1046

SERALUTINIB IMPROVES PULMONARY ARTERIAL BLOOD VESSEL VOLUME DISTRIBUTION IN PULMONARY ARTERIAL HYPERTENSION (PAH): RESULTS OF THE TORREY PHASE 2 IMAGING SUBSTUDY

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TORREY STUDY

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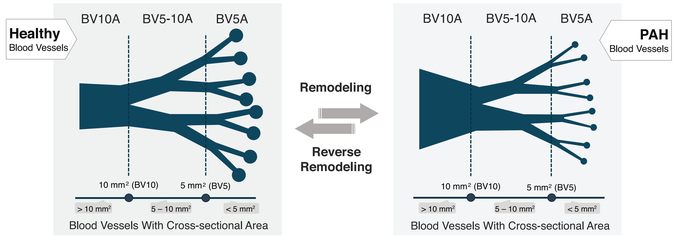
BACKGROUND

- PAH is characterized by pulmonary vascular remodeling and loss of small distal pulmonary arteries ("pruning"), leading to increased pulmonary vascular resistance (PVR) and dilation of larger proximal vessels (**Figure 1**)
- The volume of blood distribution in pulmonary vessels can be quantified by computed tomographic (CT) imaging; pulmonary vascular pruning on CT has been shown to correlate with histologic pulmonary vascular remodeling[1]
- Seralutinib, a highly potent inhibitor of PDGFRα/ß, CSF1R, and c-KIT kinase pathways that activate inflammation, proliferation, and fibrosis, has the potential to treat pulmonary vascular remodeling[2]
- The phase 2 TORREY study of inhaled seralutinib in patients with WHO Group I PH met its primary endpoint of reduction in PVR at 24 weeks[3] (NCT04456998; see QR code to the right for more information)
- In a CT substudy of TORREY, the potential of seralutinib to reverse remodel the pulmonary vasculature in PAH patients was evaluated

Seralutinib for the Treatment of PAH: Results from the Ph2 TORREY Study

Figure 1. Changes in the pulmonary vasculature quantifiable by CT imaging



BV5A: blood vessel volume (BVV) of pulmonary arteries with a cross-sectional area (CSA) < 5 mm²; BV5-10A: BVV of pulmonary arteries with a CSA between 5 – 10 mm²; BV10A: BVV of pulmonary arteries with a CSA > 10 mm²; BV510ARatio: BV5A/BV10A. Illustration adapted from FLUIDDA, Inc.

METHODS

- Thin-section, volumetric, non-contrast chest CTs were performed, followed by automated pulmonary vascular segmentation
- Baseline and Week 24 blood vessel volumes (BVVs) were determined at distinct levels defined by vessel cross-sectional area (CSA) in 19 subjects on double or triple PAH-specific background therapy
- BVVs of pulmonary arteries with a CSA < 5 mm² (BV5A) and > 10 mm² (BV10A) were calculated
- The BV5A-to-BV10A ratio (BV510ARATIO) was used to express relative redistribution of pulmonary arterial BVV
- Linear regression was used to model the treatment effect

RESULTS

Table 1. Patient characteristics

Characteristic	Total
N	19
Age, mean (SD), y	49.26 (12.07)
Sex, n (%)	
Female	18 (94.7)
Male	1 (5.3)
BMI, mean (SD)	30.42 (7.59)
Treatment, n (%)	
Seralutinib	7 (36.8)
Placebo	12 (63.2)

Characteristic	Total
PAH classification, n (%)	
Idiopathic	10 (52.6)
Heritable	2 (10.5)
Associated with CTD	3 (15.8)
Drug- or toxin-induced	3 (15.8)
Associated with congenital shunts	1 (5.3)
WHO FC, n (%)	
Class II	7 (36.8)
Class III	12 (63.2)

BMI, body mass index; CTD, connective tissue disease; FC, Functional Class; PAH, pulmonary arterial hypertension.

Figure 2. BV5A/BV10A ratio increased from baseline (BL) to Week 24 in the seralutinib group vs. placebo.

A. Box plots show median values with upper and lower quartiles for BV5A/BV10A ratio. Least squares mean difference estimate (95% CI) for seralutinib vs. placebo was 0.845 (0.105, 1.585); p = 0.028. **B.** Changes in BV5A/BV10A ratio from BL to Week 24 for individual patients. Linear regression models adjusted for baseline values and treatment arm.

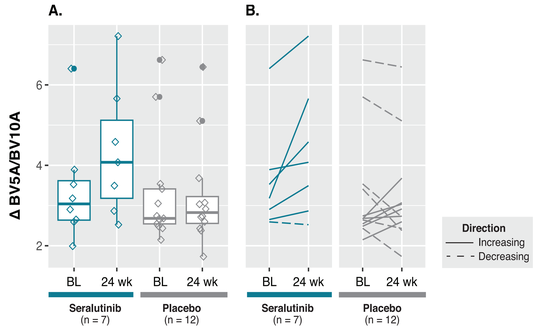
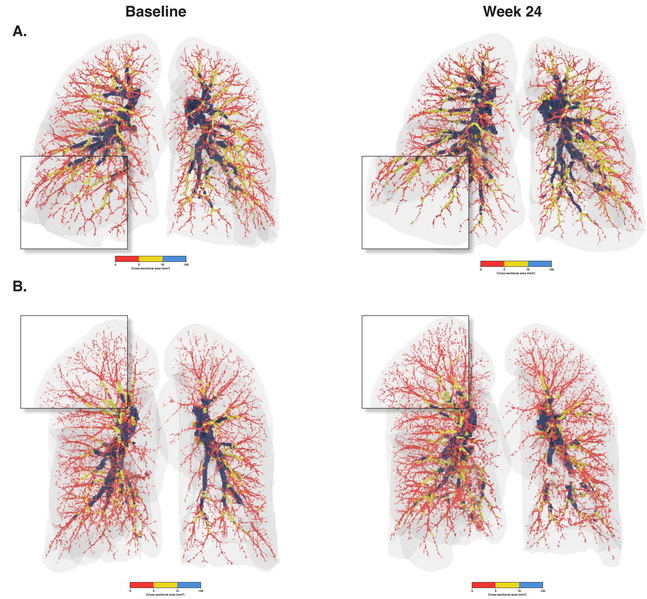


Figure 3. Change in BV5A/BV10A ratio from baseline to Week 24 correlates with change in hemodynamic parameters

Figure 4. CT images at baseline and Week 24

A. 24-year-old placebo-treated female patient with iPAH, FC II, receiving PDE5 inhibitor and prostacyclin background treatment
- Change in PVR: 283 dyne*s/cm^5 (+65.4%)
- Change in BV5A/BV10A ratio: -0.70 (-28.9%)

B. 58-year-old seralutinib-treated female patient with iPAH, FC II, receiving background treatment with an ERA, PDE5 inhibitor, and prostacyclin
- Change in PVR: -159 dyne*s/cm^5 (-39.0%)
- Change in BV5A/BV10A ratio: +2.5 (+78.0%)



NOTE: Insets indicate 1.3x magnification.

ERA, endothelin receptor antagonist; FC, Functional Class; iPAH, idiopathic pulmonary arterial hypertension; PDE5, phosphodiesterase 5; PVR, pulmonary vascular resistance.

CONCLUSIONS

- There was a significant improvement in the ratio of blood vessel volume in distal vessels relative to larger vessels (BV510ARATIO), consistent with a reverse remodeling effect of seralutinib
- The BV510ARATIO correlated with important measures of right ventricular-pulmonary artery coupling, as measured by pulmonary artery compliance and stroke volume
- To increase our understanding of the effect of seralutinib on pulmonary vascular remodeling, a CT substudy is planned for the phase 3 PROSERA trial (NCT05934526)

References: 1 Synn AJ, et al. *Pulm Circ.* 2021;11(4):20458940211061284; **2** Galkin A, et al. *Eur Respir J.* 2022;60:2102356; **3** Frantz RP, et al. *Am J Respir Crit Care Med.* 2023;207:A6726.

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