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Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes.

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Upper Airway Stimulation for Obstructive Sleep Apnea – 5-Year Outcomes

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Abstract

Objective: To present 5 year outcomes of a prospective cohort of obstructive sleep apnea (OSA) patients treated with upper airway stimulation (UAS) utilizing a unilateral hypoglossal nerve implant.

Study Design: A multicenter prospective cohort study.

Setting: Industry-supported multicenter academic and clinical trial.

Methods: From a cohort of 126 patients, 97 completed protocol and 71 patents consented to a voluntary polysomnogram. CPAP failures with moderate to severe OSA, BMI< 32kg/M2, and without unfavorable collapse on drug induced sleep endoscopy were enrolled in a phase 3 trial. Prospective outcomes included apnea hypopnea index (AHI), oxygen desaturation index (ODI), measures of sleepiness, quality of life, snoring, and adverse events.

Results: Patients who did and did not complete the protocol differed in baseline AHI, ODI and lower FOSQ scores but not in any other demographics or treatment response measures. Improvement in sleepiness (Epworth Sleepiness Scale) and quality of life was observed with normalization of scores increased from 33% to 78% and 15% to 67%, respectively. AHI response rate (AHI <20 events/hr and >50% reduction) was 75% (n=71) When a last observation carried forward analysis (LCOF) was applied, responder rate was 63% at 5 years. Serious device related events all related to lead/device adjustments were reported in 6% of patients.

Conclusions: Improvements in sleepiness, quality of life, and respiratory outcomes are observed with 5 years of UAS. Serious adverse events are uncommon. UAS is a non-anatomic surgical treatment with long-term benefit for individuals with moderate to severe OSA who have failed nasal CPAP.

Introduction

Hypoglossal never (CN XII) stimulation for obstructive sleep apnea (OSA) has demonstrated safety and efficacy at 12 months in a cohort of participants with moderate to severe OSA who were unable to accept or adhere to positive pressure therapy [1]. In the same cohort, a randomized withdrawal of therapy demonstrated a device-related therapeutic effect, and durability and returned to successful treatment values upon resumption of therapy [2]. Follow-up at 24, 36 and 48 months post implantation continued to show successful clinical outcomes, low morbidity, and a favorable safety profile [3-5].

OSA is a chronic disease. Patient-centered outcomes are critical elements of disease management. Hallmark outcomes for success include amelioration of intrusive snoring, excessive daytime sleepiness, impaired cognitive function, and a reduced quality of life [6,7]. While important, the absolute apnea–hypopnea index (AHI), in isolation, poorly correlates with these relevant disease outcomes with differing effects on the quality of life and the severity of symptoms among patients for a similar number of events during sleep [8]. Clinicians do not make treatment decisions solely based on an arbitrary AHI threshold. Assessment of successful treatment not only requires therapy to have a meaningful objective improvement, but also a successful clinical effect as reported by patients combined with effective use by the patient for many years.

The aim of this study was to evaluate long-term (60-month) safety and effects of UAS therapy on the propensity for daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), daytime functioning as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ), intrusive snoring, and sleep disordered breathing as found in an overnight polysomnography (PSG).

Methods

Participants

The STAR trial is a multicenter, IRB approved, (see Appendix 1 for IRB details) cohort that included adults with a history of moderate to severe OSA, and intolerance or inadequate adherence to CPAP. Key study exclusion criteria included a body mass index > 32 kg/m^2, neuromuscular disease including hypoglossal nerve palsy or injury, severe cardio-pulmonary disorders, active psychiatric disease, and co-morbid non-respiratory sleep disorders that would confound functional assessments related to sleep. Participants who met inclusion/exclusion criteria underwent three screening exams: an in-lab attended polysomnography (PSG), a surgical consultation visit, and drug-induced sedated endoscopy (DISE). Participants were excluded after the PSG for an AHI less than 20 or greater than 50 per hour of sleep; central and/or mixed apnea index > 25% of the AHI; or a non-supine AHI < 10. Participants were also excluded if the surgeon's office head and neck exam identified pronounced anatomical abnormalities (i.e. tonsil hypertrophy) that might prevent effective use of the device and after the DISE if complete concentric collapse was observed at the level of the velopharynx [9].

Study Procedures

Qualified participants who met pre-implant screening criteria underwent device implantation. The implanted system (Inspire Medical Systems, Inc. Maple Grove, MN, USA) consists of three components: a stimulation cuff electrode that encircles the medial division of the right hypoglossal nerve; a pressure sensing lead to guide timing of stimulation and placed within the fourth or fifth right intercostal space; and an implantable pulse generator inserted into a right mid-clavicular subcutaneous pocket. The therapy guides phasic stimulation to the hypoglossal nerve to increase airway muscle tone and luminal diameter prior to the onset of inspiration and to maintain adequate upper airway airflow.

Self-reported outcomes using validated sleep questionnaires, general health status, device metrics, and adverse events were followed at 6-month intervals for five years. PSGs per protocol were collected at 12 and 18-month follow-up visits and voluntary PSG's were performed at 3 and 5 years. The PSG studies

were scored by two independent core labs using standard 2007 scoring criteria, [10] with a hypopnea scored based on a 30% airflow reduction and a 4% oxygen desaturation. Sleep states are reported as NREM and REM sleep and arousals as >3 seconds change EEG frequency [10]. Patient-reported outcome measures included subjective sleepiness and sleep-related quality of life using the validated ESS and the FOSQ. Clinical variables including BMI, neck circumference, stimulation parameters, and blood pressure were measured at scheduled study visits to assess any changes over the course of the study. Subjective report of participant and bedpartner reported snoring was collected from participants on a categorical scale (no snoring, soft snoring, loud snoring, very intense snoring, or bed partner leaves room). All reported adverse events were reviewed and coded by the Clinical Events Committee. Serious adverse events were defined as any events that led to death, life-threatening illness, permanent impairment and related surgeries, or a new or prolonged hospitalization. Adverse events were categorized as procedure-related if related to the surgical procedure or device-related if secondary to use of the device after therapy activation.

Statistical Analysis

The primary population for analysis comprised participants who were implanted and completed follow-up at the 5-year visit. We also performed several sensitivity analyses to assess the impact of the missing long-term outcome data of AHI, FOSQ and ESS at 36 and 60 months. The sensitivity analyses included a last observation carried forward (LOCF), a repeated measures regression analysis, a multiple imputation (MI) analysis, and a maximum likelihood estimation (MLE) analysis [11]. The LOCF analysis imputed the last available follow-up value for any missing data at months 36 and 60. The repeated measures analysis included all available baseline and follow-up data in a repeated measures regression model and provided least squares estimates of the means at 36 and 60 months. The MI analysis created 10 imputed datasets for each parameter with all available baseline and follow-up data used as predictors. The means at months 36 and 60 were estimated within each imputed dataset and combined across

imputations. The MLE analysis provided estimates for the outcomes at months 36 and 60, which maximizes the probability of the observed data. A stepwise multivariable logistic model was used to determine key baseline factors associated with therapy response. Analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

Results

Participants

Ninety-seven of the 126 implanted participants (78%) completed the 5-year follow-up visit **(Figure 1)**. Among the 29 participants who did not complete the 5-year assessment, 21 were lost to follow-up within the pre-specified timeframe; five died of unrelated causes (sudden death, cardiac arrest after a fall and blunt chest trauma, homicide, malignant melanoma, and myelodysplastic syndrome), and the device was explanted in three patients (IPG removal in a non-responder, system removal non-responder, and non-elective removal in a responder due to septic arthritis). Seventy-one of the 97 protocol patients, participated in a voluntarily 5 year follow up overnight in-lab polysomnographic evaluation. The mean BMI at 5-years was 28.6 ± 2.8, which was unchanged from baseline.

Among the 97 participants who did compared to those who did not complete the protocol, baseline age, BMI, and ESS were similar, but subjects who did not complete the month 60 visit had higher AHI, ODI and lower FOSQ scores at baseline. These differences disappeared when evaluation was performed at 12 months while therapy was activated.[1] Among the seventy-one participants who voluntarily completed a 60 month PSG study, age, AHI, and BMI baseline parameters were not significantly different from those who did not complete the PSG, the 97 protocol followed patients, nor the original cohort

(Table 1). The AHI treatment response did differ at 12 months (74% vs 52%, p <0.002) but AHI treatment response at 18 and 36 months, change in sleepiness, and change in quality of life did not differ between groups that did and did not complete the 60 month PSG.

Primary Outcome Measures

The efficacy measures of AHI and ODI decreased from baseline to the 12-month assessment and remained stable at 36 and 60 months (Table 2, Figure 2). A decrease in the AHI of >50% and an AHI of <20, which was the a priori definition of success, was observed in 75% of participants with 5-year PSG (Figure 2). [12] Using other AHI cutoffs, 44% and 78% of participants had AHI < 5 and < 15 during 5-year PSG. Given the lost to follow up over the extended duration of follow up, a "last observation carried forward" (LOCF) analysis from the cohort at 12, 18 or 36 months was performed. LCOF demonstrated an average AHI at 5-years of 15.1 ± 1.5, with a median AHI of 7.6 and a response rate of 63% (5 deaths and 3 explants were counted as non-responders), which was similar to the responder rate of 66% at 12 months. Using both LOCF and multiple imputation method to account for missing data, the change of AHI from baseline was similar at 36 and 60 months, and did not change using different sensitivity analysis (Table 3). In addition to sensitivity analysis using LCOF and multiple imputation methods, we conducted the best and worst-case analysis, in which the minimal and maximal value from available post-operative AHI at 12, 18, and 36 months was used for all patients who did not complete the 60 month PSG. In the best-case analysis, the average AHI was 12.3+/-15.4 with a change of -19.8 +/- 15.8 (95% confidence interval of -22.5 to -17.0) at 60 months from baseline. The worst case analysis demonstrated an average AHI of 17.0 +/- 18.2 with a change of -15.0 +/- 16.6 (95% confidence interval of -17.9 to -12.1) at 60 months from baseline. Changes from baseline in best and worst case analysis were not significantly different.

When the 5-year AHI responders and non-responders were compared, univariate analysis demonstrated differences in age and the baseline ODI between groups. A multivariable stepwise regression analysis including age, BMI, gender, neck circumference, prior UPPP, and baseline AHI, ODI, FOSQ, and ESS demonstrated that only a lower ODI was predictive of 5 year AHI responders. (Table 4)

Self Reported Outcome Measures

FOSQ and ESS improvements observed at prior evaluation periods persisted at 5-years. The average increase of FOSQ was 3.2 units as observed, and unchanged with the sensitivity analysis. At baseline, only 15% reported a normal FOSQ score (>17.9). This increased to 67% at 5-years. The average reduction of ESS was 4.4 units. The percent of participants who reported a normal ESS score (<10) increased from 33% at baseline to 78% at 5-years. (Figure 2)

Long-term bedpartner and self-reported snoring reports demonstrated improvement from baseline and remained relatively stable from 12 to 60 months (Figure 3). Based on partner report, intrusive snoring (very intense snoring or bedpartner leaves room) was reduced from 54% at baseline to 2% at 60-months; no or soft snoring was increased from 17% to 90%. Participant self-reports of nightly use were 86%, 81% and 80% at years 1, 3 and 5.

Other Measures

As at other time points, the cohort demonstrated no changes in sleep stage distribution. Arousal index was significantly reduced (27.8 +/- 117 to 7.8 +/- 9.7 events/hr, $p < 0.0001$). Percent time with oxygen desaturation less than 90% was unchanged (8.0 +/- 10.1 to 7.4 +/- 13.3%). For patients who completed protocol follow up, stimulation parameters changed. Sensory thresholds, functional thresholds, and sub-discomfort thresholds decreased.

Adverse Events

After five years, eight participants (6% of 126) had a total of nine serious device-related adverse events requiring surgical repositioning or replacement of the neurostimulator or implanted leads. One participant had two revision procedures to reposition the neurostimulator and the sensing lead to resolve discomfort. One participant underwent stimulation lead repositioning due to unfavorable tongue movement pattern and to improve therapy response. Four participants had insulation failure with the sensing lead and underwent replacement of both the neurostimulator and sensing lead. In one, the stimulation lead was inadvertently cut and also then required replaced.

Discomfort due to electrical stimulation was the most common non-serious adverse reported event occurring 81 times during the first year. For most subjects this complaint was resolved by reprogramming of stimulus levels, and during the fifth year was reported only five times. Tongue abrasion from tongue movement was reported 28 times the first year and was reduced to two times during the fifth year. A detailed list of adverse events is provided in Table 5.

Discussion

The durability of the treatment effect of upper airway muscle stimulation therapy by the Inspire System was addressed with a 5-year follow-up of participants in the STAR trial. Both voluntary PSG measures in 71 of the original 126 participants and data from protocol visits in 97 patients, demonstrated long-term resolution of objective measures of sleep disordered breathing, daytime symptoms, and quality of life components of the disease. The major findings of the study were: (1) UAS therapy provides clinically meaningful and statistically significant improvements in PSG measures of OSA, (2) clinically meaningful and statistically significant improvements in key patient-centered outcomes in snoring, daytime

sleepiness, and sleep related quality of life were achieved, and (3) there was a very low incidence of device related adverse outcomes beyond the implant period.

Sustained effectiveness is critical in a chronic condition such as OSA that requires long-term management. The detrimental effect of OSA on activities of daily living and quality of life measures was mitigated by this therapy in a significant number of participants at 5-years. Untreated moderate-severe OSA has been associated with increased health care costs and physician visits, increased motor vehicle accidents, increased workplace errors, and loss of productivity. CPAP via a mask is the standard first-line therapy [13]. It is highly effective when used consistently. Unfortunately, many individuals cannot or do not adjust to this therapy. Challenges with CPAP acceptance and adherence in patients with moderate to severe disease have been identified as an impediment to the ability to mitigate co-morbid cardiovascular sequelae [14]. This report indicates that multi-year control of obstructive sleep apnea hypopnea syndrome can be achieved by a non-CPAP and non-anatomic surgical approach.

Patient-reported outcome measures capture the subjective aspects of the sleep apnea syndrome, and these self-reported symptoms often drive patients to be evaluated for sleep apnea [15]. PSG measures correlate loosely with OSA disease burden as well as symptom expression. These symptoms may contribute significantly to personal morbidity, as well as the direct and indirect health care costs of untreated OSA [16,17]. Improvements in several aspects of the quality of life, accompanied by use of UAS, if interrupted, results in objective and subjective recidivism as shown in the withdrawal study [2]. Other common consequences of OSA are spousal complaints related to snoring. There is currently no accepted standard objective measure of snoring, although the reliability of self-report and bed partner report of snoring intensity may be questioned, most participants in this cohort achieved a successful reduction in their snoring from loud or disruptive levels to soft or no snoring .

Cranial nerve stimulation using Inspire is an innovative first-in-class therapy. In contrast to other surgical approaches, this therapy does not directly modify the pharynx or surrounding structures. Instead, it addresses pharyngeal collapse using a more physiologic approach. This study is noteworthy both in demonstrating a high level of durable effect but also a low complication and morbidity rate. Several recent independent single-center cohort studies reported additional safety, efficacy and therapy adherence data in the real-world clinical practice setting, subsequent to FDA approval in 2014. Kent et al [18] reported a case series of 21 consecutively implanted patients. After an average of 7.8 months of follow up, the AHI was reduced from 33.3 to 5.1 ($p<0.01$) and ESS improved from 10.3 to 6.0 ($p<0.01$). Objective device adherence was 7.0 ± 2.2 hours of use per night. Heiser et al [19] reported another case series of 31 consecutive patients. After 12 months, the mean AHI was reduced from 32.9 to 7.1 and ESS from 12.6 to 5.9. All participants demonstrated high rates of therapy adherence with 6.6 ± 2.7 hours per night at 12 months using objective device reporting. In addition to these single-center studies, a multi-center post-market study of 60 patients has recently reported consistent improvements in patient outcomes after 6 and 12-month follow up [20,21] in the AHI, ESS and FOSQ as observed in the STAR trial. These single-center and multi-center post-approval studies have demonstrated that hypoglossal nerve stimulation can be effectively implemented in the routine clinical practice for managing OSA patients who could not adhere to CPAP.

The size of this prospective cohort and high number of patients with long-term follow-up data is a considerable strength of this surgical study. The assessments were consistently collected in the US and European sites, so that intra- and inter-individual comparisons could be objectively and statistically addressed. The clinical management among surgeons and sleep medicine practitioners and data integrity was maintained over five years.

The biggest limitations related to the lack of a control group, and assessment of treatment effects other than withdrawal of stimulation at 12 months. However, the effect size of objective and subjective

responses are large, of the order of other evidence-based therapies. Since the study group was predominantly, male, obese, CPAP-intolerant patients of European descent, conclusions about generalizability to women and other ethnic groups may require additional study. The inclusion and exclusion criteria (AHI range, BMI limit, and anatomic configuration of airway collapse) were consensus based and additional studies will likely address these issues. Also, since the current study evaluating a novel treatment appropriately excluded participants with active cardiovascular disease, data while adequate to address AHI, ODI, snoring, quality of life, and behavioral sleepiness, were insufficient to address blood pressure and cardiac effects of long-term therapy.

This is the first report of a medical or surgical device intervention for OSA that systematically followed participants with PSG measures and quality of life outcomes over a 5-year period. UAS therapy can provide clinically and statistically significant improvements in disease-defining PSG values, self-reported quality of life, daytime alertness, and snoring. Results indicate that in a selected group of participants with moderate to severe OSA who are unable to accept or adhere to CPAP, hypoglossal nerve stimulation therapy can provide significant improvement in objective measures of sleep disordered breathing and important sleep related quality of life outcome measures. The effect is maintained across a 5-year follow-up period.

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Figure 1

Study flow at yearly time points is shown over 5 years till study completion. Included patients underwent protocol evaluation and follow up. Non-included patients with description are on right. Seventy one patients completed non-protocol voluntary polysomnograms (PSG) at 5 years

Figure 2.

Long-term outcome of AHI, sleep quality of life (FOSQ), and daytime sleepiness (ESS) response rate over 60 months. The mean and standard error was estimated using repeated measures. The long-term outcome of oxygen desaturation index (ODI) matched closely to AHI. For therapy response rate, AHI response defined as AHI > 50% reduction to < 20 events/hour; ESS score < 10 defined as normal daytime sleepiness; FOSQ score > 17.9 defined as normal sleep-related quality of life.

373 Figure 3.

374 Bedpartner report of snoring intensity over time.

375 Table 1

Parameter	Original Cohort (N=126)	Complete Month 60 (N = 97)	Not Complete Month 60 (N = 29)	p-value (complete versus non-complete)	Month 60 PSG	No Month 60 PSG	p-value (60 month PSG versus No PSG)
Baseline Age	54.5 (10.2)	54.4 (10.3)	55.1 (10.2)	0.73	54.5 (9.9)	54.6 (10.7)	0.98
Baseline BMI	28.4 (28.5)	28.6 (2.5)	27.8 (2.8)	0.16	28.6 (2.5)	28.1 (2.8)	0.30
Baseline AHI	32.0 (11.8)	30.5 (10.8)	37.2 (13.5)	0.01	30.4 (9.4)	34.1 (14.1)	0.09
Baseline ODI	28.9 (9.6)	27.5 (10.8)	33.5 (14.4)	0.02	27.2 (10.0)	31.0 (13.9)	0.09
Baseline FOSQ	14.3(3.2)	14.7 (2.9)	13.52(3.9)	0.03	14.8 (2.6)	13.7 (3.8)	0.07
Baseline ESS	11.6(5.2)	11.3 (5.2)	12.4 (4.0)	0.33	11.6 (5.0)	11.5 (5.0)	0.86
Outcomes							
Change AHI Month 12		-16.0 (16.3)	-17.8 (18.4)	0.63			
Change AHI Month 36		-19.9 (12.5)	-13.9 (17.8)	0.13			
Month 12 responder					79% (56/71)	54% (28/53)	0.003
Month 18 responder					70% (50/71)	60% (30/50)	0.25
Month 36 responder					80% (53/66)	65% (20/31)	0.13
Change FOSQ Month 12		-3.0 (2.9)	-2.8 (3.9)	0.82	N=70 -2.7 (2.7)	N=53 -3.2 (3.6)	0.43
Change FOSQ Month 36		-2.9 (3.6)	-1.7 (4.7)	0.22	N=70 -2.7 (3.0)	N=43 -2.6 (4.8)	0.89
Change ESS Month 12		4.7 (5.1)	4.0 (4.9)	0.53	N=70 5.0 (5.1)	N=53 4.3 (4.8)	0.46
Change ESS Month 36		4.4 (5.6)	4.0 (4.6)	0.72	N=70 4.3 (5.8)	N=43 4.6 (5.1)	0.84

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379 **Table 2. Summary of Primary and Secondary Outcomes**

Outcome Measure	Baseline N Mean ± SD Median	Month 12 N Mean ± SD Median	Month 36 N Mean ± SD Median	Month 60 N Mean ± SD Median
AHI	126 32.0 ± 11.8 29.3	124 15.3 ± 16.1 9.0	98 11.5 ± 14.0 6.0	71 12.4 ± 16.3 6.2
ODI (4%)	126 28.9 ± 18.2 25.4	124 14.0 ± 15.6 7.4	98 9.1 ± 11.7 4.8	71 9.9 ± 14.5 4.6
FOSQ	126 14.3 ± 3.2 14.6	123 17.3 ± 2.9 18.2	113 17.4 ± 3.5 18.8	92 18.0 ± 2.2 18.7
ESS	126 11.6 ± 5.0 11	123 7.0 ± 4.3 6	113 7.0 ± 5.0 6	92 6.9 ± 4.7 6

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382 **Table 3. Change from baseline at 36 and 60 months as observed and estimated using last observation carried**

383 **forward (LOCF) and multiple imputation.**

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		Change from Baseline		
Parameter	Visit	As Observed N Mean ± SE (95% CI)	LOCF N Mean ± SE (95% CI)	Multiple Imputation Mean ± SE (95% CI)
AHI	36 Month	n=97 -19.1 ± 1.4 (-21.8, -16.4)	n=126 -17.8 ± 1.3 (-20.4, -15.1)	-18.2 ± 1.5 (-21.1, -15.3)
	60 Month	n=71 -18.0 ± 1.7 (-21.4, -14.6)	n=126 -17.0 ± 1.4 (-19.7, -14.3)	-17.1 ± 1.7 (-20.5, -13.6)
FOSQ	36 Month	n=113 2.7 ± 0.4 (2.0, 3.4)	n=126 2.7 ± 0.3 (2.0, 3.4)	2.7 ± 0.4 (2.0, 3.5)
	60 Month	n=92 3.2 ± 0.3 (2.6, 3.8)	n=126 3.0 ± 0.3 (2.4, 3.6)	3.2 ± 0.3 (2.6, 3.8)
ESS	36 Month	n=113 -4.4 ± 0.5 (-5.5, -3.4)	n=126 -4.3 ± 0.5 (-5.3, -3.3)	-4.4 ± 0.5 (-5.4, -3.4)
	60 Month	n=92 -4.4 ± 0.6 (-5.5, -3.2)	n=126 -4.2 ± 0.5 (-5.2, -3.2)	-4.3 ± 0.6 (-5.4, -3.2)

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387 Table 4. Predictors of 60 month AHI responders

Baseline Characteristics	**Month 60 Responders N = 53 Mean (SD) or % (N)**	**Month 60 Non-responders N = 18 Mean (SD) or % (N)**	**Odds Ratio**	**95% confidence limits (p-value)**
Age	56.0 (9.3)	50.1 (10.4)	1.07	1.01, 1.13 (0.03)
Gender (% Male)	81% (43)	83% (15)	0.86	0.21, 3.55 (0.83)
BMI	28.6 (2.5)	28.8 (2.3)	0.97	0.77, 1.21 (0.76)
Neck Size	40.8 (3.5)	41.5 (2.9)	0.93	0.79, 1.11 (0.43)
Baseline AHI	29.3 (7.6)	33.7 (13.1)	0.95	0.90, 1.01 (0.09)
Baseline ODI	25.5 (8.5)	32.2 (12.4)	0.94	0.88, 0.99 (0.02)
Prior UPPP (%)	32% (17)	6% (1)	0.13	0.02, 1.02 (0.052)
Baseline FOSQ	14.8 (2.7)	15.0 (2.3)	0.96	0.78, 1.19 (0.73)
Baseline ESS	11.3 (4.9)	12.7 (5.3)	0.95	0.85, 1.06 (0.32)

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390 Table 5 Adverse Events

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Adverse Events	No. of Events 0 - 12M	No. of Events 12 - 24M	No. of Events 24 - 36M	No. of Events 36 - 48M	No. of Events Post 48M	No. of Events Total	No. of Participants with event (% of 126)
Procedure-related non-serious adverse event							
Post-operative discomfort related to incisions	47	1	2	1	1	52	30.2% (38)
Post-operative discomfort independent of incisions	41	0	1	0	0	42	27.0% (34)
Temporary tongue weakness	34	0	0	0	0	34	18.3% (23)
Intubation effects	18	0	0	0	0	18	11.9% (15)
Headache	8	0	0	0	0	8	6.3% (8)
Other post-op symptoms	22	0	0	0	0	22	11.1% (14)
Mild infection	1	0	0	0	0	1	0.8% (1)
Device-related non-serious adverse event							
Discomfort due to electrical stimulation	81	23	26	7	5	142	60.3% (76)
Tongue abrasion	28	12	4	3	2	49	27.0% (34)
Dry mouth	10	5	2	0	3	20	15.1% (19)
Mechanical pain associated with presence of the device	7	2	3	1	1	14	11.1% (14)
Temporary internal device usability or functionality complaint	12	8	1	3	1	25	16.7% (21)
Temporary external device usability or functionality complaint	11	11	8	9	6	45	26.2% (33)
Other acute symptoms	21	14	1	2	1	39	24.6% (31)
Mild infection	1	0	0	0	0	1	0.8% (1)