

Long-Term Use of a Nasal Expiratory Positive Airway Pressure (EPAP) Device as a Treatment for Obstructive Sleep Apnea (OSA)

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SCIENTIFIC INVESTIGATIONS

Study Objectives: Evaluate the long-term durability of treatment response and safety of a nasal expiratory positive airway pressure (EPAP) device used to treat obstructive sleep apnea (OSA).

Design: A prospective, multicenter, single-arm, open-label extension to a 3-month EPAP vs sham randomized clinical trial

Setting: 13 sites including both academic and private sleep disorder centers

Patients: OSA patients in the EPAP arm of the EPAP vs sham randomized study who used the EPAP device ≥ 4 h per night, ≥ 5 nights per week on average during months 1 and 2 of the 3-month trial and had $\geq 50\%$ reduction in AHI or AHI reduction to < 10 documented by polysomnography, comparing the 3-month device-on PSG to the week-one device-off PSG.

Interventions: Treatment with a nasal EPAP device (N = 41) for 12 months. Polysomnography (PSG) on the patients wearing the device was performed after 12 months of treatment. The month 12 device-on PSG data from the analyzable subject cohort (N = 34) was compared to the week 1 device-off PSG from the EPAP vs sham trial.

Measurements and Results: Of the 51 patients eligible, 34 were still using the EPAP device at the end of 12 months. Median AHI was reduced from 15.7 to 4.7 events/h (week 1 device-

off versus month 12 device-on). The decrease in the AHI (median) was 71.3% ($p < 0.001$). The median proportion of sleep time with snoring was reduced by 74.4% ($p < 0.001$). Over 12 months of EPAP treatment, the Epworth Sleepiness Scale decreased (11.1 ± 4.2 to 6.0 ± 3.2 , $p < 0.001$), and the median percentage of reported nights used (entire night) was 89.3%.

Conclusions: Nasal EPAP significantly reduced the AHI, improved subjective daytime sleepiness and reduced snoring after 12 months of treatment. Long-term adherence to EPAP was excellent in those who had a positive clinical response at month 3 of the EPAP vs sham study.

Clinical Trial Registration: ClinicalTrials.gov

Trial name: Extension Study of Original Protocol AERO C009 for Obstructive Sleep Apnea-hypopnea (AERO C009E).

URL: <http://clinicaltrials.gov/ct2/show/NCT00849043?term=Ventus+Medical&rank=2>

Registration Number: NCT00849043.

Keywords: Obstructive sleep apnea, expiratory positive airway pressure, CPAP

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Obstructive sleep apnea (OSA) is a common disorder¹ often resulting in adverse cardiovascular consequences, daytime sleepiness, and disturbed nocturnal sleep of the patient and bed partner.^{2,3} An expiratory positive airway pressure (EPAP) nasal device (Provent Sleep Apnea Therapy, Ventus Medical Inc., Belmont, CA) has been developed to provide a new therapeutic option for OSA patients (**Figure 1**). Prior studies⁴⁻⁸ have documented safety and efficacy, including a large multicenter, randomized, double-blind, sham-controlled trial with 3-month follow-up (EPAP vs sham study). An open label extension of the 3-month EPAP vs sham study was conducted to evaluate the long-term durability of EPAP treatment response after 12 months of follow-up.

METHODS

Study Design

The study was a prospective, 13-site, single-arm, open-label extension clinical trial (study investigators listed in

BRIEF SUMMARY

Current Knowledge/Study Rationale: Because there are few alternatives to using positive airway pressure in OSAS, a non-invasive nasal expiratory positive pressure device was developed; this treatment showed efficacy in some patients at 3 months. This research was done to explore long term efficacy and evaluated patient after one year of treatment.

Study Impact: Although CPAP treatment remains the treatment of choice in OSAS, the nasal expiratory positive pressure device is an additional treatment option in some patients. Because compliance and efficacy may be maintained after 12 months of use, this treatment may be considered for long term use in selected patients.

Acknowledgments). The study design illustrating the connection between the EPAP vs sham 3-month study and the EPAP open label extension study with 12-month follow-up is shown in **Figure 2**. The study was registered on clinicaltrials.gov (NCT00849043). The local institutional review board (or authorized national institutional review board) at each site approved the study.

Figure 1—Nasal EPAP device

Single use valves are inserted into each nostril and sealed with adhesive.

Patient Recruitment and Study Initiation

Patients in the EPAP arm of the EPAP vs Sham study⁸ who met adherence and efficacy criteria were enrolled. The inclusion and exclusion criteria are provided in the Supplement, **Table S1**. Inclusion criteria included $\geq 50\%$ reduction in AHI or an AHI reduction to < 10 documented by polysomnography, comparing the 3-month device-on PSG to the week 1 device-off PSG. The other key inclusion criteria related to compliance, defined as EPAP device use ≥ 4 h per night, ≥ 5 nights per week on average during months 1 and 2 of the 3-month trial. After signing informed consent, patients were instructed to continue nightly use of the nasal EPAP device.

Nasal EPAP Device

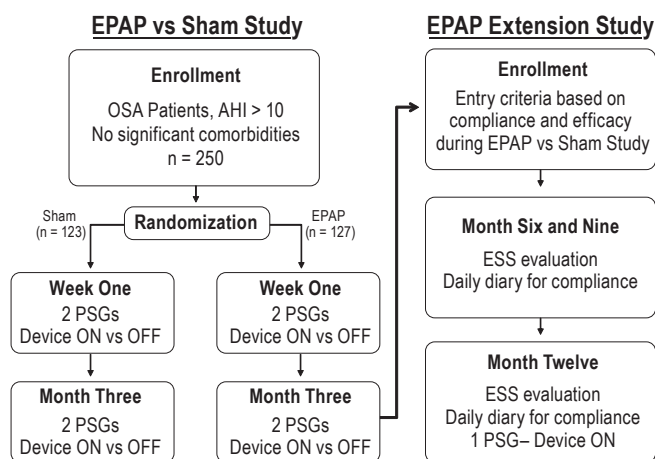
The nasal EPAP device consists of a single-use valve inserted into each nostril and held in place by adhesive. The valve has minimal inspiratory resistance but an expiratory resistance of 80 cm H₂O/L/sec at a flow rate of 100 mL/sec. The adhesive substrate, similar to that found in adhesive bandages, was applied to the outer edges of the nares, resulting in a leak-free seal between the valve and the nose.

Treatment Evaluations

During the 4-week period preceding the 6-, 9-, and 12-month office visits, patients were asked to complete a daily diary entry each morning after awakening, documenting if the device was in place in the morning. Each follow-up office visit included a medical evaluation by the study physician as well as completion of the Epworth Sleepiness Scale (ESS),⁹ a subjective measure of propensity to fall asleep in common situations.

Polysomnography

Attended polysomnography (PSG) was performed using standard techniques including monitoring of EEG derivations (frontal, central, and occipital), right and left electro-oculographic derivations, a chin electromyographic (EMG) derivation, nasal pressure, an oral thermal sensor, chest and

Figure 2—EPAP vs sham and EPAP open label extension study design

abdominal effort belts, a body position monitor, a left leg EMG derivation, a single ECG channel, and pulse oximetry. A quantitative snoring sound volume meter with a microphone was also used (Q-Snor, Braebon Medical Corporation). A specially designed nasal cannula (Ventus Medical Inc., Belmont, CA) was used to securely attach to the nasal EPAP device to allow for standard measurement of nasal airflow via nasal pressure during PSG (**Figure 3**).

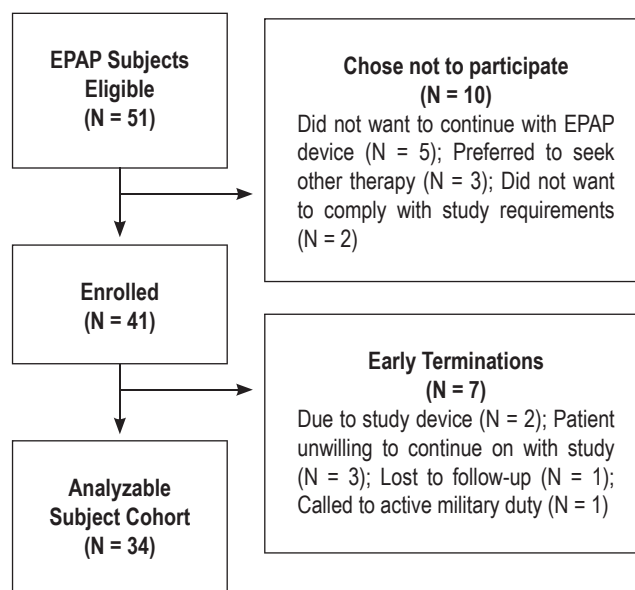
The polysomnographic and snore data were analyzed by a central scoring center. Sleep was manually staged in 30-sec epochs, and arousals and respiratory events were scored using the recommended criteria published in the American Academy of Sleep Medicine Scoring Manual.¹⁰ Hypopneas were defined as reductions in airflow $\geq 30\%$ from baseline with a duration > 10 sec associated with a drop in arterial oxygen saturation (SpO₂) $\geq 4\%$. The arterial oxygen desaturation index (ODI) was the number of desaturations $\geq 3\%$ per hour of total sleep time (TST).

The reported snore data was derived by calculating the percentage of TST during which the sound level detected by the Q-Snor device was > 10 dB above the ambient sound level. This approach was employed to reconcile site differences in the Q-Snor calibration of noise minimum values and thus absolute dB values of sound level recorded by the Q-Snor device.

Statistical Analysis

Analysis was performed on the analyzable subject cohort that included all patients in whom data was available. The primary and secondary endpoints were established *a priori*. The primary end point of the study was the percent change in AHI between the week 1 device-off PSG (from the EPAP vs sham study) to the month 12 device-on PSG. The secondary endpoint was the change in ESS between baseline of the EPAP vs sham study and month 12 of the EPAP open label extension study.

The paired *t*-test and the sign-rank test were used to test the null hypothesis that the mean within-subject measurement was equal to zero. A $p < 0.05$ was considered statistically significant. Results are presented as means \pm standard deviation or median (25th, 75th percentile).

Figure 3—Nasal cannula attached to EPAP device**Figure 4**—Diagram of patient flow**Table 1**—Patient demographics

	N = 41
Age (years)	50.1 ± 13.6
Gender	63.4% male
BMI (kg/m ²)	32.5 ± 7.5

RESULTS

Patient Flow, Demographics, and Dropouts

A patient flow diagram is provided in **Figure 4**. Forty-one (41) patients were enrolled.

The patient demographics are shown in **Table 1**.

There were 7 patients who terminated early from the study, leaving a cohort of 34 analyzable subjects. The 7 early terminations were due to patient unwillingness to continue on with the study (N = 3), study device (N = 2), lost to follow-up (N = 1), and called to active military duty (N = 1).

AHI, ODI, and Arousal Index

There were statistically significant reductions in the median AHI, ODI, and arousal index when comparing the week 1 device-off to month 12 device-on results. The data are presented in **Figure 5**.

Snoring

The median proportion of sleep time spent snoring was reduced by 74.4% ($p < 0.001$).

Sleep Architecture and Effect of Position and Sleep Stage

There was a statistically significant increase in the amount of stage N2 sleep; however, this was not clinically significant. The amount of stage N1, N3, and REM sleep did not have a statistically significant change. The EPAP device significantly reduced

the AHI during both NREM and REM sleep, as well as in the supine and non-supine positions.

The TST and sleep stage durations (% of TST), as well as the effects of body position and sleep stage, are provided in the Supplement, **Table S2**.

Impact on Subjective Sleepiness

Use of the nasal EPAP device resulted in a significant long-term reduction in subjective sleepiness as measured by the Epworth Sleepiness Scale (ESS). The data are presented in **Figure 6**.

Adherence to Therapy

The median percentage (25, 75 percentile) of reported nights the device was worn for the entire night was 89.3% (81.8, 95.2). The median percentage of nights that the diary was completed was 98.8% (97.6, 100.0).

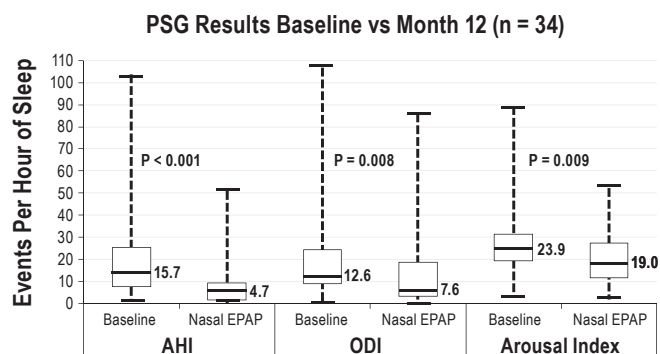
Adverse Events

There were no serious device-related adverse events. Device-related adverse events were reported by 42% (17/41) of patients. The most frequently reported events were difficulty exhaling, nasal discomfort, dry mouth, headache, and insomnia.

DISCUSSION

The major finding of the study was that the patients who were compliant with the EPAP device at month three in the EPAP vs sham study, and had a positive response to it, continued to

Figure 5—Baseline vs month 12 PSG results



show benefit at twelve months. Of the 51 patients eligible, 34 were still using the EPAP device at the end of 12 months. AHI was significantly reduced and subjective sleepiness was significantly decreased compared to device-off nights on the week 1 sleep study of the EPAP vs sham study. The unwanted effects of EPAP treatment were mild. Median device use (adherence), as reported by patient diary, was excellent, with the nasal EPAP device worn all night for approximately 89% of nights.

We found that the effectiveness of nasal EPAP is similar or compares favorably to other treatments. Although CPAP is considered the gold standard of treatment, inadequate adherence to CPAP is common.^{11,12} In a study comparing oral appliances and CPAP, the mean AHI dropped from baseline of 21.3/hour to 4.8/hour with CPAP and to 14.0/hour with an oral appliance.¹²

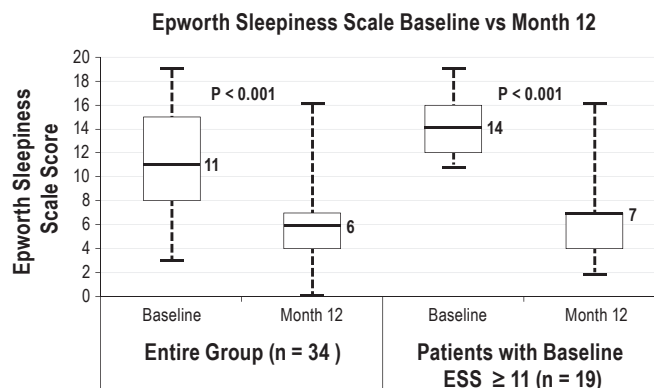
Our study has a number of limitations. In the original EPAP vs sham study, there were a large number of exclusion criteria, including patients with severe arterial oxygen desaturation, those who had prior upper airway surgery, or those who had been treated with CPAP. The top four reasons for exclusions were prior CPAP treatment, other serious uncontrolled medical conditions, other sleep disorders, and medications affecting neurocognitive function. The exclusions were designed so that 3 months of sham treatment would not impose a significant health risk and that treatment-naïve patients would be studied. Thus, the results of the study may not generalize to a more heterogeneous population that may contain CPAP failures, prior upper airway surgery, or severe arterial oxygen desaturation.

Another possible limitation of our study was that determination of adherence depended on patient report rather than an objective measure. However, adherence was similar on both the sham and active device in the EPAP vs sham study.

No baseline predictors of treatment success were identified by post hoc analysis. Objective confirmation of efficacy using home sleep studies or in-lab polysomnography and follow-up with the physician to assure adequate adherence is consistent with recommendations for other treatments for OSA.²

In summary, a large, randomized, double-blind, sham-controlled study documented that the nasal EPAP device effectively reduced the AHI and improved oxygenation at month 3; and the 12-month open label extension study showed continued efficacy at 12 months, with significant improvement in subjective sleepiness with good adherence. Thus, nasal EPAP is an effective treatment option for many OSA patients.

Figure 6—ESS – Baseline vs Month 12



ABBREVIATIONS

AHI, apnea hypopnea index
 AE, adverse event
 BMI, body mass index
 CPAP, continuous positive airway pressure
 EPAP, expiratory positive airway pressure
 ESS, Epworth Sleepiness Scale
 ODI, oxygen desaturation index
 OSA, obstructive sleep apnea
 SpO₂, arterial oxygen saturation measured by pulse oximetry

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DISCLOSURE STATEMENT

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Table S1—Inclusion and exclusion criteria**Inclusion Criteria**

1. Based upon scoring at the study site, the 3-month “device-on” PSG [from the EPAP vs Sham three-month study] has a $\geq 50\%$ reduction in AHI compared to the 1-week “device-off” PSG AHI, or the 3-month “device-on” PSG AHI < 10
2. Used the EPAP device at least 4 hours per night, 5/7 nights per week on average during months 1 and 2 of the EPAP vs Sham three-month study
3. The study physician and investigator believe that continued EPAP device use does not represent a significant safety risk for the patient
4. Patient understands and is willing and able to comply with study requirements

Exclusion Criteria

1. Use of any device that interferes with nasal or oral breathing
2. Persistent blockage of one or both nostrils which prevents airflow in one or both nostrils
3. Any chronic sores or lesions on the inside or outside of the nose
4. Chronic use of nasal decongestants other than nasal steroids
5. Oxygen saturation $< 75\%$ for $> 10\%$ of the diagnostic PSG
6. Oxygen saturation $< 75\%$ for $> 25\%$ of the first 4 hours of the diagnostic PSG
7. Prior or near-miss motor vehicle accident due to sleepiness in the past 12 months
8. Current use of hypnotics, anxiolytics, sedating antidepressants, anticonvulsants, sedating antihistamines, stimulants, or other medications likely to affect neurocognitive function and/or alertness
9. History of allergic reaction to acrylic-based adhesives (such as those found in BAND-AIDS)
10. Current acute upper respiratory (including nasal, sinus, or middle ear) inflammation or infection or perforation of the tympanic membrane (subject may be reconsidered for participation after acute episode resolves)
11. History of frequent and/or poorly treated severe nasal allergies or sinusitis which may interfere with the ability to use the EPAP device
12. Narcolepsy, idiopathic hypersomnolence, chronic insomnia, restless legs syndrome, REM sleep behavior disorder or any other diagnosed or suspected sleep disorder other than OSA that could affect sleepiness scales or the likelihood of apneas/hypopneas during a PSG
13. Current use of diurnal or nocturnal supplemental oxygen
14. History of CPAP use in the home for the treatment of OSA. Temporary use of CPAP in a laboratory setting does not exclude the patient from participating.
15. History of use of oral appliances in the home for the treatment of OSA
16. History of prior surgery for OSA (e.g., somnoplasty, uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty, mandibular advancement, Pillar procedure). May participate if prior surgery was limited to the nose, sinuses, and/or turbinates, etc.
17. Currently working night or rotating shifts
18. Consumption of > 10 caffeinated beverages per day (approximately 1000 mg per day)
19. History of severe cardiovascular disease, including New York Heart Association Class III or IV heart failure, coronary artery disease with angina or myocardial infarction in the past 6 months, stroke in the past 6 months
20. History of cardiac rhythm disturbance (defined as a 5-beat run of sustained ventricular tachycardia or bradycardia if < 30 beats per min for a 10-second run or previously undiagnosed and untreated atrial fibrillation or Mobitz II or third-degree heart block)
21. Uncontrolled hypertension, defined as SBP > 180 or DBP > 105 mm Hg
22. Uncontrolled hypotension, defined as SBP < 80 or DBP < 55 mm Hg
23. History of severe respiratory disorders (including respiratory muscle weakness, bullous lung disease, bypassed upper airway, pneumothorax, pneumomediastinum, etc.) or unstable respiratory disease (e.g., asthma or chronic obstructive pulmonary disease with exacerbation in the last 3 months)
24. Any other serious, uncontrolled medical condition that may impair follow-up or put the subject at undue risk
25. Females of child bearing age who are pregnant or intending to become pregnant. Proof of non-pregnancy with a urine or blood test is not required.
26. Consumes on average more than 3 drinks of alcohol per day
27. Chronic neurologic disorders affecting neurocognitive abilities or daily function
28. Cancer, unless in remission for more than 1 year. A subject with a history of a small basal cell carcinoma (without metastasis) that was excised with wide margins may be included at the discretion of the Investigator.
29. Current psychiatric illness likely to impair ability to participate in study without undue risk
30. Smokers whose habit interferes with the overnight PSG
31. Any known illicit drug usage

Table S2—Sleep architecture and effects of position and sleep stage

	Week 1 Device Off	Month 12 Device On	p Value (Absolute Change)
N = 34			
TST	365.0 ± 61.6	349.3 ± 79.2	0.28
Wake After Sleep Onset	50.9 ± 34.7	48.6 ± 31.2	0.91
Stage N1	15.9 ± 10.1	14.8 ± 9.9	0.46
Stage N2	57.3 ± 9.5	60.4 ± 12.1	0.027
Stage N3	10.2 ± 8.8	8.6 ± 8.2	0.47
Stage REM	16.6 ± 6.3	16.3 ± 6.6	0.67
N = 30			
AHI NREM ¹	12.6 (6.0, 22.2)	2.9 (1.2, 8.3)	< 0.001
AHI REM ¹	16.8 (5.7, 53.0)	3.7 (0.9, 14.4)	< 0.001
N = 21			
AHI Supine ¹	22.0 (9.3, 41.9)	6.5 (2.5, 20.1)	< 0.001
AHI Non-Supine ¹	3.2 (1.8, 10.3)	0.8 (0.0, 1.7)	= 0.001

Values are median (25, 75 quartile) or, mean ± standard deviation ¹Patients with > 20 minutes in each position and state