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Exploratory analysis of a *PDGFRB* protein quantitative trait locus and seralutinib treatment response in the phase 3 PROSERA PAH study

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BACKGROUND

- rs2304058 is a common intronic *PDGFRB* polymorphism and genome-wide significant *cis*-protein quantitative trait locus (pQTL) in independent population-scale studies, with the G allele (population frequency 51%) associated with higher circulating PDGFRβ^{1,2}
- Prior work hypothesized that rs2304058 genotype may influence response to PDGFR-targeted therapy.³ To date, an association between rs2304058 and treatment efficacy has not been established
- Seralutinib is an inhaled PDGFRα/β, CSF1R, and c-KIT inhibitor in development for pulmonary arterial hypertension (PAH)
- This exploratory pharmacogenomic sub-study tested whether rs2304058 influenced response to seralutinib

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 6-minute walk distance (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 α=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 ≥6 and CTD-associated PAH (CTD-APAH)
- Gossamer Bio is preparing to file an NDA submission in September 2026 following recent discussion with the FDA

METHODS

- 306 PROSERA participants consented to genetic testing. Whole-blood targeted DNA sequencing was performed using a custom TWIST NGS panel that included *PDGFRB*. The Illumina DRAGEN Bio-IT Platform (v4.0.3) was used for quality control and variant calling
- PDGFRβ protein expression in plasma was quantified using a custom Olink® Focus 21 assay
- A pre-specified statistical analysis plan was finalized prior to study completion
- Within-genotype treatment effect of seralutinib vs placebo on 6MWD and NT-proBNP was assessed with Aligned-Rank Stratified Wilcoxon (ARSW): 1. residualize endpoint: Δ6MWD ~ 6MWD_{baseline} + strata*; 2. Wilcoxon rank-sum on aligned residuals → Hodges–Lehmann location shift (seralutinib – placebo) with 95% CI
- All p-values are nominal and unadjusted for multiplicity

*Randomization strata include WHO functional class, CTD-APAH, and use of parenteral prostacyclin or sotatercept.

RESULTS

Characteristic	Overall (N=306)	CC n=52	CG n=148	GG n=106
Female, n (%)	262 (85.6)	42 (80.8)	125 (84.5)	95 (89.6)
Age, years	49.8 (13.88)	53.2 (14.01)	49.6 (13.39)	48.5 (14.33)
PAH etiology, n (%)				
Idiopathic	193 (63.1)	33 (63.5)	95 (64.2)	65 (61.3)
Heritable	32 (10.5)	6 (11.5)	13 (8.8)	13 (12.3)
CTD-APAH	61 (19.9)	9 (17.3)	29 (19.6)	23 (21.7)
Other	20 (6.6)	4 (7.7)	11 (7.4)	5 (4.7)
Prostacyclin use, n (%)	184 (60.1)	34 (65.4)	97 (65.5)	53 (50)
≥3 Background therapies, n (%)	163 (53.3)	28 (53.8)	87 (58.8)	48 (45.3)
WHO FC, n (%)				
II	76 (24.8)	12 (23.1)	40 (27)	24 (22.6)
III	230 (75.2)	40 (76.9)	108 (73)	82 (77.4)
REVEAL Lite 2 ≥6, n (%)	170 (55.6)	27 (51.9)	86 (58.1)	57 (53.8)
PVR at screening, dyne·s/cm ⁵	813.6 (406.15)	740.8 (331.4)	828.9 (444.19)	828 (382.66)
6MWD, m	375.7 (71.52)	354.2 (80.26)	380.9 (64.73)	378.8 (74.75)
NT-proBNP, ng/L	990 (1562.24)	716 (999.78)	1039.5 (1578.38)	1055.3 (1752.45)

Table 1. Baseline characteristics of the PROSERA genetic analysis population stratified by rs2304058 genotype. Data shown as mean (SD) or n (%). 6MWD, six-minute walk distance; CTD-APAH, connective tissue disease–associated PAH; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SD, standard deviation; WHO FC, World Health Organization Functional Class.

RESULTS (continued)

Baseline circulating PDGFRβ protein showed an allele-dose expression gradient

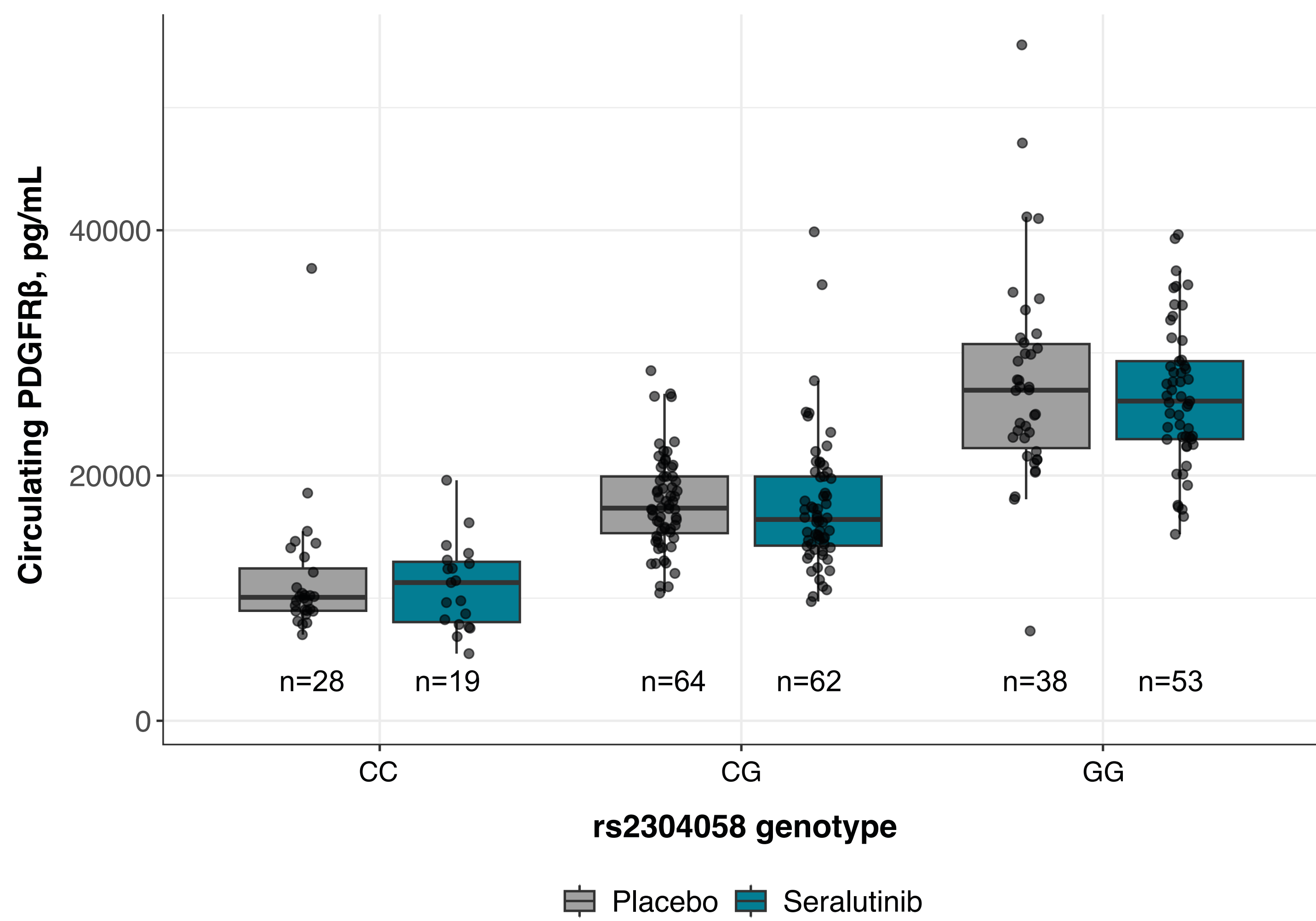


Figure 1. Circulating PDGFRβ increases with rs2304058 G-allele dose. Baseline circulating PDGFRβ (pg/mL) by rs2304058 genotype (CC/CG/GG) and treatment arm in the PROSERA genetic analysis population, confirming rs2304058 as a *cis*-pQTL for PDGFRβ. pQTL, protein quantitative trait locus.

6MWD and NT-proBNP treatment effects increased with rs2304058-G allele dosage

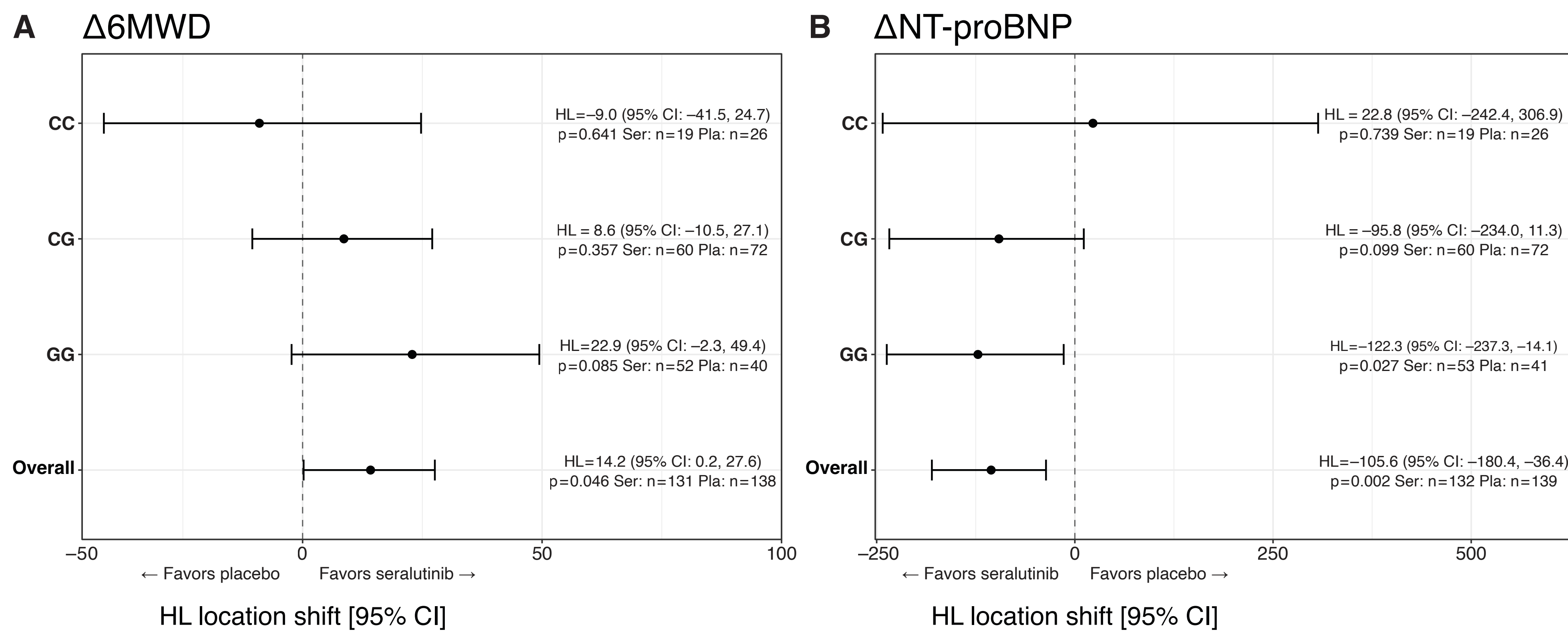


Figure 2. Week 24 treatment effects on 6MWD and NT-proBNP by *PDGFRB* rs2304058 genotype. Forest plots showing Hodges-Lehmann (HL) location shift estimates (seralutinib – placebo) with 95% confidence intervals (CI) for change from baseline at week 24 in 6MWD, m (A) and NT-proBNP, ng/L (B), stratified by rs2304058 genotype (CC, CG, GG) and overall. A directional allele-dose gradient was observed for both endpoints, with the largest treatment effect in GG homozygotes. 6MWD, six-minute walk distance; Pla, placebo; Ser, seralutinib.

Allele-dose 6MWD efficacy gradient in prespecified subgroups

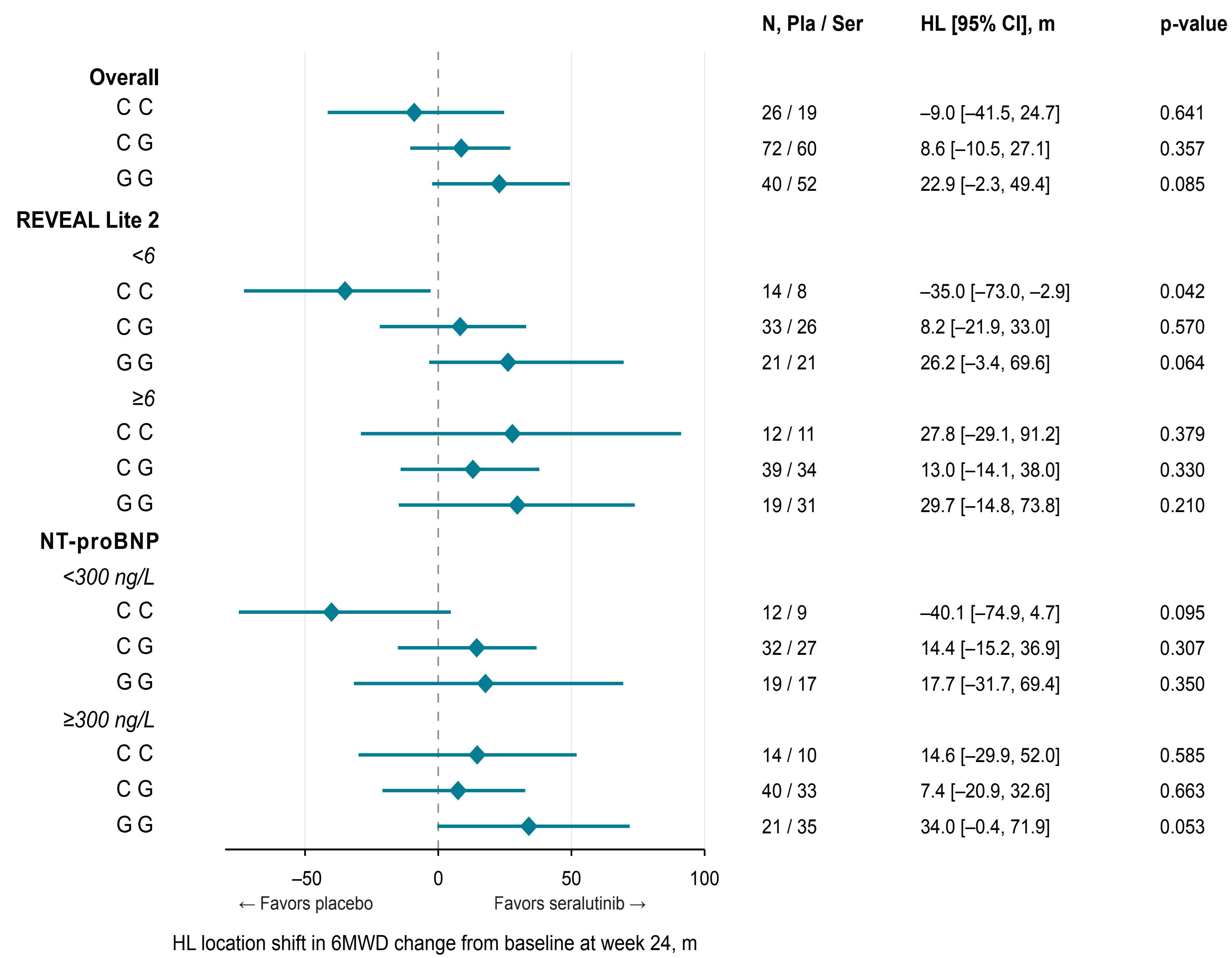


Figure 3. Week 24 6MWD treatment effect by *PDGFRB* rs2304058 genotype and prespecified disease severity subgroups defined by baseline characteristics. Hodges-Lehmann (HL) location shift estimates (seralutinib – placebo) with 95% CI from ARSW models stratified by rs2304058 genotype (CC/CG/GG), overall, and within prespecified subgroups. Median REVEAL Lite 2 in PROSERA intent-to-treat population = 6. 6MWD, six-minute walk distance; CI, confidence interval; NT-proBNP, N-terminal pro–B-type natriuretic peptide; Pla, placebo; REVLITE2, Registry to Evaluate Early and Long-term PAH Disease Management Lite 2; Ser, seralutinib.

DISCUSSION

- In this pharmacogenetic analysis of a *PDGFRB* pQTL in a PDGFR-targeted therapy trial in PAH, a compelling allele-dose efficacy gradient was observed linking rs2304058 and circulating PDGFRβ to clinical response
- A directional G-allele–dose gradient favoring seralutinib was observed in lower disease severity subgroups, with the largest effects in GG homozygotes
- Genetic subgroups may be underpowered to detect a treatment effect
- Concordance from genotype to protein to treatment effect supports PDGFRβ engagement and suggests pathway activity can modulate sensitivity to seralutinib
- These exploratory results warrant further prospective evaluation for precision medicine approaches

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