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**Supplementary File**

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## **Safety and Efficacy of Ambrisentan–Phosphodiesterase Type 5 (PDE5) Inhibitor Combination Therapy for Japanese Pulmonary Arterial Hypertension Patients in Real-World Clinical Practice**

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Supplementary Table 1. Safety information by presence/absence of CTD-PAH

	All patients	CTD-PAH	non-CTD-PAH
Number of patients included	48	8	40
Number of patients with onset of ADRs (%)	10 (20.8)	2 (25.0)	8 (20.0)
Number of ADRs	14	3	11
Number of events by types of ADRs (%)			
Headache	4 (8.3)	0	4 (10.0)
Face oedema	2 (4.2)	0	2 (5.0)
Angina pectoris	1 (2.1)	0	1 (2.0)
Hyperaemia	1 (2.1)	1 (12.50)	0
Dyspnoea	1 (2.1)	0	1 (2.0)
Pulmonary hypertension	1 (2.1)	0	1 (2.0)
Nausea	1 (2.1)	0	1 (2.0)
Hepatic function abnormal	1 (2.1)	0	1 (2.0)
Oedema	1 (2.1)	1 (12.50)	0
Sudden death	1 (2.1)	1 (12.50)	0

Supplementary Table 2. Changes in functional parameters from baseline to post-treatment

(A) Presence or absence of CTD-PAH

			CTD-PAH			Non-CTD-PAH		
			n	Mean±SD	Means of variation	n	Mean±SD	Means of variation
Pulmonary function	FVC (%)	At baseline	4	77.9±26.6	-	10	84.5±17.5	-
		Post-treatment	4	83.7±20.2	5.8 (-5.4,17.0)	10	89.70±12.4	5.2 (-2.3, 12.7)
		Test	w: P=0.2500			w: P=0.3105		
	TLC (%)	At baseline	3	84.4±41.4	-	7	87.1±10.4	-
		Post-treatment	3	92.1±30.7	7.7 (-20.3, 35.8)	7	83.6±14.3	-3.5 (-15.4, 8.4)
		Test	w: P=0.5000			w: P=0.4688		
	FEV <sub>1</sub> (%)	At baseline	5	78.5±23.9	-	11	82.8±15.5	-
		Post-treatment	5	84.1±18.4	5.6 (-1.8, 13.0)	11	82.2±10.6	-0.6 (-9.0, 7.7)
		Test	w: P=0.1875			w: P=0.5771		
	SpO <sub>2</sub> (%)	At baseline	2	98.5±0.7	-	6	82.8±16.5	-
		Post-treatment	2	96.0±0.0	-2.5 (-8.9, 3.9)	6	88.8±11.7	6.0 (-5.5, 17.5)
		Test	w: P=0.5000			w: P=0.4688		
	SaO <sub>2</sub> (%)	At baseline	1	93.8	-	6	95.6±2.1	-
		Post-treatment	1	95.5	1.7	6	95.8±1.0	0.3 (-2.28, 2.78)
		Test	w: P=1.0000			w: P=1.0000		
	DLco (mL/min/mmHg)	At baseline	4	25.3±12.0	-	8	42.7±19.6	-
		Post-treatment	4	24.0±13.1	-1.3 (-7.8,5.3)	8	57.6±26.9	14.9 (-11.1, 40.9)

		Test	w: P=0.6250			w: P=0.0156		
Hemodynamics	RAP (mmHg)	At baseline	2	9.0±2.8	-	15	7.9±4.9	-
		Post-treatment	2	3.5±0.7	-5.5 (-37.3,26.3)	15	5.6±2.2	-2.3 (-5.6, 1.0)
		Test	w: P=0.5000			w: P=0.2800		
	PAWP (mmHg)	At baseline	2	4.5±2.1	-	16	8.6±2.6	-
		Post-treatment	2	7.0±0.0	2.5 (-16.6, 21.6)	16	9.5±2.8	0.9 (-1.4, 3.2)
		Test	w: P=0.5000			w: P=0.4461		
	mPAP (mmHg)	At baseline	2	47.5±9.2	-	18	44.6±14.8	-
		Post-treatment	2	26.5±6.4	-21 (-46.4, 4.4)	18	31.9±8.8	-12.7 (-19, -6.3)
		Test	w: P=0.5000			w: P=0.0005		
	CO (L/min)	At baseline	2	2.8±1.8	-	16	4.2±2.2	-
		Post-treatment	2	5.2±2.2	2.4 (-1.7, 6.5)	16	5.3±1.7	1.1 (-0.8, 3.0)
		Test	w: P=0.5000			w: P=0.0833		
	PVR (dyn·sec·cm <sup>-5</sup> )	At baseline	2	1595.4±1205.4	-	17	873.2±627.3	-
		Post-treatment	2	351.8±259.0	-1243.6 (-9827.9, 7340.7)	17	389.7±254.8	-483.5 (-841.4, -125.7)
		Test	w: P=0.5000			w: P=0.0110		
Saturation (%)	At baseline	2	76.4±30.6	-	6	96.0±2.3	-	
	Post-treatment	2	96.8±1.8	20.4 (-238.8, 279.6)	6	94.9±1.5	-1.1 (-4.2, 1.9)	
	Test	w: P=1.0000			w: P=0.5625			
CI (L/min/m <sup>2</sup> )	At baseline	2	2.0±1.1	-	18	2.6±1.0	-	
	Post-treatment	2	3.6±1.4	1.7 (-1.2, 4.6)	18	4.0±3.7	1.8 (-0.2, 3.9)	
	Test	w: P=0.5000			w: P=0.0074			

	SvO <sub>2</sub> (%)	At baseline	1	69.7	-	12	67.8±14.3	-	
Post-treatment		1	70.2	0.5	12	74.9±6.4	7.1 (-3.7, 17.8)		
Test		w: P=1.0000				w: P=0.2334			
Echocardiography	TRPG (mmHg)	At baseline	5	59.2±31.9	-	17	63.3±23.8	-	
		Post-treatment	5	33.8±9.9	-25.4 (-56.5, 5.7)	17	50.8±23.5	-12.5 (-21.6, -3.3)	
		Test	w: P=0.0625				w: P=0.0104		
Clinical status	6MWD (m)	At baseline	1	250.0	-	4	343.3±210.6	-	
		Post-treatment	1	415.0	165	4	439.8±121.2	96.5 (-104.2, 297.2)	
		Test	w: P=1.0000				w: P=0.1250		
	BNP (pg/mL)	At baseline	5	497.7±456.2	-	11	288.5±272.1	-	
		Post-treatment	5	216.9±250.5	-280.7 (-703.0, 141.6)	11	112.6±155.0	-175.9 (-350.3, -1.4)	
Test	w: P=0.3125				w: P=0.0674				

Data are presented as mean ± standard deviation (SD), 95% CI, 95% confidence interval; FVC, forced vital capacity; TLC, total lung capacity; FEV1, forced expiratory volume in one second; SaO<sub>2</sub>, blood oxygen saturation; SpO<sub>2</sub>, percutaneous oxygen saturation; DLco, diffusing capacity for carbon monoxide; RAP, right arterial pressure; PAWP, mean pulmonary arterial wedge pressure; mPAP, mean pulmonary arterial pressure; CO, cardiac output; PVR, pulmonary vascular resistance; CI, cardiac index; SvO<sub>2</sub>, mixed venous oxygen saturation; TRPG, transtricuspid pressure gradient; 6MWD six-minute walk distance; BNP, brain natriuretic peptide.

W: paired Wilcoxon test

(B) Type of combination therapy

			Initial combination			Sequential combination		
			n	Mean±SD	Means of variation	n	Mean±SD	Means of variation
Pulmonary function	FVC (%)	At baseline	11	83.4±21.9	-	3	80.0±9.5	-
		Post-treatment	11	88.7±15.9	5.3 (-1.8, 12.4)	3	85.5±8.7	5.5 (3.5, 7.5)
		Test	w: P=0.3096			w: P=0.2500		
	TLC (%)	At baseline	7	79.2±17.6	-	3	102.8±23.2	-
		Post-treatment	7	81.8±14.1	2.6(-10.2, 15.5)	3	96.3±28.4	-6.5 (-29.7, 16.6)
		Test	w: P=0.8125			w: P=0.5000		
	FEV <sub>1</sub> (%)	At baseline	11	80.0±19.6	-	5	85.0±14.4	-
		Post-treatment	11	82.3±15.5	2.4 (-4.8, 9.7)	5	83.9±4.0	-1.1 (-16.4, 14.1)
		Test	w: P=0.8311			w: P=1.0000		
	SpO <sub>2</sub> (%)	At baseline	7	85.0±16.1	-	1	99.0	-
		Post-treatment	7	89.7±10.9	4.7 (-5.1, 14.5)	1	97.0	-2
		Test	w: P=0.7344			-		
	SaO <sub>2</sub> (%)	At baseline	6	95.2±2.2	-	1	96.3	-
		Post-treatment	6	95.8±1.1	0.58(-2, 3.2)	1	96.0	-0.3
		Test	w: P=0.6875			-		
	DLco (mL/min/ mmHg)	At baseline	9	38.7±19.2	-	3	31.3±20.9	-
		Post-treatment	9	41.9±22.2	3.2 (-2.0, 8.4)	3	59.6±44.2	28.36 (-104.3, 161.1)
		Test	w: P=0.0977			w: P=1.0000		

Hemodynamics	RAP (mmHg)	At baseline	13	8.8±4.9	-	4	5.5±3.0	-
		Post-treatment	13	4.9±1.9	-3.9 (-7.5, -0.3)	4	6.8±2.9	1.25 (-3.3, 5.8)
		Test	w: P=0.0508			w: P=0.6250		
	PAWP (mmHg)	At baseline	13	7.9±2.6	-	5	9.0±3.5	-
		Post-treatment	13	8.8±2.9	0.9 (-25.0, -13.0)	5	10.4±2.4	1.4 (-4.0, 6.8)
		Test	w: P=0.4629			w: P=0.5000		
	mPAP (mmHg)	At baseline	14	49.3±14.3	-	6	34.7±7.5	-
		Post-treatment	14	30.3±8.9	-19 (-25.0, -13.0)	6	34.0±7.7	-0.7 (-4.9, 3.5)
		Test	w: P=0.0002			w: P=0.8125		
	CO (L/min)	At baseline	14	3.9±2.4	-	4	4.7±0.9	-
Post-treatment		14	5.5±1.6	1.58 (-0.5, 3.7)	4	4.7±2.1	0.0 (-3.6, 3.6)	
Test		w: P=0.0238			w: P=1.0000			
PVR (dyn·sec·cm <sup>-5</sup> )	At baseline	14	1135.3±714.7	-	5	428.1±222.7	-	
	Post-treatment	14	362.3±211.6	-773.0 (-1198.6, -347.3)	5	451.1±351.0	23.0 (-316.4, 362.3)	
	Test	w: P=0.0023			w: P=1.0000			
Saturation (%)	At baseline	7	90.3±15.9	-	1	96.6	-	
	Post-treatment	7	95.7±1.3	5.4 (-9.1, 20.0)	1	92.5	-4.1	
	Test	w: P=0.6875			-			
CI (L/min/m <sup>2</sup> )	At baseline	14	2.3±1.1	-	6	3.0±0.6	-	
	Post-treatment	14	4.9±4.1	2.6 (0.1, 5.2)	6	3.0±0.7	-0.1 (-1.1, 1.0)	
	Test	w: P=0.0005			w: P=0.8438			

	SvO <sub>2</sub> (%)	At baseline	9	65.6±15.6	-	4	73.3±7.3	-
		Post-treatment	9	76.1±5.2	10.5 (-3.2, 24.3)	4	70.8±7.7	-2.4 (-14.6, 9.7)
		Test	w:P=0.0977			w:P=0.6250		
Echocardiography	TRPG (mmHg)	At baseline	12	73.4±27.1	-	10	49.1±14.7	-
		Post-treatment	12	49.0±27.0	-24.4 (-38.0, -10.8)	10	44.5±15.8	-4.6 (-12.3, 3.1)
		Test	w:P=0.0068			w:P=0.1270		
Clinical status	6MWD (m)	At baseline	5	324.6±187.1	-	0	-	-
		Post-treatment	5	434.8±105.6	110.2 (-30.7, 251.1)	0	-	-
		Test	w:P=0.0625			-		
	BNP (pg/mL)	At baseline	10	379.0±281.8	-	6	311.9±445.4	-
		Post-treatment	10	98.5±136.8	-280.6(-497.4,-63.7)	6	223.2±245.7	-88.8 (-303.7, 126.2)
		Test	w:P=0.0137			w:P=1.0000		

Data are presented as mean ± standard deviation (SD), 95% CI, 95% confidence interval; FVC, forced vital capacity; TLC, total lung capacity; FEV1, forced expiratory volume in one second; SaO<sub>2</sub>, blood oxygen saturation; SpO<sub>2</sub>, percutaneous oxygen saturation; DLco, diffusing capacity for carbon monoxide; RAP, right arterial pressure; PAWP, mean pulmonary arterial wedge pressure; mPAP, mean pulmonary arterial pressure; CO, cardiac output; PVR, pulmonary vascular resistance; CI, cardiac index; SvO<sub>2</sub>, mixed venous oxygen saturation; TRPG, transtricuspid pressure gradient; 6MWD, six-minute walk distance; BNP, brain natriuretic peptide.

W: paired Wilcoxon test



(C) Concomitant use of intravenous epoprostenol

		n	Mean±SD	Means of variation	
Hemodynamics	RAP (mmHg)	At baseline	4	7.3±5.4	-
		Post-treatment	4	4.0±1.4	-3.3(-10.9,4.4)
		Test	w: P=0.3750		
	PAWP (mmHg)	At baseline	5	9.6±3.6	-
		Post-treatment	5	8.0±2.3	-1.6(-7.2, 4.0)
		Test	w: P=0.6250		
	mPAP (mmHg)	At baseline	5	41.4±26.6	-
		Post-treatment	5	29.2±10.4	-12.2(-35.6, 11.2)
		Test	w: P=0.4375		
	CO (L/min)	At baseline	4	4.7±1.4	-
		Post-treatment	4	4.9±1.1	0.1 (-3.9, 4.2)
		Test	w: P=0.8750		
	PVR (dyn·sec·cm <sup>-5</sup> )	At baseline	5	530.1±495.6	-
		Post-treatment	5	338.4±167.1	-191.7 (-699.0, 315.6)
		Test	w: P=0.8125		
	Saturation (%)	At baseline	1	92.4	-
		Post-treatment	1	94.9	2.5
		Test		-	
	CI (L/min/m <sup>2</sup> )	At baseline	5	3.0±0.9	-
		Post-treatment	5	3.0±0.4	-0.1 (-1.5, 1.5)

		Test	w: P=0.8125		
	SvO <sub>2</sub> (%)	At baseline	4	72.9±11.1	-
		Post-treatment	4	75.5±1.4	2.7 (-15.5, 20.8)
		Test	w: P=0.8750		
Echocardiography	TRPG (mmHg)	At baseline	6	52.5±34.8	-
		Post-treatment	6	43.5±23.1	-9 (-23.3, 5.3)
		Test	w: P=0.1563		
Clinical status	6MWD (m)	At baseline	1	306.0	-
		Post-treatment	1	325.0	19
		Test	-		
	BNP (pg/mL)	At baseline	3	411.6±219.8	-
		Post-treatment	3	153.1±236.2	-258.5 (-575.1, 58.2)
	Test	w: P=0.2500			

Data are presented as mean ± standard deviation (SD), 95% CI, 95% confidence interval; FVC, forced vital capacity; TLC, total lung capacity; FEV1, forced expiratory volume in one second; SaO<sub>2</sub>, blood oxygen saturation; SpO<sub>2</sub>, percutaneous oxygen saturation; DLco, diffusing capacity for carbon monoxide; RAP, right arterial pressure; PAWP, mean pulmonary arterial wedge pressure; mPAP, mean pulmonary arterial pressure; CO, cardiac output; PVR, pulmonary vascular resistance; CI, cardiac index; SvO<sub>2</sub>, mixed venous oxygen saturation; TRPG, transtricuspid pressure gradient; 6MWD, six-minute walk distance; BNP, brain natriuretic peptide.

W: paired Wilcoxon test