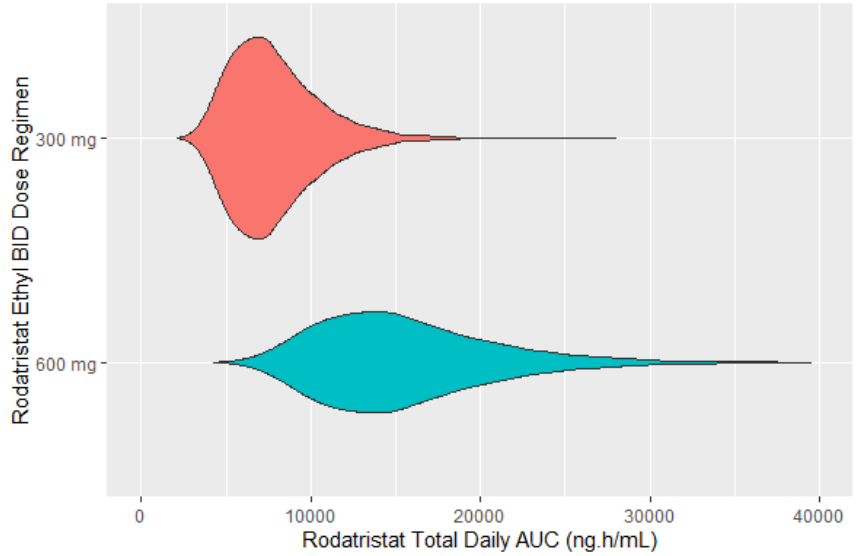
Population PK Model

- 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-weight[1] 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



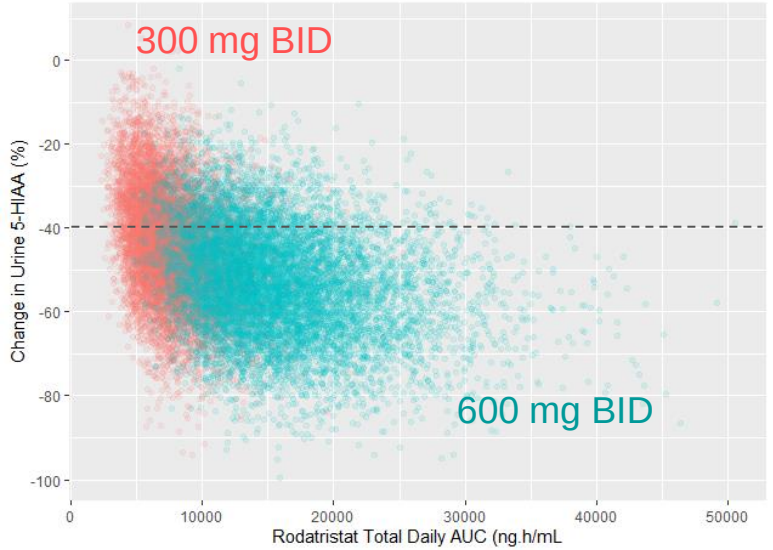
1. Mean 80 kg, standard deviations 20 kg, minimum 40 kg, maximum 150 kg, similar to GRIPHON (Sitbon et al, N Engl J Med 2015; 373:2522-2533).

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