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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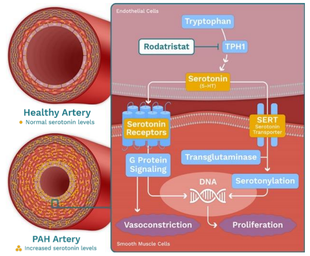
Rodatristat Ethyl

- 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)

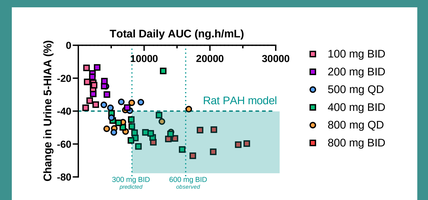
Putative mechanism of action of rodatristat in PAH



Prior Animal and Human Data

- Disease-modifying effects of rodatristat ethyl have been demonstrated in the rat SU5416 hypoxia and monocrotaline models.[4] 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[5]:
  - 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

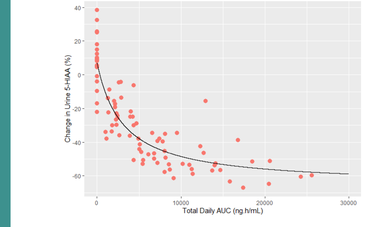


This analysis was conducted to characterize the PK/PD relationship of rodatristat with urinary 5-HIAA

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

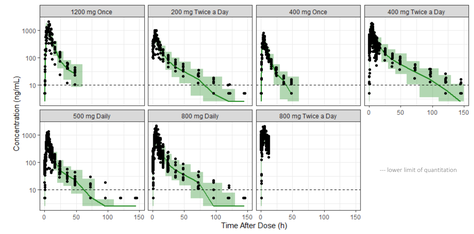
Observed (points) and fitted model (line) of relationship between steady-state change in daily 5-HIAA urinary output and total daily rodatristat AUC at Day 14



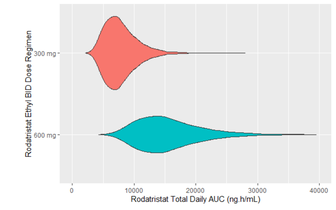
Population PK Model

- 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-weight[6] 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

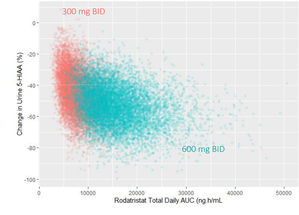


Simulations and Conclusion

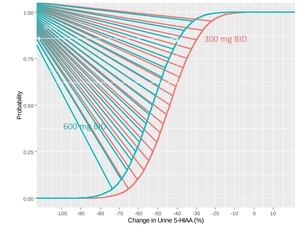
- Based on the variability in expected AUC and the PK/PD relationship, PD response was estimated for each dose regimen (top figure)
- Empiric cumulative probability distribution was derived from simulated data (bottom figure)
- The probabilities of a 40% reduction in 5-HIAA after administration of twice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



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.
4. Aiello et al., J Pharmacol Exp Ther 2017; 360:267-279
5. Wring et al., European Respiratory Society International Congress, 2019
6. 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).

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