Supplemental Material

Are Hemodynamics Surrogate Endpoints in Pulmonary Arterial Hypertension?

Supplemental Table 1. Criteria to establish the change in a hemodynamic measure (ΔHD) as a mediator in the relationship between treatment assignment and clinical events at 12 weeks in the subgroup of patients with idiopathic pulmonary arterial hypertension.

	Hemodynamic measure					
	ΔRAP	**ΔmPAP**	**ΔCO**	**ΔCI**	**ΔPVR**	**ΔPA Compliance**
1. Treatment assignment has a significant effect on ΔHD	Mean difference (95% CI) between treatment and placebo -1.9 mm Hg (-2.8, -1.1) p < 0.001	Mean difference (95% CI) between treatment and placebo -2.5 mm Hg (-4.0, -1.1) p < 0.001	Mean difference (95% CI) between treatment and placebo 0.40 L/min (0.21, 0.58) p < 0.001	Mean difference (95% CI) between treatment and placebo 0.22 L/min/m^2 (0.12, 0.32) p < 0.001	Mean difference (95% CI) between treatment and placebo -2.3 Wood units (-3.1, -1.4) p < 0.001	Mean difference (95% CI) between treatment and placebo 0.21 mL/mm Hg (0.12, 0.30) p < 0.001
2. ΔHD has a significant effect on the odds of a clinical event	OR (95% CI) per 1 mm Hg increase 1.08 (1.02, 1.16) p = 0.011	OR (95% CI) per 1 mm Hg increase 1.01 (0.97, 1.06) p = 0.494	OR (95% CI) per 1 L/min increase 0.66 (0.45, 0.98) p = 0.033	OR (95% CI) per 1 L/min/m^2 unit increase 0.46 (0.23, 0.95) p = 0.031	OR (95% CI) per 1 Wood unit increase 1.04 (0.98, 1.10) p = 0.186	OR (95% CI) per 1 mL/mmHg increase 0.63 (0.29, 1.36) p = 0.240
3. Treatment assignment has a significant effect on the odds of a clinical event	OR (95% CI) for treatment vs. placebo 0.40 (0.22, 0.72) p = 0.002	OR (95% CI) for treatment vs. placebo 0.41 (0.23, 0.74) p = 0.003	OR (95% CI) for treatment vs. placebo 0.43 (0.24, 0.76) p = 0.004	OR (95% CI) for treatment vs. placebo 0.43 (0.24, 0.76) p = 0.004	OR (95% CI) for treatment vs. placebo 0.45 (0.25, 0.82) p = 0.009	OR (95% CI) for treatment vs. placebo 0.43 (0.24, 0.77) p = 0.004
4. The effect of treatment assignment on the odds of a clinical event is attenuated with the addition of ΔHD to the model (compare with #3 above)	OR (95% CI) for treatment vs. placebo 0.45 (0.25, 0.81) p = 0.008	OR (95% CI) for treatment vs. placebo 0.42 (0.24, 0.75) p = 0.004	OR (95% CI) for treatment vs. placebo 0.48 (0.26, 0.87) p = 0.016	OR (95% CI) for treatment vs. placebo 0.48 (0.26, 0.88) p = 0.016	OR (95% CI) for treatment vs. placebo 0.48 (0.26, 0.88) p = 0.018	OR (95% CI) for treatment vs. placebo 0.45 (0.25, 0.81) p = 0.008
% variability explained by ΔHD (95% CI)	12.2 (0.8, 38.1)	1.8 (-9.3, 16.2)	13.9 (1.4, 42.9)	14.1 (1.5, 42.2)	7.1 (-10.3, 45.0)	4.9 (-14.5, 24.7)

All models include adjustment for baseline hemodynamic value and study. ΔRAP=change in right atrial pressure; ΔmPAP=change in mean pulmonary artery pressure; ΔCO=change in cardiac output; ΔCI=change in cardiac index; ΔPVR=change in pulmonary vascular resistance; ΔPA compliance=change in pulmonary artery compliance; ΔHD=change in hemodynamic measure at 12 weeks as compared to baseline; OR=odds ratio; CI=confidence interval.

Supplemental Table 2. Criteria to establish the change in a hemodynamic measure (ΔHD) as a mediator in the relationship between treatment assignment and clinical events at 12 weeks; in AIR study patients hemodynamics 60 minutes post-iloprost inhalation were used to calculate the change values.

	Hemodynamic measure					
	ΔRAP	**ΔmPAP**	**ΔCO**	**ΔCI**	**ΔPVR**	**ΔPA Compliance**
1. Treatment assignment has a significant effect on ΔHD	Mean difference (95% CI) between treatment and placebo -1.2 mm Hg (-1.8, -0.61) p = 0.020	Mean difference (95% CI) between treatment and placebo -2.3 mm Hg (-3.3, -1.2) p = 0.019	Mean difference (95% CI) between treatment and placebo 0.37 L/min (0.24, 0.50) p < 0.001	Mean difference (95% CI) between treatment and placebo 0.22 L/min/m^2 (0.15, 0.29) p < 0.001	Mean difference (95% CI) between treatment and placebo-2.1 Wood units (-2.7, -1.5) p < 0.001	Mean difference (95% CI) between treatment and placebo 0.14 mL/mm Hg (0.08, 0.21) p < 0.001
2. ΔHD has a significant effect on the odds of a clinical event	OR (95% CI) per 1 mm Hg increase 1.04 (0.99, 1.09) p = 0.107	OR (95% CI) per 1 mm Hg increase 1.01 (0.98, 1.04) p = 0.381	OR (95% CI) per 1 L/min increase 0.69 (0.52, 0.92) p = 0.010	OR (95% CI) per 1 L/min/m^2 unit increase 0.53 (0.32, 0.87) p = 0.012	OR (95% CI) per 1 Wood unit increase 1.08 (1.03, 1.13) p = 0.002	OR (95% CI) per 1 mL/mmHg increase 0.68 (0.22, 2.13) p = 0.450
3. Treatment assignment has a significant effect on the odds of a clinical event	OR (95% CI) for treatment vs. placebo 0.43 (0.28, 0.66) p < 0.001	OR (95% CI) for treatment vs. placebo 0.48 (0.31, 0.72) p < 0.001	OR (95% CI) for treatment vs. placebo 0.48 (0.32, 0.74) p < 0.001	OR (95% CI) for treatment vs. placebo 0.49 (0.32, 0.74) p < 0.001	OR (95% CI) for treatment vs. placebo 0.47 (0.30, 0.72) p < 0.001	OR (95% CI) for treatment vs. placebo 0.48 (0.31, 0.73) p < 0.001
4. The effect of treatment assignment on the odds of a clinical event is attenuated with the addition of ΔHD to the model (compare with #3 above)	OR (95% CI) for treatment vs. placebo 0.44 (0.29, 0.68) p = 0.003	OR (95% CI) for treatment vs. placebo 0.48 (0.32, 0.73) p < 0.001	OR (95% CI) for treatment vs. placebo 0.53 (0.34, 0.81) p = 0.003	OR (95% CI) for treatment vs. placebo 0.53 (0.34, 0.82) p = 0.004	OR (95% CI) for treatment vs. placebo 0.53 (0.33, 0.82) p = 0.005	OR (95% CI) for treatment vs. placebo 0.49 (0.32, 0.76) p = 0.001
% variability explained by ΔHD (95% CI)	3.8 (-2.1, 12.5)	1.8 (-3.6, 11.5)	11.9 (2.8, 38.0)	12.2 (2.5, 39.6)	15.9 (4.0, 51.6)	3.4 (-5.3, 15.8)

All models include adjustment for baseline hemodynamic value and study. ΔRAP=change in right atrial pressure; ΔmPAP=change in mean pulmonary artery pressure; ΔCO=change in cardiac output; ΔCI=change in cardiac index; ΔPVR=change in pulmonary vascular resistance; ΔPA compliance=change in pulmonary artery compliance; ΔHD=change in hemodynamic measure at 12 weeks as compared to baseline; OR=odds ratio; CI=confidence interval.