SUPPLEMENTAL MATERIAL:

(1) Supplemental Table 1: Clinical event definitions by study

Study name:	Clinical event definition:
AIR	- Death - Lung or heart transplantation - Hospitalization for PAH - Refractory systolic arterial hypotension - Worsening right heart failure - Rapidly progressive cardiogenic, hepatic or renal failure - Addition of new PAH medication - A decline in measure of hemodynamic function
ARIES-I	- Death - Lung transplantation - Hospitalization for PAH - Atrial septostomy - Addition of other PAH therapeutic agents - An increase of 1 or more WHO functional class - Worsening right ventricular failure - Rapidly progressing cardiogenic, hepatic, or renal failure - Refractory systolic hypotension
ARIES-II	- Death - Lung transplantation - Hospitalization for PAH - Atrial septostomy - Addition of other PAH therapeutic agents - An increase of 1 or more WHO functional class - Worsening right ventricular failure - Rapidly progressing cardiogenic, hepatic, or renal failure - Refractory systolic hypotension
BREATHE-1	- Death - Lung transplantation - Hospitalization for worsening PAH - Atrial septostomy - Lack of clinical improvement leading to discontinuation - Need for epoprostenol therapy
PHIRST	- Death - Lung transplantation - Atrial septostomy - Hospitalization due to worsening PAH - Initiation of new PAH therapy - Worsening WHO functional class
STRIDE-I	- Death - Epoprostenol use - Atrial septostomy - Need for lung transplantation
STRIDE-II	- Death - Hospitalization for worsening PAH

	- Atrial septostomy - Need for heart/lung or lung transplantation - Addition of any new type of chronic PAH treatment due to worsening PAH
STRIDE-IV	- Death - Hospitalization for worsening PAH - Need for heart/lung or lung transplantation - Atrial septostomy - Addition of any new type of chronic PAH treatment due to worsening PAH
SUPER	- Death - Hospitalization due to worsening PAH - Lung transplantation - Addition of additional medication due to worsening PAH
Treprostinil	- Death - Lung transplantation - Clinical deterioration

(2) Results of sensitivity analysis removing NYHA class IV patients.

Our data included 127 (5%) patients who were NYHA class IV. These patients accounted for 25 (13%) of the clinical events. Removing the NYHA class IV patients does not appreciably change any of the results (Supplemental Table 1). The proportion of the effect of treatment on the odds of developing a clinical event at 12 weeks that was explained by Δ6MWD was 20.4% (95% CI: 9.8% to 30.3%) after removing these patients, rather than 22.1% among the full cohort. Additionally, we found a threshold effect value of 49.3 m, slightly larger than the threshold effect of 41.8 m found among the full cohort.

Supplemental Table 2: Criteria to establish Δ6MWD as a mediator, data excludes NYHA class IV patients

Criteria to establish Δ6MWD as a mediator in the relationship between treatment assignment and development of a clinical event at 12-weeks follow-up	Results
Treatment assignment has a significant effect on Δ6MWD from baseline to 12-weeks follow-up	Mean difference: 22.5 (95% CI: 15.9, 29.1)
Δ6MWD has a significant effect on the odds of developing a clinical event	Odds ratio: 0.89 per 10 m (95% CI: 0.87, 0.91)
Treatment assignment has a significant effect on the odds of developing a clinical event as 12-weeks follow-up	Odds ratio: 0.39 (95% CI: 0.28, 0.55)
The effect of treatment assignment on the odds of developing a clinical event (compare with above) is attenuated with the addition of Δ6MWD to the model	Odds ratio: 0.48 (95% CI: 0.33, 0.68)

(3) Results of sensitivity analysis removing patients participating in the PHIRST trial.

Removing the PHIRST patients from the mediation analysis did not change the results reported in the manuscript (Supplemental Table 2). The proportion of the effect of treatment on the odds of developing a clinical event at 12 weeks that was explained by Δ6MWD was 24.6% (95% CI: 12.1% to 37.1%), compared with 22.1%.

Supplemental Table 3: Criteria to establish Δ6MWD as a mediator, data excludes PHIRST trial

Criteria to establish Δ6MWD as a mediator in the relationship between treatment assignment and development of a clinical event at 12-weeks follow-up	Results
Treatment assignment has a significant effect on Δ6MWD from baseline to 12-weeks follow-up	Mean difference: 23.3 (95% CI: 16.0, 30.7)
Δ6MWD has a significant effect on the odds of developing a clinical event	Odds ratio: 0.88 per 10 m (95% CI: 0.86, 0.90)
Treatment assignment has a significant effect on the odds of developing a clinical event at 12-weeks follow-up	Odds ratio: 0.43 (95% CI: 0.31, 0.62)
The effect of treatment assignment on the odds of developing a clinical event (compare with above) is attenuated with the addition of Δ6MWD to the model	Odds ratio: 0.53 (95% CI: 0.36, 0.78)

As reported in the manuscript, excluding this study resulted in a smaller threshold value of 25.7 meters.