

Sleep and Breathing electronic supplement for:

**Transvenous Phrenic Nerve Stimulation improves central sleep apnea, sleep quality and quality of life regardless of prior positive airway pressure-treatment**

Alan R. Schwartz, MD<sup>a,b</sup>; Lee R. Goldberg, MD, MPH<sup>a</sup>; Scott McKane, MS<sup>c</sup>; Timothy I. Morgenthaler, MD<sup>d</sup>

<sup>a</sup>University of Pennsylvania Perelman School of Medicine; <sup>b</sup>Universidad Peruana Cayetano Heredia (Lima, Peru); <sup>c</sup>Respicardia, Inc., Minnetonka, Minnesota; <sup>d</sup>Mayo Clinic, Rochester, MN

**Correspondence:**

Alan R. Schwartz MD  
Email: aschwar02@gmail.com

**Table 1. Polysomnogram and Clinical Metrics - Prior PAP-treated**

Endpoint	6 Months of Therapy			12 Months of Therapy	
	Baseline (N=53)	Result (N=45)	Change from baseline	Result (N=41)	Change from baseline
Apnea Hypopnea Index (events/hour)	52 [35, 63]	20 [10, 31]	-29 [-40, -11] <.001	16 [10, 32]	-30 [-45, -7] <.001
Central Apnea Index (events/hour)	30 [17, 47]	3 [1, 8]	-25 [-40, -12] <.001	2 [0, 6]	-24 [-48, -15] <.001
Obstructive Apnea Index (events/hour)	2 [0, 4]	3 [1, 5]	1 [-1, 4] 0.017	2 [1, 5]	0 [-1, 3] 0.076
Mixed Apnea Index (events/hour)	1 [0, 5]	0 [0, 1]	-1 [-5, 0] 0.002	0 [0, 1]	-1 [-5, -0] <.001
Hypopnea Index (events/hour)	12 [2, 19]	9 [4, 15]	0 [-9, 3] 0.621	10 [6, 19]	2 [-7, 7] 0.562
4% Oxygen Desaturation Index (events/hour)	45 [33, 61]	16 [8, 32]	-25 [-39, -12] <.001	16 [8, 27]	-26 [-42, -6] <.001
Arousal Index (events/hour)	39 [30, 54]	20 [12, 29]	-17 [-30, -9] <.001	18 [14, 26]	-18 [-32, -8] <.001
Percent of Sleep with O2 Saturation<90% (%)	12 [4, 27]	3 [0, 17]	-3 [-17, 1] 0.003	5 [1, 13]	-5 [-13, -0] <.001
Percent of Sleep in N1 (% of sleep)	33 [19, 42]	21 [13, 29]	-10 [-16, 1] <.001	21 [14, 27]	-7 [-17, 3] 0.023
Percent of Sleep in N2 (% of sleep)	51 [42, 58]	57 [50, 65]	5 [-1, 13] 0.001	58 [48, 65]	4 [-5, 12] 0.116
Percent of Sleep in N3 (% of sleep)	3 [0, 7]	2 [0, 7]	0 [-2, 2] 0.622	2 [0, 7]	0 [-1, 1] 0.784
Percent of Sleep in REM (% of sleep)	10 [5, 16]	15 [10, 21]	3 [-2, 6] 0.052	15 [6, 21]	4 [-5, 8] 0.251
Epworth Sleepiness Scale (points)	12 [7, 16]	7 [4, 11]	-3 [-6, 0] <.001	8 [5, 10]	-3 [-8, 0] <.001
Fatigue Severity Scale	5.2 [3.4, 6.2] (n=53)	4.7 [3.2, 5.4] (n=47)	-0.4 [-1.3, 0.4] P=0.017	4.6 [3.3, 6.0]	-0.2 [-1.4, 0.6] 0.084
Median [Q1,Q3] / Nominal 2-sided p-value from Wilcoxon Signed-Rank test for change from baseline to visit.					

**Table 2. Polysomnogram and Clinical Metrics - PAP-naive**

Endpoint	6 Months of Therapy			12 Months of Therapy	
	Baseline (N=93)	Result (N=81)	Change from baseline	Result (N=78)	Change from baseline
Apnea Hypopnea Index (events/hour)	41 [31, 56]	20 [9, 35]	-18 [-35, -6] <.001	19 [9, 34]	-19 [-33, -6] <.001
Central Apnea Index (events/hour)	21 [12, 36]	1 [0, 5]	-17 [-27, -8] <.001	1 [0, 4]	-17 [-30, -10] <.001
Obstructive Apnea Index (events/hour)	2 [1, 4]	3 [1, 9]	1 [-1, 6] <.001	4 [1, 10]	2 [-1, 6] <.001
Mixed Apnea Index (events/hour)	1 [0, 4]	0 [0, 0]	-1 [-3, 0] <.001	0 [0, 1]	-1 [-3, 0] <.001
Hypopnea Index (events/hour)	12 [4, 20]	7 [2, 17]	-1 [-7, 5] 0.273	8 [4, 17]	-1 [-7, 7] 0.582
4% Oxygen Desaturation Index (events/hour)	35 [24, 51]	20 [7, 33]	-12 [-28, -2] <.001	17 [8, 29]	-15 [-29, -3] <.001
Arousal Index (events/hour)	40 [27, 57]	21 [15, 31]	-14 [-28, -4] <.001	22 [15, 35]	-12 [-33, -4] <.001
Percent of Sleep with O2 Saturation<90% (%)	7 [2, 19]	5 [1, 16]	-2 [-7, 2] 0.026	3 [1, 12]	-3 [-9, 1] <.001
Percent of Sleep in N1 (% of sleep)	35 [21, 49]	27 [18, 38]	-4 [-19, 5] 0.004	28 [19, 40]	-4 [-18, 4] 0.002
Percent of Sleep in N2 (% of sleep)	45 [40, 56]	51 [40, 64]	4 [-6, 16] 0.020	53 [44, 59]	4 [-3, 13] 0.005
Percent of Sleep in N3 (% of sleep)	2 [0, 10]	2 [0, 11]	0 [-3, 2] 0.272	1 [0, 5]	0 [-4, 1] 0.015
Percent of Sleep in REM (% of sleep)	10 [6, 16]	13 [9, 19]	1 [-3, 8] 0.003	13 [8, 21]	3 [-2, 11] <.001
Epworth Sleepiness Scale (points)	8 [5, 13]	6 [3, 9]	-2 [-6, 0] <.001	5 [3, 8]	-3 [-6, 0] <.001
Fatigue Severity Scale	4.4 [3.3, 5.7] (n=93)	3.4 [2.3, 4.8] (n=83)	-0.5 [-1.9, 0.2] P<.001	3.4 [2.4, 5.1]	-0.5 [-1.6, 0.4] 0.003
Median [Q1,Q3] / Nominal 2-sided p-value from Wilcoxon Signed-Rank test for change from baseline to visit.					

**Table 3. Patient Global Assessment**

Endpoint (N=14)	Prior PAP-treated		PAP-naive	
	6 Months	12 Months	6 Months	12 Months
Any improvement in PGA (%) <sup>a</sup>	85% (40/47)	84% (36/43)	72% (60/83)	74% (60/81)

<sup>a</sup> Reported as percent (n/N).

PGA = Patient global assessment

**Table 4. Comparison of Results from 6 Month Randomized Period of Trial**

Variable	Prior PAP-treated			PAP-naive		
	TPNS Change from baseline (n=25)	Control Change from baseline (n=22)	Between group p- value	TPNS Change from baseline (n=36)	Control Change from baseline (n=51)	Between group p- value
Apnea hypopnea index (events/hour)	-27 -40, -12	1 -5, 16	<.001	-20 -37, -8	0 -10, 15	<.001
Central apnea index (events/hour)	-30 -45, -13	1 -10, 11	<.001	-17 -32, -12	-3 -12, 7	<.001
Arousal Index (events/hour)	-17 -28, -7	1 -6, 12	0.002	-20 -33, -8	-4 -20, 2	<.001
Percent of sleep with oxygen saturation<90% (%)	-3 -17, 2	2 -4, 6	0.020	-4 -9, 0	0 -8, 4	0.052
Percent of sleep in rapid eye movement (%)	1 -5, 5	-2 -7, 2	0.263	1 -3, 8	0 -4, 4	0.085
Epworth Sleepiness Scale (points)	-4 -7, 0	1 -1, 2	0.004	-2 -6, 0	0 -3, 3	0.002

Reported as median and interquartile range.

P-value from Mann-Whitney test for difference in change from baseline between groups (2-sided).

TPNS = Transvenous phrenic nerve stimulation