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Targeted genetic profiling of PAH-predisposing genes and exploratory seralutinib response by genotype in the phase 3 PROSERA study

David Montani¹, Robin Osterhout², Florence Coulet³, Raymond L. Benza⁴, Richard N. Channick⁵, Kelly M. Chin⁶, Robert P. Frantz⁷, Hossein-Ardeschir Ghofrani⁸, Luke S. Howard⁹, Vallerie V. McLaughlin¹⁰, Gisela Meyer¹¹, Olivier Sitbon¹, Jean-Luc Vachiéry¹², Roham T. Zamanian¹³, Robert F. Roscigno², Jean-Marie Bruey², Anna R. Hemnes¹⁴

¹Université Paris-Saclay, Inserm UMR_S 1358 HPPIIT, AP-HP, Department of Respiratory and Intensive Care Medicine (FHU Courmand, ERN-LUNG), Hôpital Bicêtre, Le Kremlin Bicêtre, France; ²Gossamer Bio, Inc., San Diego, CA, USA; ³Sorbonne Université, Département de génétique médicale, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France; ⁴Eastern Virginia Medical School, Macon and Joan Brock Virginia Health Sciences at Old Dominion University, Sentara Health, Norfolk, VA, USA; ⁵University of California Los Angeles, UCLA Medical Center, Los Angeles, CA, USA; ⁶UT Southwestern Medical Center, Dallas, TX, USA; ⁷Mayo Clinic, Rochester, MN, USA; ⁸Universities of Giessen and Marburg Lung Center (UGMLC), Institute for Lung Health (ILH), Cardio-Pulmonary Institute (CPI), Member of the German Center for Lung Research (DZL), Giessen, Germany; ⁹Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK; ¹⁰University of Michigan, Ann Arbor, MI, USA; ¹¹Irmandade Da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil; ¹²Université Libre de Bruxelles, HUB – Hôpital Erasme, Bruxelles, Belgium; ¹³Stanford University School of Medicine, Stanford, CA, USA; ¹⁴Vanderbilt University Medical Center, Nashville, TN, USA.



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BACKGROUND

- Pathogenic variants in pulmonary arterial hypertension (PAH)—predisposing genes, particularly *BMPR2*, are linked to earlier disease onset, more severe clinical phenotypes and reduced vasodilator responsiveness¹
- Whether genetic background modifies response to targeted PAH therapies remains uncertain
- A planned analysis of the phase 2 sotatercept PULSAR trial showed preserved six-minute walk distance (6MWD) and pulmonary vascular resistance (PVR) benefit in *BMPR2* carriers vs noncarriers, supporting genotype-independent efficacy for an activin/BMP-axis therapy²
- Seralutinib, an inhaled PDGFR α / β , CSF1R, and c-KIT inhibitor, targets mechanistically distinct targeted pathways linked to pathogenic vascular remodeling³
- We conducted an exploratory genetic analysis in the PROSERA phase 3 study of inhaled seralutinib in PAH (NCT05934526) to evaluate therapy response across *BMPR2* subgroups

Phase 3 PROSERA Study (NCT05934526)⁴

- PROSERA is a global phase 3 study of inhaled seralutinib in patients with WHO Group 1 PH, FC II–III, with prevalent disease on standard of care therapy and limited functional capacity
- Seralutinib increased 6MWD from baseline to week 24 in the overall population by 28.2 m compared with 13.5 m in the placebo group, yielding a placebo-corrected effect of 13.3 m (p=0.0320), which did not meet the prespecified $\alpha=0.025$, but remains relevant under conventional p<0.05 criteria
- Seralutinib treatment effects on 6MWD were directionally consistent across clinically relevant prespecified subgroups, with greater benefits observed in patients with higher baseline disease burden, including REVEAL Lite 2 $\geq$ 6 and CTD-PAH
- Gossamer Bio is preparing to file an NDA submission in September 2026 following recent discussion with the FDA

METHODS

- Whole blood samples were obtained from 306 consenting participants (151 placebo / 155 seralutinib)
- Targeted DNA sequencing of PAH-predisposing genes was performed via a custom TWIST NGS panel with ~500 $\times$ coverage of introns, exons, and 3’/5’ UTRs; NovaSeq 6000 (2 $\times$ 100 bp PE). PAH-predisposing genes included *ACVRL1*, *AQP1*, *BMPR2*, *CAV1*, *ENG*, *GDF2*, *KCNK3*, *KDR*, *SMAD9*, *TBX4*, *BMPR1B*, *EIF2AK4*, *KCNA5*, *SOX17*⁵
- Bioinformatics:** Illumina DRAGEN Bio-IT Platform (v4.0.3), FASTQ quality assessment (FastQC v0.11.8), adapter trimming and quality filtering (Trim Galore v0.6.0 / cutadapt v2.5), alignment (BWA 0.7.17 to GRCh38.p14, Ensembl v113), alignment QC (Picard 2.20.3, RSeQC v4.0.0) and variant annotation (Ensembl VEP v113 with CADD v1.6, REVEL v1.3, SpliceAI v1.3)
- Curation:** ACMG/AMP 2015 classification; pathogenic/likely pathogenic (class 4/5) variants in definitive PAH-predisposing genes
- BMPR2* efficacy population:** Included all participants in the genetic cohort, excluding those with pathogenic or likely pathogenic variants in non-*BMPR2* PAH genes, CTD-APAH, and/or congenital heart disease with simple pulmonary to systemic shunt. The resulting population includes 49 with pathogenic or likely pathogenic *BMPR2* variants and 173 with no pathogenic *BMPR2* variants (231 combined)
- Endpoints:** Change from baseline in 6MWD and NT-proBNP at week 24
- Statistics:** Pre-specified Biomarker Analysis Plan finalized prior to study completion (v1.1, 14-Nov-2025); $\alpha=0.05$, two-sided. Non-parametric methods applied:
 - Within-stratum treatment effect with Aligned-Rank Stratified Wilcoxon (ARSW): 1. residualize endpoint: $\Delta 6MWD \sim 6MWD_{baseline} + WHO\ FC + PPACT$; 2. Wilcoxon rank-sum on aligned residuals $\rightarrow$ Hodges–Lehmann location shift (seralutinib – placebo) with 95% CI
 - BMPR2* $\times$ treatment interaction with Aligned Rank Transform: 1. residualize endpoint: $\Delta 6MWD \sim 6MWD + WHO\ FC + PPACT$; 2. rank residuals; 3. test treatment $\times$ genotype effect modification: $lm(rank \sim treatment \times genotype)$ with Type III sum of squares

RESULTS

Pathogenic PAH-Predisposing Genes Identified in 20% of Study Participants

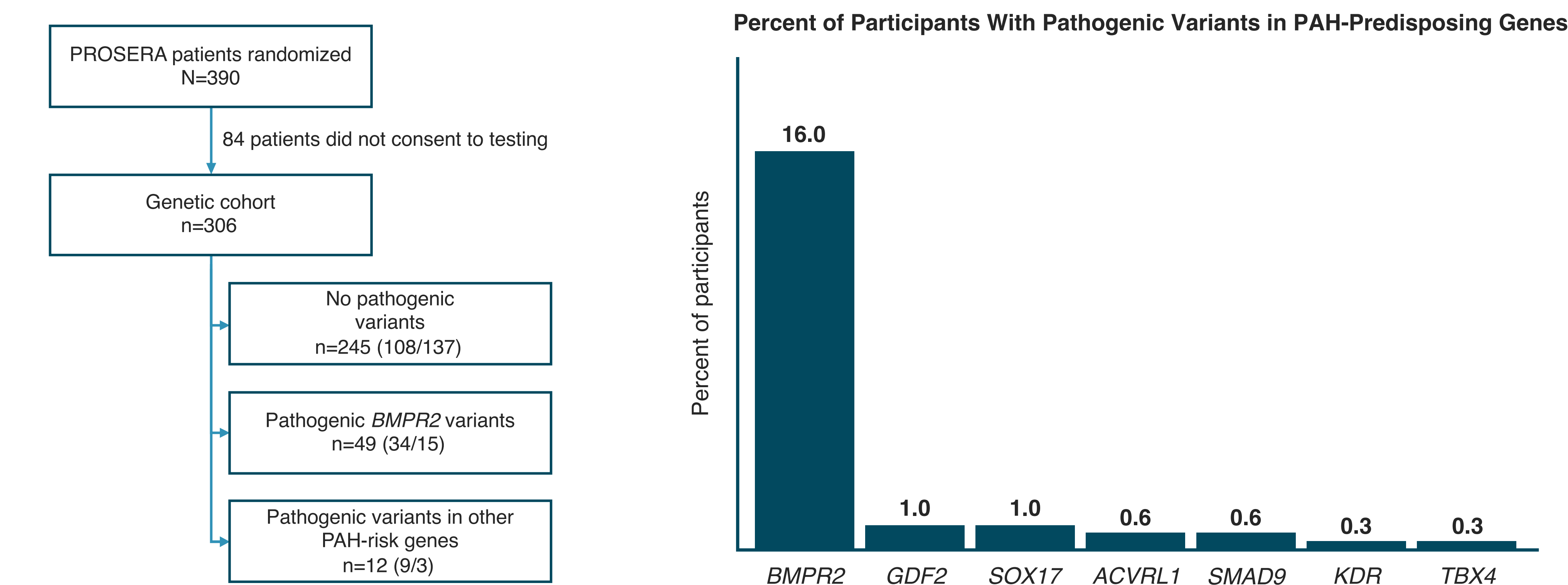


Figure 1. Disposition and prevalence of pathogenic and likely pathogenic variants in PAH-predisposing genes in PROSERA. N includes total (placebo/seralutinib).

- BMPR2* prevalence 49/306 (16.0%) aligns with expected frequency in PAH cohorts⁶
- Most patients with pathogenic or likely pathogenic variants were classified as idiopathic (n=34/193) or heritable PAH (n=23/32)
- Variants of uncertain significance (VUS) in PAH-predisposing genes were identified in 52 patients. The most common genes with VUS were *TBX4* (22), *KDR* (10), *EIF2AK4* (8 heterozygous), and *BMPR2* (5)

Baseline *BMPR2* Phenotype Is Consistent With Expectations

Characteristic	Genetic Cohort	<i>BMPR2</i> Analysis	
	Overall (N=306)	<i>BMPR2</i> variants (n=49)	No variant (n=173)
Female, n (%)	262 (85.6)	39 (79.6)	147 (85.0)
Age, years	49.8 (13.88)	44.1 (13.70)	50.7 (13.20)
PAH classification, n (%)			
Idiopathic	193 (63.1)	26 (53.1)	159 (91.9)
Heritable	32 (10.5)	22 (44.9)	9 (5.2)
CTD-APAH	61 (19.9)	[excluded]	[excluded]
Drug-associated	6 (1.9)	1 (2.0)	5 (2.9)
CHD with shunt	14 (4.6)	[excluded]	[excluded]
≥ 3 Background PAH meds, n (%)	163 (53.3)	30 (61.2)	86 (49.7)
WHO FC, n (%)			
II	76 (24.8)	17 (34.7)	39 (22.5)
III	230 (75.2)	32 (65.3)	134 (77.5)
6MWD, m	375.7 (71.52)	398.2 (56.95)	377.2 (68.84)
NT-proBNP, ng/L	990.0 (1562.24)	626.9 (1174.95)	953.7 (1435.28)
PVR, dyne-s/cm ⁵	813.6 (406.15)	880.8 (398.41)	812.1 (406.95)

Table. Baseline characteristics of the overall and *BMPR2* efficacy analysis populations. Data are mean (SD) unless otherwise indicated. The *BMPR2* efficacy population excluded participants with CTD-APAH, CHD with shunt, and pathogenic variants in other PAH-predisposing genes. 6MWD, six-minute walk distance; CHD with shunt, congenital heart disease with simple pulmonary to systemic shunt; CTD-APAH, connective tissue disease–associated PAH; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SD, standard deviation; WHO FC, World Health Organization Functional Class.

Seralutinib Efficacy by *BMPR2* Genotype

- No variant subgroup (n=150 at week 24):** Seralutinib favorable on 6MWD (+11.3 m [95% CI: –7.0, 27.0]; p=0.198) and nominally significant on NT-proBNP (–153.4 ng/L [95% CI: –245.5, –71.5]; p<0.001)
- BMPR2* subgroup (n=42 at week 24):** Treatment effects were non-significant with high uncertainty (6MWD –2.2 m [95% CI: –33.0, 37.0]; p=0.888; NT-proBNP –83.3 ng/L [95% CI: –278.9, 104.8]; p=0.328)
- BMPR2* as treatment effect modifier:** Not significant for 6MWD (p=0.737) and NT-proBNP (p=0.198)

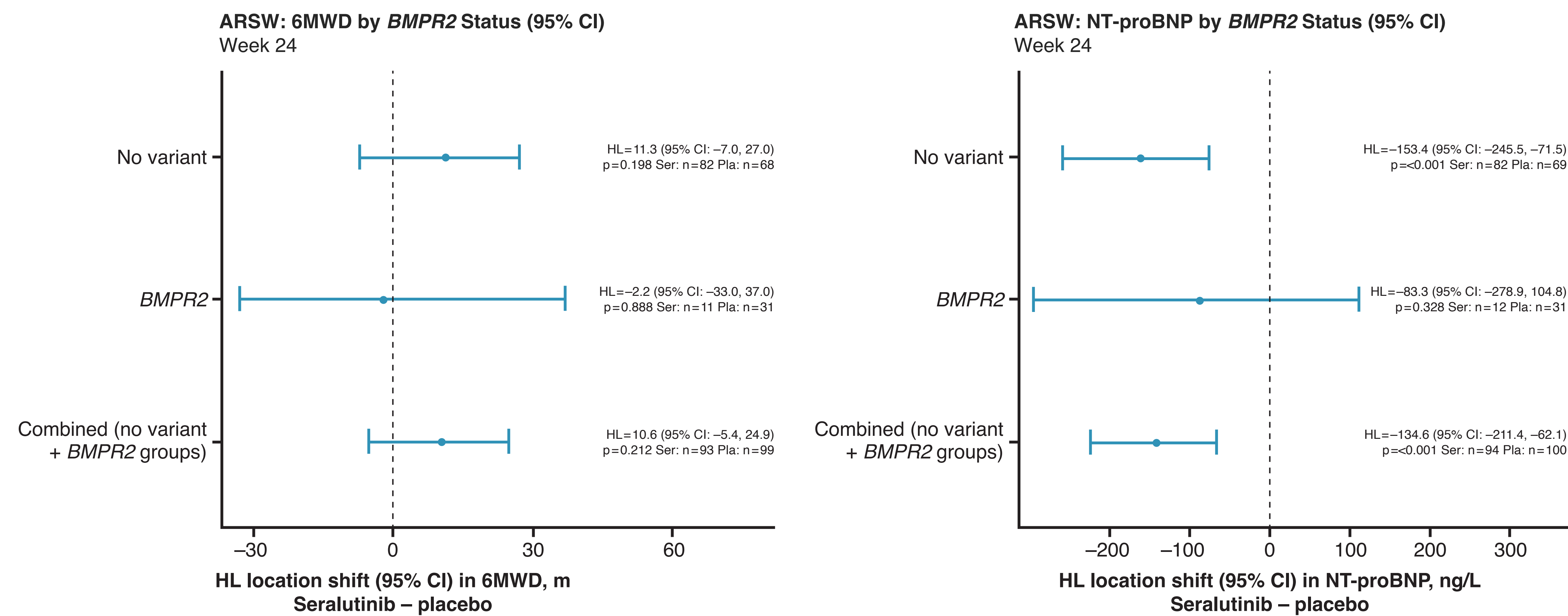


Figure 2. Week 24 seralutinib treatment effect on 6MWD (left) and NT-proBNP (right) by *BMPR2* mutation status. Forest plots show Hodges–Lehmann (HL) location shifts (seralutinib – placebo) with 95% CIs from Aligned-Rank Stratified Wilcoxon (ARSW) analyses in the *BMPR2* efficacy population. The *BMPR2* group has pathogenic or likely pathogenic variants in *BMPR2*, the “No variant” group has no pathogenic variants. 6MWD, six-minute walk distance; NT-proBNP, N-terminal pro–B-type natriuretic peptide; Pla, placebo; Ser, seralutinib.

CONCLUSIONS

- Targeted genetic profiling in a phase 3 PAH trial identified clinically relevant genetic subgroups
- BMPR2* prevalence was consistent with published PAH cohorts
- Seralutinib efficacy on 6MWD and NT-proBNP was preserved in participants without pathogenic PAH variants; *BMPR2* subgroup estimates were limited by small on-treatment n and arm imbalance
- BMPR2* was not a significant treatment-effect modifier
- These preliminary results do not support *BMPR2* genotype as an enrichment criterion for future studies

References: 1 Evans JD, et al. *Lancet Respir Med.* 2016;4(2):129–137. 2 Montani D, et al. *Am J Respir Crit Care Med.* 2025;211(6):1028–1037. 3 Pullamsetti SS, et al. *Int J Mol Sci.* 2023;24(16):12653. 4 Ghofrani HA, et al. *Am J Resp Crit Care Med.* 2026;212(suppl 2):aamag286.279. 5 Welch CL, et al. *Genet Med.* 2023;25(11):100925. 6 Gräf S, et al. *Nat Commun.* 2018;9(1):1416.
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