Background

- Excess serotonin (5-HT) has been implicated in vascular remodeling and vasoconstriction in patients with pulmonary arterial hypertension (PAH)\(^1\,2\).
- Tryptophan hydroxylase 1 (TPH1) is the rate-limiting enzyme for biosynthesis of serotonin and is upregulated in PAH arterial endothelial cells\(^3\,4\).
- Targeting the serotonin pathway via inhibition of peripheral serotonin and local production in diseased tissues, rather than individual receptor-mediated or receptor-independent mechanisms, may result in the ability to halt or reverse pulmonary vascular remodeling\(^3\).

**RODATRISTAT ETHYL**

- Rodatristat ethyl is a first in class prodrug for rodatristat, a potent inhibitor of tryptophan hydroxylase, the rate limiting enzyme in the biosynthesis of serotonin from dietary tryptophan\(^6\).
- Rodatristat ethyl has demonstrated efficacy in monocrotaline and SUGEN hypoxia nonclinical models of PAH\(^7\,8\) and dose-dependent reductions of 5-hydroxyindoleacetic acid, the major metabolite of serotonin in plasma and urine of healthy human subjects\(^9\).
- Rodatristat is anticipated to ameliorate PAH by halting or reversing pulmonary vascular remodeling caused by increased serotonin production in pulmonary artery cells and resulting proliferation of pulmonary artery smooth muscle cells.

**Study Design**

**ELEVATE 2**: A Multicenter Study of Rodatristat Ethyl in Patients with WHO Group 1 Pulmonary Arterial Hypertension

**Study Endpoints**

**Primary Analysis at 24 Weeks**
- Effect of rodatristat ethyl on the percent change from baseline pulmonary vascular resistance (PVR), as measured by right heart catheterization (RHC) at week 24

**Key Secondary at 24 Weeks**
- Effect of rodatristat ethyl from baseline to week 24 on an array of endpoints including time to clinical worsening, WHO FC, 6MWD, echocardiography, N-terminal pro-brain natriuretic peptide, REVEAL Lite 2 score, and PAH-SYMПАCT®
- Assessment of the pharmacokinetics of rodatristat ethyl on plasma and urinary 5-HIAA as a biomarker of serotonin biosynthesis

**Key Exploratory**
- Time to clinical improvement defined as >10% increase in 6MWD or 30 meters, improvement to or maintenance of WHO FC II symptoms, in the absence of clinical deterioration or death
- Change from baseline in actual daily activity as determined by actigraphy: daily activity level duration will be categorized as light to vigorous, moderate to vigorous, and total movement measured, and actigraphy endpoint assessments will occur between day 1 and week 24

**Study Population**

- Ninety subjects with WHO Group 1 PAH (Functional class 2-3) at clinical sites across 18 countries

**Key Inclusion Criteria**
- ≥18 years old
- WHO Group 1 PAH
- Functional Class II or III
- 6MWD of 100-550 m (baseline)
- Mean pulmonary artery pressure of 220 mmHg
- Pulmonary vascular resistance ≥400 dynes/sec/cm⁵

**Key Exploratory**
- Time to clinical improvement defined as >10% increase in 6MWD or 30 meters, improvement to or maintenance of WHO FC II symptoms, in the absence of clinical deterioration or death
- Change from baseline in actual daily activity as determined by actigraphy: daily activity level duration will be categorized as light to vigorous, moderate to vigorous, and total movement measured, and actigraphy endpoint assessments will occur between day 1 and week 24

**References**

3. Robinovitch, et al. Once daily oral dosing of rodatristat ethyl has demonstrated efficacy in monocrotaline and SUGEN hypoxia nonclinical models of PAH.
10. Université Paris-Saclay, Université Paris-Diderot, Paris (France)

**Acknowledgments/Disclosures**

The authors would like to thank the participating investigators and patients and families.

Disclosures: M.H., Acceleron, Altavant, Bayer, GSK, Janssen and Merck & Co., Inc., Cary, NC (USA) 
Université Paris-Saclay, Université Paris-Diderot, Paris (France)