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

TORREY STUDY

7th World Symposium on Pulmonary Hypertension
Barcelona, Spain
29 June - 1 July 2024

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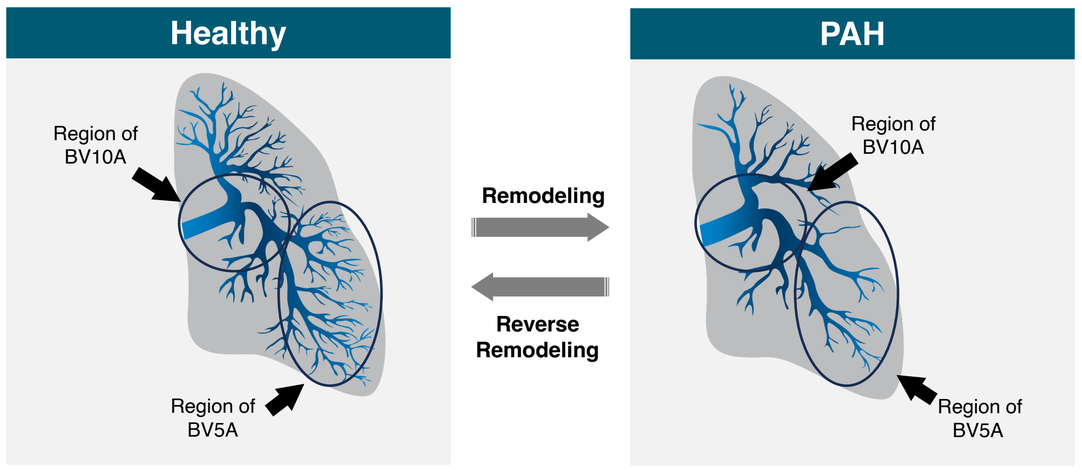
BACKGROUND

- 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)
- In this CT substudy of TORREY, the potential of seralutinib to reverse remodel the pulmonary vasculature in PAH patients was evaluated

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 mm^2; BV10A, BVV of pulmonary arteries with a CSA > 10 mm^2.

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 mm^2 (BV5A) and > 10 mm^2 (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; WHO, World Health Organization.

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 BL values and treatment arm.

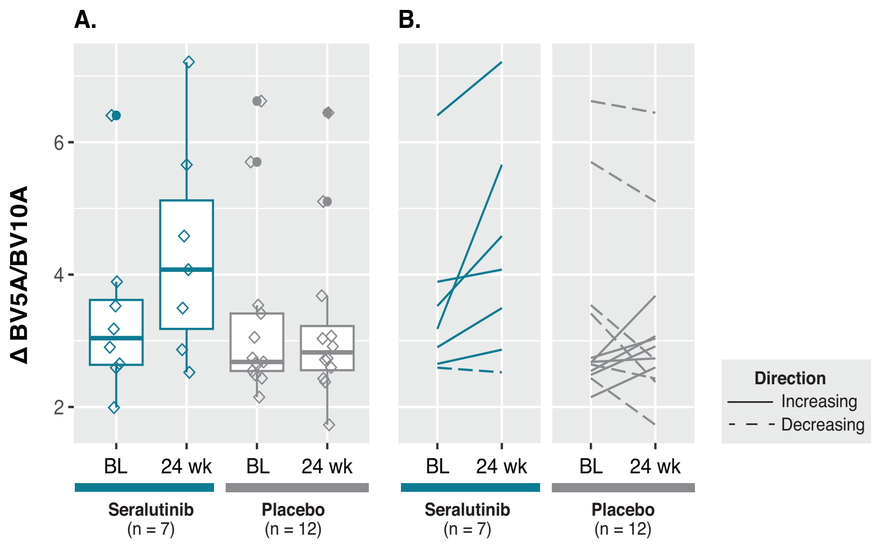


Figure 3. Change in BV5A/BV10A ratio from Baseline to Week 24 correlates with change in hemodynamic parameters

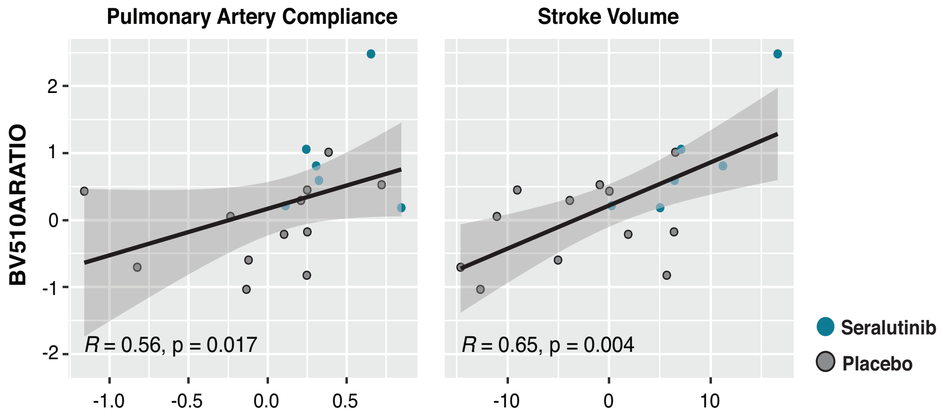


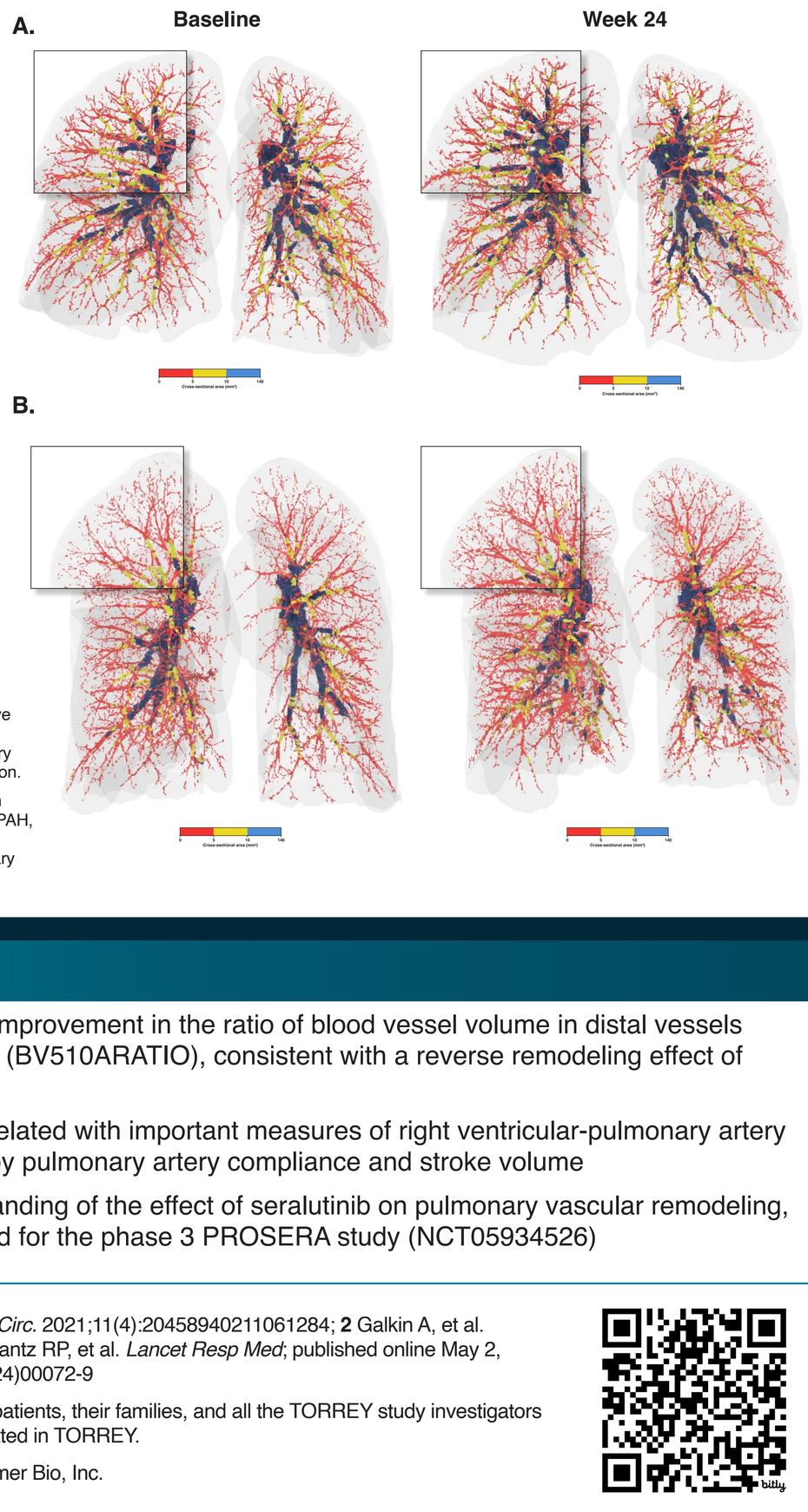
Figure 4. CT images at Baseline and Week 24

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 ERA, PDE5 inhibitor, and prostacyclin background treatment

- Change in PVR: -159 dyne*s/cm^5 (-39.0%)
- Change in BV5A/BV10A ratio: +2.5 (+78.0%)



NOTE: The images shown are representative examples. The highlighted sections were chosen to illustrate changes in the pulmonary vasculature. Insets indicate 1.3x magnification.

CT, computed tomography; 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 study (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. *Lancet Resp Med*; published online May 2, 2024. doi.org/10.1016/S2213-2600(24)00072-9

Acknowledgements: We thank all patients, their families, and all the TORREY study investigators and study coordinators who participated in TORREY.

This study was supported by Gossamer Bio, Inc.