INTERIM RESULTS FROM THE PHASE 1B AND PHASE 2 TORREY OPEN-LABEL EXTENSION STUDY OF SERALUTINIB IN PULMONARY ARTERIAL HYPERTENSION (PAH)

TORREY STUDY

V Simposio Latinoamericano Hipertensión Pulmonar en Niños y Adolescentes
II Simposio Latinoamericano Hipertensión Pulmonar en Adultos

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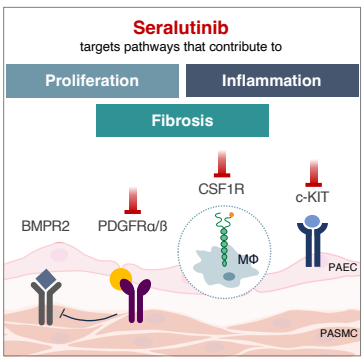
BACKGROUND

- Inhibiting the PDGFR pathway reverses pulmonary vascular remodeling in animal models of PAH[1,2]
- Safety concerns with oral imatinib in the IMPRES PAH trial have led to efforts to develop novel tyrosine kinase inhibitors (TKIs) with an improved benefit-risk profile[3]
- Seralutinib is a distinct next-generation TKI with greater potency and selectivity compared to imatinib, targeting PDGFRα/ß, CSF1R, and c-KIT, thereby acting on inflammatory, proliferative, and fibrotic drivers of pulmonary vascular remodeling (**Figure 1**)[4]
- Seralutinib is the only TKI intentionally developed for PAH as an inhaled treatment
- The phase 2 TORREY study of inhaled seralutinib in patients with WHO Group 1 pulmonary hypertension (NCT04456998) met its primary endpoint by significantly reducing pulmonary vascular resistance (PVR)[5]
- Inhaled seralutinib was well tolerated, avoiding many of the side effects observed with oral imatinib
- Patients who completed TORREY had the option to enroll in an open-label extension (OLE) study (NCT04816604); interim results as of March 4, 2024, are presented

Figure 1. Seralutinib mechanism of action.

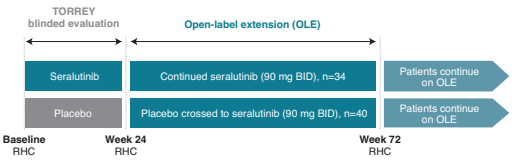


Blunt arrows indicate inhibition. BMPR2, bone morphogenetic protein receptor type 2; c-KIT, mast/stem cell growth factor receptor kit; CSF1R, colony stimulating factor 1 receptor; MΦ, macrophage; PAEC, pulmonary artery endothelial cell; PASMC, pulmonary artery smooth muscle cell; PDGFR, platelet-derived growth factor receptor.

METHODS

- 73 (of 80) patients from TORREY and 1 (of 8) patients from a phase 1B study (NCT03926793) were enrolled
- All patients received inhaled seralutinib 90 mg twice daily by dry powder inhaler
- The aim of the study was to evaluate
  - Long-term safety and tolerability
  - Efficacy parameters, including hemodynamics at Week 72
- PVR was measured by right heart catheterization (RHC) at Week 72 (**Figure 2**)
- All analyses are descriptive

Figure 2. Study schema.



RESULTS

- At OLE entry, 34 patients continued on seralutinib (continued-seralutinib group) and 40 switched from placebo to seralutinib (placebo-crossed group)

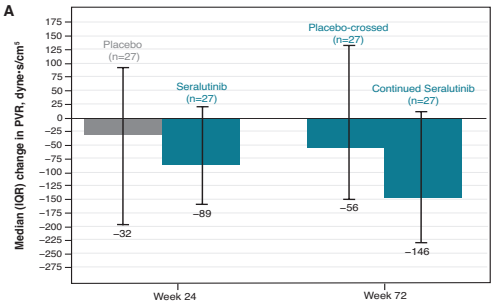
Table 1. Baseline disease characteristics at start of OLE. Data presented as mean (SD) unless otherwise noted.

Characteristic	Placebo crossed (n=40)	Continued seralutinib (n=34)	Total (N=74)
Age at PAH diagnosis, y	41.4 (11.85)	42.8 (15.67)	42.0 (13.66)
Years since PAH diagnosis	9.54 (7.336)	7.30 (6.412)	8.51 (6.972)
PAH classification, n (%)			
Idiopathic/Heritable	22 (55.0)/5 (12.5)	17 (50.0)/10 (29.4)	39 (52.7)/15 (20.3)
CTD / D and T, repaired CHD	9 (22.5)/4 (10.0)	2 (5.9)/5 (14.7)	11 (14.9)/9 (12.2)
Background PAH treatment, n (%)			
Double/triple therapy	16 (40.0)/22 (55.0)	13 (38.2)/20 (58.8)	29 (39.2)/42 (56.8)
Parenteral prostacyclins/PRA	19 (47.5)	15 (44.1)	34 (45.9)
WHO Functional Class, n (%)			
II	17 (42.5)	25 (73.5)	42 (56.8)
III	17 (42.5)	6 (17.6)	23 (31.1)
IV	3 (7.5)	0	3 (4.1)
REVEAL 2.0 risk score ≥ 6, n (%)	21 (52.5)	14 (41.2)	35 (47.3)
PVR, dyne·s/cm^5	669.3 (257.71)	611.7 (279.75)	643.7 (267.36)
6MWD, m	408.7 (115.16)	422.3 (91.56)	415.0 (104.51)
NT-proBNP, ng/L	888.8 (1652.61)	464.1 (542.47)	691.4 (1274.22)

6MWD, six-minute walk distance; CHD, congenital heart disease; CTD, connective tissue disease; D and T, drugs and toxins; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open-label extension; PAH, pulmonary arterial hypertension; PRA, prostacyclin receptor agonist; PVR, pulmonary vascular resistance; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SD, standard deviation; WHO, World Health Organization.

Figure 3. PVR continues to improve in patients receiving seralutinib at OLE entry.
A. Median (IQR) change in PVR. **B.** Median PVR values (dyne·s/cm^5).

A



B

Visit	Placebo/ Placebo crossed	Seralutinib/ Continued seralutinib
Baseline	650.0	620.0
Week 24	647.0	505.0
Week 72	603.0	475.0

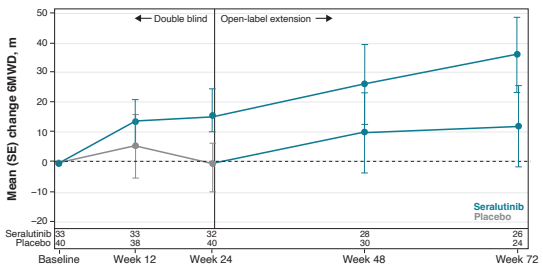
IQR, interquartile range; OLE, open-label extension; PVR, pulmonary vascular resistance.

Table 2. Favorable cardiopulmonary hemodynamics for OLE patients who had RHC at Week 24 and Week 72.

Median (IQR) Placebo, n=27 Seralutinib, n=27	Placebo		Placebo crossed	Seralutinib		Continued seralutinib
	BL	Δ BL to W24	Δ BL to W72	BL	Δ BL to W24	Δ BL to W72
mPAP, mmHg	48.0 (44, 56)	0.0 (−6, 5)	−1.0 (−9, 5)	51.0 (42, 56)	−3.0 (−6, 0)	−4.0 (−8, 3)
CI, L/min/m^2	2.5 (2.1, 2.9)	0.0 (−0.3, 0.5)	0.0 (−0.3, 0.4)	2.6 (2.4, 3.0)	0.1 (−0.2, 0.4)	0.05 (−0.1, 0.6)
SVI, mL/m^2	36.36 (32.00, 42.59)	−2.33 (−6.55, 2.56)	0.25 (−4.73, 6.97)	37.93 (32.93, 43.06)	−0.35 (−4.43, 4.83)	0.81 (−4.64, 8.46)
mRAP, mmHg	8.0 (7, 10)	1.0 (−3, 3)	0.0 (−3, 3)	8.0 (6, 11)	−1.0 (−2, 2)	−1.0 (−4, 1)

BL, Baseline; CI, cardiac index; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; OLE, open-label extension; RHC, right heart catheterization; SVI, stroke volume index; W, Week.

Figure 4. 6MWD increases in the OLE in the continued-seralutinib group and in the placebo-crossed group.



6MWD, six-minute walk distance; OLE, open-label extension; SE, standard error.

- No new safety signals associated with TKIs
- Seralutinib was generally well tolerated during the OLE treatment period
- Similar frequency of ≥ 3x hepatic enzyme elevation in the OLE (5 of 74 patients, 6.8%) and in TORREY (3 of 44 patients, 6.8%) with seralutinib

Table 3. Incidence of treatment-emergent adverse events (TEAEs) by preferred term ≥10%.

	Total (N=74)
Patients with a TEAE, n (%)	71 (95.9)
Headache	19 (25.7)
Cough	18 (24.3)
COVID-19	17 (23.0)
Diarrhoea	15 (20.3)
Dyspnoea	13 (17.6)
Nausea	13 (17.6)
Nasopharyngitis	10 (13.5)
Arthralgia	9 (12.2)
Fatigue	8 (10.8)
Pyrexia	8 (10.8)
Rash	8 (10.8)

CONCLUSIONS

- The open-label extension data demonstrate a promising long-term efficacy profile up to 72 weeks, with continued improvement in PVR and exercise capacity
- Seralutinib was safe and well tolerated, with no new safety signals over the OLE treatment period to date (up to 2.4 years of exposure)
- These data support inhaled seralutinib as a novel anti-proliferative therapy in clinical development for PAH
- The phase 3 PROSERA study of seralutinib in patients with PAH is now enrolling (NCT05934526)

References: 1 Schermuly RT, et al. *J Clin Invest* 2005; 115(10):2811-21. **2** Antoniu SA. *Expert Opin Ther Targets* 2012; 16(11):1055-63. **3** Hoeper MM, et al. *Circulation* 2013; 127(10):1128-38. **4** Galkin A, et al. *Eur Respir J* 2022; 60(6):210235. **5** Frantz RP, et al. *Lancet Respir Med.* 2024;12(7):523-534.

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