Supplemental Online Content

Schwartz AR, Jacobowitz O, Eisele DW, et al. Targeted hypoglossal nerve stimulation for patients with obstructive sleep apnea: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. Published online April 6, 2023. doi:10.1001/jamaoto.2023.0161

This supplemental material has been provided by the authors to give readers additional information about their work.

Supplemental Methods

Study Design

The THN3 study (clinicaltrials.gov identifier NCT02263859) was an international, multi-center, randomized, controlled trial. The trial protocol was designed by the investigators (ARS, OJ, JM) and the sponsor (**Figure 1**). All patients were implanted with the THN therapy system (aura6000™, ImThera Medical, San Diego, CA) under an Investigational Device Exemption from the US Food and Drug Administration. Patients were randomly assigned in a 2:1 ratio to begin receiving THN therapy at 1 or 4 months after implant for the Treatment (early activation) and Control groups (late activation), respectively. The 2:1 allocation scheme was used to hasten the development of requisite experience in delivering active therapy and to facilitate patient enrollment and retention at study sites. Short-term efficacy was assessed by comparing changes in SDB measures from pre-implant baseline to 4 months between Treatment and Control groups. Long-term efficacy was measured after receiving 11 months of therapy (12 and 15 months after implant, respectively, for Treatment and Control groups combined) compared to pre-implant baseline.

Randomization was conducted with block sizes of 3 and 6 subjects stratified by site. Allocation schedules for up to 102 randomizations at each site were predetermined from random numbers generated with statistical software by independent consultants. Schedules were not disclosed to sponsor or site personnel involved in the conduct of the trial. The randomization assignment was retrieved by the study coordinator from the randomization schedule at the time of randomization. The site study coordinator was otherwise blinded to the remainder of the randomization schedule. Thereafter, the protocol mandated knowledge of randomization assignment (active Treatment vs. Control) because the patient and study personnel needed to know whether to activate the device at Month 1 for use at home. Similarly, study personnel and participants were aware that stimulation was required during titration and endpoint sleep studies in the Treatment group, as specified by the protocol. Nevertheless, sleep studies were anonymized and scored without explicit knowledge of the treatment assignment, although a variable degree of stimulation artifact could sometimes be appreciated in the recordings.

The protocol was approved by the institutional review board or ethics committee of each of 20 sites (**Table e1**). All participants provided written informed consent. The trial was overseen by a Clinical Events Committee to classify system- and procedure-relatedness as well as severity of adverse events. Measures of SDB were derived from polysomnographic studies scored according to the criteria set forth in the 2007 edition of the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events[1]. Hypopneas were defined according to the recommended definition as a flow reduction of ≥30% for ≥10 seconds with desaturation ≥4%.

Subject Eligibility

Patients were qualified to participate in the study if they were medically stable and had a baseline apnea/hypopnea index (AHI) of 20-65 events/hr, a body mass index (BMI) ≤ 35 kg/m^2, age ≥ 18 years and a history of intolerance or unsuccessful treatment with positive airway pressure therapy. Major exclusion criteria consisted of central apnea events comprising at least 10% of baseline AHI, positional OSA defined by non-supine AHI < 10 events/h, apnea index > 30 events/h, oxygen desaturation of 10% or more for >15 events/h, clinically enlarged tonsils (grade 3-4), lingual tonsil hypertrophy (grade 3-4), Friedman tongue position IV, uncontrolled rhinitis, nasal obstruction, extant active implanted medical device and excessive use of alcohol, tobacco, caffeine

or recreational drugs. A complete list of eligibility criteria appears in Supplement (**Table e2**). In **Figure e1**, subject flow through the entire protocol is illustrated.

Pre-screening of prior polysomnography reports or home sleep test results was used to identify potentially eligible patients. Two baseline polysomnographic studies were used to confirm eligibility, with parameters computed as the average of the two sleep studies scored by a core laboratory (Somnometrix, Wilmington NC). See Supplement **Figure e2** for further details.

System, Implant and Follow-up

The THN system consists of an implanted pulse generator, a multi-contact hypoglossal nerve electrode, a remote control/pulse generator charging system and programmer ("clinical manager") system (**Figure e3**). Implantation of the THN system has been previously described[2]. Briefly, a horizontal incision of approximately 5-6 cm was created inferior to the submandibular gland for the multipolar stimulation lead. Approximately 2 cm of the proximal hypoglossal nerve was exposed circumferentially, leaving the perineurium and axial vascularization intact. The electrode cuff was placed and the lead was stabilized with a suture sleeve attached to the adjacent fascia. Next, an ipsilateral infraclavicular subcutaneous pocket was created 5-10 mm below the superficial fascia through an approximately 5 cm medio-lateral incision. The lead was tunneled from the submandibular incision to the chest incision. The pulse generator was placed in the pocket and attached to nearby fascia with sutures through the header. The proximal end of the lead was inserted into the pulse generator header and held in place with set screws tightened with a torque wrench. System integrity was verified with impedance measurements. The THN system was typically implanted on the patient's right side. Minor updates to THN stimulating system occurred over the course of the trial, as detailed in the **Figure e2 legend**.

One month following surgery, subjects in the Treatment group reported to their sites for activation of THN therapy and training on the use and charging of their device. Prior to the initial titration sleep study, subjects were asked to report the levels of stimulation for each contact at which they could first perceive an effect ("capture threshold") and the lowest level of stimulation associated with discomfort, which in their judgment would be sufficient to disturb sleep ("sensory limit"). This range was used to guide amplitudes applied therapeutically during sleep. Thereafter, a stimulus titration protocol was implemented as follows (and described and illustrated in **Figure e4**. Once in stable sleep, stimulation levels of each contact were systematically evaluated to determine the optimal set of contacts (Supplement **Figure e4, top panel**), and a therapeutic program for improving tidal airflow, reducing apneas/hypopneas, stabilizing blood oxygen levels and minimizing arousals was assembled (Supplement **Figure e4, bottom panel**). At the conclusion of the night, subjects were instructed to use THN therapy nightly and recharge the system as needed. Pre-specified titration sleep studies for the Treatment group were scheduled at Months 2, 3 and 10 with the possibility of additional sleep study titration nights, if needed. Control patients followed a parallel schedule, with activation one night after the Month 4 endpoint visit and additional scheduled titration studies at Months 5, 6 and 13.

Endpoints and Statistical Analysis

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). The balance of baseline characteristics between Treatment and Control groups was assessed with standardized mean differences.

The primary safety endpoint was defined as an estimate of the incidence of system- and procedure-related adverse events through 365 days post-implant, including any unanticipated adverse device effects. Responder rates were used to evaluate efficacy endpoints, in which responders were defined by ≥50% reduction in AHI to ≤20/hr and a ≥25% reduction in ODI from baseline. There were two co-primary short-term and two co-primary long-term efficacy endpoints. The short-term co-primary endpoints consisted of comparisons of: (i) AHI responder rate and (ii) ODI responder rate in the Treatment compared to Control group at Month 4. The long-term co-primary endpoints required a ≥50% responder rate in the pooled Treatment and Control group in (iii) AHI and (iv) ODI at Month 12/15.

For short term endpoints, a one-sided Fisher's exact test was used to determine if the response rates in the Treatment group were greater than the Control group. For long-term endpoints, a one-sided exact binomial test was used to ascertain if the pooled response rates exceeded 50%. Co-primary endpoints as defined by the study protocol were to be tested for one-sided p-values < 0.0245 without correction for multiple comparisons. Additionally, all endpoints were evaluated with effect size estimates comprising standardized mean differences and stochastic probability of superiority[3]. Probability of superiority estimates effect size non-parametrically by indicating the likelihood that scores in one group are higher than another, with values of 0.5 and 1 corresponding to equal probability and complete superiority, respectively. Effect sizes were reported as point estimates with 95% confidence intervals. Evidence provided in several previous hypoglossal stimulation trials including THN trials demonstrated improvements in sleep apnea[4–6], indicating that one-sided tests would optimally test the primary hypothesis in THN3. The trial sample size was prospectively established at 141 patients, driven by the long-term AHI endpoint, to achieve 85% power with 12.5% attrition at an assumed response rate of 62.5%.

Secondary efficacy endpoints comprised comparisons of improvement between Treatment and Control at Month 4 of AHI, ODI, the Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and EuroQol 5-D (EQ-5D) Visual Analog Scale. Ancillary endpoints included: (1) the EQ-5D Index computed according to the United States utility values[7], and (2) whether patients were satisfied with their outcome and whether they would repeat the procedure if they had it to do all over again.

We also conducted exploratory analyses for the purpose of identifying THN3 subpopulations with an enhanced AHI responder rate. These analyses were guided by known predictors of hypoglossal stimulation responses from baseline anthropometric, demographic and sleep study variables. Univariate logistic regression was used to screen potential predictor candidates. Thresholds were applied to candidate predictors and adjusted to optimize the response rate while preserving at least 40% of the overall THN3 population within each subgroup. Receiver operating characteristic curves were then generated to determine the optimal threshold that predicted primary endpoints for the subpopulation.

Supplemental Results

Subjects

Between May 2015 and June 2018, 138 eligible subjects were implanted at 20 study sites after screening a total of 1,289 patients (**Figure e1**). 188 of the total sample became ineligible when at least one of two screening nocturnal sleep studies failed to meet eligibility criteria. Enrolled subjects were predominantly middle age to older Caucasian men with severe obstructive sleep apnea, reflecting the demographics of the disorder in the US population (**Table 1**). The groups did not differ with respect to cardiovascular comorbidities, previous uvulopalatopharyngoplasty, or concomitant medication use. Hypertension and the use of antidepressants and sedative/hypnotics were common in both groups. The BMI was 29.9 ± 3.0 kg/m^2 (mean ± SD) and neck size was 41.9 ± 3.5 cm. Subjects were generally normotensive with low rates of comorbidities. Baseline characteristics of Treatment and Control groups were generally well-balanced, with the exception that the Treatment group had a greater proportion of women and a slightly higher, although not clinically meaningful, average AHI and T90 than the Control group.

The median implantation procedure duration was 77.5 minutes (range 37 to 166 minutes). 72% of patients were discharged on the day of surgery. Follow-up was completed by 134 subjects (88 Treatment group, 46 Control group). Of the 4 Treatment patients who did not complete follow-up, 2 withdrew consent, 1 was lost to follow-up and 1 requested explant due to relocation.

Safety profile

During the 365-day period following implant, two severe related adverse events occurred (in 1.4% of patients): a lead dislodgement requiring revision in one patient, and neck pain due to lead tension that was alleviated with revision of the lead suture sleeve in another patient. Four other severe unrelated adverse events also occurred in four patients, including stress cardiomyopathy, esophageal adenocarcinoma, multiple fractures and malignant melanoma (**Table e3**). An additional ten revisions, replacements or explants occurred in nine patients, comprising five IPG replacements, two system explants, one lead replacement with IPG revision, one lead revision and one IPG revision. Overall, 100 patients experienced 164 procedure- and study-related adverse events. The leading related adverse events consisted of perioperative wound infection, inflammation, hematoma or discomfort (38 events), incisional numbness (19 events), discomfort due to stimulation (46 events) and lack or loss of therapeutic effect (13 events). A complete list of related adverse events by category appears in Supplement (**Table e3**).

Effectiveness

Responses in Treatment vs. Control group at Month 4: In the randomized controlled trial, THN achieved a greater proportion of AHI and ODI responders at Month 4 in the Treatment compared to the Control group (between group pre-specified hypothesis test p-values of 0.0002 and 0.0154 and standardized mean differences and CIs of 0.725 (0.360, 1.163) and 0.434 (0.070, 0.843) for AHI and ODI responder rates, respectively.), fulfilling the short-term co-primary endpoints (**Table 2**). THN treatment was associated with improvements in secondary outcomes including clinically meaningful reductions in AHI and ODI (**Figure 2**), and improvements in quality of life indicators, which are described by units and standardized effect size differences for each parameter,

respectively: ΔESS: -3.3 [-4.8, -1.9], -0.864 (-1.288, -0.499); ΔFOSQ (1.5 [0.3, 2.6]), 0.478 (0.102, 0.927); and ΔEQ-5D visual analog scale (4.7 [0.9, 8.6], 0.423 (0.088, 0.772) (**Table 3)**. Of note, AHI fell substantially more in the Treatment compared to control group at Month 4 (**Figure 2**). In addition, the Snore Outcomes Survey showed meaningful reductions in snoring in the Treatment vs. Control group (see Supplement, **Table e7**). EQ-5D index also improved (probability of superiority 0.610 (0.512, 0.706)), but little change in BMI, blood pressure or pulse was observed over the course of the trial (see Supplement, **Table e8**). With one exception, effects of THN therapy on primary and secondary endpoints persisted in sensitivity analyses, after uni- and multi-variate adjustment, baseline differences in sex, AHI and T90: in a model of ODI RR with sex and AHI as covariates, the Treatment vs. Control difference decreased to 17.8% (95% CI: -0.5%, 36.1%).

Responses in the combined Treatment and Control groups at Month 12/15: At long-term follow-up, the combined Treatment and Control groups demonstrated AHI and ODI response rates of 42.5% and 60.4%, respectively (**Table 2**). Although the AHI responder rate did not meet the pre-specified threshold (≥50%), responses in ODI did (**Table 2**). The disproportionate increase in ODI relative to AHI response rates can be attributed to improvements in pharyngeal patency since obstructive apneas fell to negligible levels while hypopneas persisted (see Discussion).

Consistent with these responses, significant improvements were also observed in secondary outcomes including AHI and ODI (**Figure 2**, **left and right panels; Table e4,** Supplement **Figure e5**) and daytime quality of life (ESS, FOSQ, EQ-5D VAS and EQ-5D Index (Supplement **Figure e5**). Ancillary measures also revealed improvements in sleep architecture, consisting of reductions in transitional N1 sleep and commensurate increases in N2 sleep (Supplement **Table e6**). We also found meaningful improvements in the Snore Outcomes Survey over the course of the trial (Supplement **Table e7**), but did not detect significant changes in heart rate or blood pressure (Supplement **Table e8**).

Impact of sleep efficiency on outcomes in post-hoc analyses: Recent findings suggest that sleep continuity could predict hypoglossal nerve stimulation responses[8], prompting us to examine the influence of sleep efficiency at baseline on AHI response rates. A receiver operating characteristic demonstrated an optimal cut-point for sleep efficiency of 84.6% that distinguished AHI responders from non-responders with an area under the curve of 0.62. Comparing subgroups with sleep efficiency at baseline above and below an 85% threshold (N = 57 vs. 81, 41.3% vs. 58.7%), we found enhanced Month 4 response rates in AHI of 59.5% vs. 20% (standardized mean difference 0.881 [0.293, 1.662]) and in ODI of 73% vs. 30% (0.952 [0.363, 1.787]) in Treatment vs. Control groups, respectively. Pooled Month 12/15 response rates for AHI and ODI reached or exceeded the pre-specified threshold at 50.9% (0.018 [-0.234, 0.273]) and 64.9% (0.312 [0.053, 0.648]), respectively. Responses in secondary endpoints paralleled primary endpoints, with generally enhanced improvements in the treated subgroup compared to the general population. Improvements in secondary and ancillary outcomes (sleep apnea and patient-reported metrics, and systolic blood pressure) are also detailed for AHI responder and non-responder subgroups in Supplement (**Table e9** and **Figure e6**).

Patient Satisfaction Measures

Patients reported high degrees of satisfaction with THN with 83% indicating that they were satisfied or very satisfied with their outcome, 88% expressing a willingness to undergo the treatment again, and 89% stating that

they would recommend the procedure to others. 82% of patients reported THN use on 5 or more nights per week, and that it was either easy or very easy to use.

Table e1. List of Study Contributors at implanting and testing sites that participated in the Targeted Hypoglossal Nerve stimulation trial (THN3)

Study Site / Facility Name	Location	Number of Implanted Subjects	Investigator(s)	Sub-Investigator(s)	Site Coordinator
Advanced ENT Associates	Atlanta, GA	16	**Dr. Sam Mickelson**		Faraa Mobini
FutureSearch Trials of Neurology, L.P	Austin, TX	1	**Dr. John Hudson**	Dr. Robert Nason	Kevin Ford
Johns Hopkins Sleep Disorders Center	Baltimore, MD	17	**Dr. Alan Schwartz**	Dr. Luu Pharm Dr. David Eisele Dr. Jonathan Jun Dr. Philip Smith	Tracy Klopfer
ENT Associates of South Florida	Boca Raton, FL	6	**Dr. Nathan Nachlas**	Dr. Lee Mandel Dr. Melyssa Hancock	Patricia Manley
Medical University of South Carolina	Charleston, SC	4	**Dr. David Neskey**	Dr. Shaun A. Nguyen Dr Eric Lentsch Dr Ted Meyer	Kentira Rucker
ENT Associates of San Diego	Chula Vista, CA	3	**Dr. Paul Schalch**		Alen Putros
Intrepid Research	Cincinnati, OH	2	**Dr. Bruce Corser**	Dr. Joseph Hellman	Erica Eves
Morton Plant Mease Healthcare	Clearwater, FL	13	**Dr. Mitchell Miller**		Marietta Bibbs
Center for ENT and Allergy (CENTA)	Indianapolis, IN	7	**Dr. Tod Huntley**		Brandon Boyd
Cedars-Sinai Sinus and Sleep Apnea Center	Los Angeles, CA	9	**Dr. Martin Hopp**	Dr. David M. Alessi Dr. Robert O. Ruder Dr. Daryoush Saadat Dr. Raj Terkonda	Denice Dubuclet
Norton Healthcare (Formerly	Louisville, KY	8	**Dr. David Winslow**	Dr. Walter App Dr. Andrew Gould	Nancy McDonald

Kentucky Research Group)				Pamela Ann McCullough	
The University of Tennessee Health Science Centre	Memphis, TN	2	**Dr. M. Boyd Gillespie**		Ezer Benaim, MD
ENT and Allergy Associates	New York, NY	6	**Dr. Ofer Jacobowitz**		Catherine Parodo
SENTA Clinic	San Diego, CA	7	**Dr. Brian Weeks**	Jeannine Shively, PA	Allen Putros
OUS					
UCL Louvain Cliniques universitaires Saint-Luc Pneumologie	Bruxelles, Belgium	2	**Dr. Philippe Rombaux**		Tom de Vree
Bnai-Zion Medical Center	Haifa, Israel	12	**Dr. Arie Oliven**	Dr. Alexander Brodsky Dr. Ron Peled	Tzameret Avivi
Universität Klinikum	Mannheim, Germany	8	**Dr. Joachim Maurer**	Dr. J. Ulrich Sommer Dr. Anna Corlette Eichler Dr. Sarah Leitzbach	Oliver Schmidt
Hopital Pitié-Salpêtrière	Paris, France	1	**Dr. Valerie Attali**	Chloé Bertolus	Stéphane Attard
Hospital CUF Porto	Porto, Portugal	10	**Dr. Victor Certal**	Marta Gonçalves Rui Pratas	Sara Oliveira
Foch Hospital	Suresnes, France	4	**Dr. Frédéric Chabolle**	Marc Blumen	Sellami Sahar

Biostatistician

Role	Name	Affiliation
Medical Research Biostatistician	John Shen, MS	OcTech Consulting, Inc. St. Paul, MN

Clinical Events Committee

Role	Member	Affiliation	City, State
CEC Chairperson, Voting Member Otolaryngology, Head and Neck Surgeon	**Charles Tesar**	Sharp Memorial Hospital, San Diego	San Diego, California
CEC Voting Member Otolaryngology, Head and Neck Surgeon	**John Houck Jr., M.D**	Department of Otorhinolaryngology College of Medicine University of Oklahoma Health Science Center	Oklahoma City, Oklahoma
CEC Voting Member Pulmonary and Critical Care Medicine	**Steven Kavy, M.D**	Sharp Rees-Stealy Medical Group, San Diego	La Mesa, California
CEC Assistant *(for final CEC adjudicated AE data entry in the EDC)*	**Brita Lindstrom, R.N, MPH**		San Diego, California

Table e2. THN3 Trial Eligibility Criteria

Inclusion Criteria

1. Willing and capable of providing informed consent
2. Willing and capable of receiving the implant and utilizing the remote control and charger to activate the therapy and charge the implant
3. Willing and capable of returning for all follow-up evaluations and sleep studies
4. Willing and capable of completing all questionnaires
5. Is ≥ 18 years old
6. Has failed or does not tolerate PAP therapy
7. Has failed, refuses or is not indicated for alternative OSA treatments (e.g. surgery, oral appliances, and behavioral treatments)
8. AHI ≥ 20 (moderate to severe OSA) based on in-lab polysomnography studies conducted no more than 45 days prior to aura6000 system implantation

Exclusion criteria

General
1. Implanted with another active implantable device.
2. Actively enrolled in a clinical study of a different medical device or drug.

Concomitant Medications
3. Taking opioids, narcotics, medications or supplements that in the opinion of the investigator may alter consciousness, the pattern of respiration, sleep architecture, or with known effect on sleep-wake function or alertness.

Medical History
4. Currently receiving treatment for severe cardiac valvular dysfunction, NYHA Class III or IV heart failure, unstable angina or recent (< 6 month) myocardial infarction or cardiac arrhythmias.
5. Moderate to severe pulmonary hypertension defined as WHO Group II or higher.
6. Persistent uncontrolled hypertension (defined as systolic pressure ≥160 mm Hg or a diastolic pressure of ≥ 100 mm Hg) despite medications.
7. Neurodegenerative disorders or intrinsic neuromuscular disease or other neurologic deficits (e.g., multiple sclerosis, muscular dystrophy, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy, transient ischemic attack or cerebrovascular accident).
8. Active psychiatric disease (psychotic illness, major depression or acute anxiety attacks) that in the opinion of the investigator could prevent subject compliance with the requirements of the investigational study testing
9. Previous upper respiratory tract (URT) surgery (e.g., uvula, soft palate or tonsils) < 60 days prior to Screening PSG #1
10. Chronic obstructive pulmonary disease (FEV1: FVC ratio < 70) or vital capacity of < 80% predicted)
11. Active history of pulmonary disease (including COPD, emphysema, and asthma)
12. Need for chronic supplemental oxygen therapy for any reason, PaO2 < 70 mm Hg
13. Other sleep disorders that confound functional assessments of sleepiness, such as narcolepsy with cataplexy, idiopathic hypersomnolence, insomnia, REM sleep behavior disorder, or sleep movement disorders, such as restless leg syndrome or periodic limb movement, producing sleep disturbances unrelated to OSA.

Lifestyle / Work
14. Excessive use of alcohol, tobacco, caffeine, or recreational drugs.

15. Unwilling or unable to refrain from consumption of alcoholic beverages for 24 hours prior to the start of each PSG study
16. Unwilling or unable to refrain from use of PAP, oral appliances for OSA, positional devices, OSA surgery, or medications for OSA from enrollment through the completion of the Month 12 follow-up visit (except as permitted in the Control Group).
17. Subject has sleep hygiene behavior(s) that would substantially interfere with measurement outcomes during an overnight PSG study
18. Subject has an occupation for which untreated OSA presents a substantial risk to safety
19. Presence of occupational (shift work) or anticipation of shift changes (during the next two years)
20. Residing at, or planning to move within 2 years to a location where the subject would no longer be willing or capable of returning for all follow-up evaluations and sleep studies.

Physical Exam
21. BMI ≥ 35 kg/m2
22. Active systemic infection
23. Pedal edema grade ≥ 2+
24. Clinical evidence of renal insufficiency, acute or chronic renal failure, or undergoing dialysis or expected to institute dialysis within 6 months
25. Clinical evidence of immunodeficiency
26. Life expectancy of < 2 years
27. Any condition likely to require future MRI, diathermy or other procedure producing strong RF fields
28. Pregnant or planning to become pregnant in the next year (must have a negative serum or urine pregnancy test within 14 days prior to implant and maintain adequate contraception during the study)
29. Any reason for which, in the judgment of the investigator, the subject is considered to be a poor surgical or study candidate, which may include, but is not limited to: any medical, social, or psychological problems that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study

Upper Airway Exam
30. Tonsil grading system 3 and 4
31. Lingual Tonsil Hypertrophy Grading System (LTH) 3 and 4.
32. Friedman Tongue Position (FTP) IV
33. Hypoglossal nerve palsy (limited tongue movement or inability to move the tongue), tongue dysfunction, atrophy, hypertrophy, fasciculation, or problems swallowing or speaking.

Surgical Consult
34. Rhinitis or nasal obstruction that is not well-controlled by medication or prior surgery
35. Severe mandibular deficiency/retrognathia or syndromic craniofacial abnormalities.
36. Prior surgery interfering with surgical exposure or implant safety
37. Previous surgical resection or radiation therapy for cancer or congenital malformations in the larynx, tongue, or throat.
38. ASA Status ≥ 4
39. Subject has torticollis or neck or facial spasm that could increase the risk of dislodgement
40. Any reason for which, in the judgment of the investigator, the subject is considered to be a poor surgical or study candidate, which may include, but is not limited to: and medical, anatomical, social, or psychological problems that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study

PSG Criteria
41. AHI ≥ 65 on each of two screening polysomnograms (PSG)
42. Apnea Index (AI) > 30 events per hour on Screening PSGs

43. SaO2 >10% falls index > 15 events per hour on Screening PSGs
44. ≥ 10% central apnea events as a proportion of the sum of apnea and hypopnea events per hour on Screening PSGs
45. Positional OSA as defined by: non-supine AHI < 10 on Screening PSGs
46. Predominantly REM OSA as defined by: non-REM AHI < 20 and > 50% difference in AHI between the REM and non-REM sleep on Screening PSGs
47. Evidence of Cheyne-Stokes breathing.

Table e3. Adverse Events

The following summary of adverse events (AEs) include all related AEs reported through 365 days after system implantation. All AEs were adjudicated by the Clinical Events Committee and classified using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (version 21.0). Preferred terms were further grouped by the Principal Investigator (ARS) to provide a concise, organized safety summary. The tables include (1) serious related and unrelated/unknown AE, (2) Non-serious Procedure-Related AE, and (3) Non-serious Study-Related AE.

Three events did not resolve at the end of 12 months: a device lead issue, implant site pruritis, and incision site hypoesthesia. Four other events resolved with residua: insomnia, incision site hypoesthesia, glossodynia and decreased joint range of motion. All other events resolved without sequelae.

In addition, four serious non-related AEs were also reported: stress cardiomyopathy, esophageal adenocarcinoma, multiple fractures and malignant melanoma. All listings are current as of August 31, 2021. NOS, not otherwise specified; N/A, not available.

Serious Adverse Events			
Event Type	**Event Description**	**No. of events**	**% of patients with an event**
Study-related	Painful neck extension	1	0.7
	Electrode cuff dislodgement	1	0.7
Unrelated/Unknown	Esophageal cancer	1	0.7
	Bone fractures	1	0.7
	Cardiomyopathy	1	0.7
	Melanoma	1	0.7
Total events		**6**	**4.3**
Total no. patients		**6**	**4.3**

Non-Serious Procedure-Related Adverse Events (AE)		
Row Labels	**Sum of No.**	**% of patients with AE**
Cuff dislodgement	3	2.2
Lead visible in neck	1	0.7
Other post-op symptoms	1	0.7
Post-op discomfort not-related to incisions	6	4.3
Post-op discomfort related to incisions	17	12.3
Temporary tongue weakness	9	6.5
Temporary weakness	2	1.4
Wound healing (e.g., erythema, seroma)	21	15.2
Temporary incisional numbness	19	13.8
Total events	**79**	
Total no. patients	**46**	**33.3**

Non-Serious Study-Related Adverse Events (AE)		
Row Labels	**No. of events**	**% of patients with AE**
Device malfunction	2	1.4
Discomfort associated with device presence	7	5.1
Discomfort due to stimulation	46	33.3
Dry Mouth upon awakening	1	0.7
Electrode dislodgement	2	1.4
Lack or loss of therapeutic effect	13	9.4
Other symptoms*	6	4.3
Temporary external device usability or functionality complaint	2	1.4
Tongue abrasion	6	4.3
Total events	**85**	
Total no. patients	**54**	**39.1**
*Other symptoms include drooling, incisional erythema, headaches, insomnia, visible neck lead (1 patient in each)		

Table e4. Sleep Apnea Responses to Targeted Hypoglossal Nerve Stimulation

Apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) for Treatment and Control groups at baseline, Month 4 and Month 12/15. Means ± SD, medians with interquartile intervals, and probabilities of superiority are shown. Compared to the Control group, the Treatment group demonstrated therapeutic superiority in AHI and ODI at Month 4, but not at Baseline or at Month 12/15, since these probabilities and associated confidence intervals exceeded 0.50, reflecting untreated equivalence at Baseline, therapeutic improvement in the Treatment group at Month 4 and equivalent impact of THN in Treatment and Control groups at Month 12/15. Please note that the probability of superiority is reported due to the deviation of AHI and ODI from normality. The deviation takes two forms: (1) the underlying distribution of both AHI and ODI and especially (2) the heterogeneity of patient response to THN.

Table e4: **Summary of AHI over Time**						
AHI	**Baseline**		**Month 4**		**Month 12/15**	
(events/hr)	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**	**Control**
Mean ± SD	38.7 ± 10.07	35.4 ± 8.77	24.1 ± 20.04	32.0 ± 16.78	27.6 ± 20.87	26.1 ± 21.06
Median	36.8	34.6	17.1	31.8	19.7	18.1
(Q1, Q3)	(32.1 to 45.9)	(29.1 to 41.6)	(7.7 to 38.0)	(18.4 to 44.0)	(10.8 to 41.0)	(11.4 to 35.7)
Probability of Superiority (95% CI)	0.399 (0.300, 0.502)		0.646 (0.550, 0.738)		0.481 (0.377, 0.585)	
Summary of ODI over Time						
ODI	**Baseline**		**Month 4**		**Month 12/15**	
(events/hr)	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**	**Control**
Mean ± SD	37.4 ± 9.97	36.0 ± 9.47	26.3 ± 20.40	33.8 ± 17.07	27.0 ± 20.27	26.2 ± 20.79
Median	35.8	33.7	19.5	33.8	19.5	19.7
(Q1, Q3)	(31.5 to 44.6)	(29.2 to 43.6)	(9.6 to 39.6)	(19.6 to 49.3)	(11.8 to 38.9)	(12.7 to 38.2)
Probability of Superiority (95% CI)	0.461 (0.358, 0.566)		0.639 (0.541, 0.733)		0.495 (0.391, 0.599)	

Table e5. Sleep Apnea Responses to Targeted Hypoglossal Nerve Stimulation in REM vs. NREM Sleep

eTable 5. REM vs. NREM Sleep at Baseline and Month 12/15				
Endpoint	**Baseline**	**Month 12/15**	**Standardized Mean Difference (95% CI)**	**Probability of Superiority (95% CI)**
AHI, REM (events/hr) Mean (SD), N Median (Q1, Q3)	37.0 (17.1), 138 38.9 (24.4 to 49.6)	30.3 (22.2), 130 27.7 (12.0 to 47.0)	-0.358 (-0.600, -0.130)	0.638 (0.554, 0.723)
AHI, NREM (events/hr) Mean (SD), N Median (Q1, Q3)	36.8 (10.8), 138 35.1 (28.8 to 46.1)	26.0 (21.9), 134 18.5 (9.5 to 39.8)	-0.616 (-0.895, -0.376)	0.731 (0.657, 0.806)

Apnea hypopnea indices (AHI) are reported for Baseline (pre-implant) and 12-month time points, as well as for the change between time points, for the pooled Treatment and Control groups. NREM, non-rapid eye movement; REM, rapid eye movement; SD, standard deviation; IQR, interquartile range.

Table e6. Targeted Hypoglossal Nerve Stimulation Effect on Sleep Architecture at Month 12/15 (vs. Baseline)

eTable 6. Targeted Hypoglossal Nerve Stimulation Effect on Sleep States				
Endpoint	**Baseline**	**Month 12/15**	**Standardized Mean Difference (95% CI)**	**Probability of Superiority (95% CI)**
Total Sleep Time (min) Mean (SD), N Median (Q1, Q3)	351.2 (50.9), 138 351.3 (320.1 to 384.0)	322.4 (48.8), 134 320.3 (288.5 to 356.0)	-0.582 (-0.792, -0.387)	0.687 (0.604, 0.761)
N1 Sleep Time (min) Mean (SD), N Median (Q1, Q3)	79.8 (34.9), 138 75.9 (52.8 to 97.3)	57.3 (35.0), 134 49.5 (32.5 to 71.5)	-0.650 (-0.888, -0.444)	0.687 (0.604, 0.761)
N2 Sleep Time (min) Mean (SD), N Median (Q1, Q3)	200.6 (43.9), 138 202.9 (168.8 to 229.8)	192.0 (46.7), 134 191.0 (160.5 to 222.0)	-0.196 (-0.389, -0.005)	0.575 (0.493, 0.657)
N3 Sleep Time (min) Mean (SD), N Median (Q1, Q3)	13.8 (18.3), 138 4.8 (0.5 to 21.8)	12.9 (19.6), 134 1.5 (0.0 to 19.0)	-0.019 (-0.203, 0.157)	0.549 (0.470, 0.627)
REM Sleep Time (min) Mean (SD), N Median (Q1, Q3)	57.0 (24.7), 138 56.0 (41.3 to 71.3)	60.3 (31.3), 134 55.8 (39.0 to 84.0)	0.096 (-0.095, 0.290)	0.526 (0.440, 0.608)
Arousal Index (events/hr) Mean (SD), N Median (Q1, Q3)	60.5 (15.7), 138 57.4 (49.6 to 71.9)	46.4 (23.2), 134 40.1 (27.3 to 62.8)	-0.718 (-0.951, -0.519)	0.754 (0.679, 0.828)

Effect of targeted hypoglossal nerve stimulation on sleep stages, represented as mean, standard deviation (SD) and mean of each sleep stage divided by mean Total Sleep. Arousal Index is represented as #/hour.

Table e7. Snore Outcomes Survey (SOS) Responses to Target Hypoglossal Nerve Stimulation in Treatment and Control groups

The SOS utilizes Likert-type scales to characterize snoring intensity, duration and frequency as well as the potential relationship between snoring and sleep-disordered breathing symptoms. Lower scores indicate greater snoring severity and the potential for concomitant sleep-disordered breathing. Scores range from 0 to 100 on a normalized scale.

eTable 7. Snore Outcomes Survey (SOS) Responses to Target Hypoglossal Nerve Stimulation in Treatment and Control groups			
Endpoint	**Treatment (T)**	**Control (C)**	**Standardized Mean Difference T - C (95% CI)**
M4 SOS	32.1 (27.1, 37.3)	5.8 (1.8, 9.9)	1.428 (1.069, 1.858)
Endpoint	**Pooled 11M Active Therapy (P): Treatment (T) and Control (C)**		**Standardized Mean Difference P - 0 (95% CI)**
M12/15 SOS	36.6 (32.6, 40.5)		1.735 (1.509, 2.033)

Table e8. Responses in Other Outcomes to Targeted Hypoglossal Nerve Stimulation

eTable 8. Responses in Other Outcomes to Targeted Hypoglossal Nerve Stimulation				
Endpoint	**Baseline**	**Month 12/15**	**Standardized Mean Difference (95% CI)**	**Probability of Superiority (95% CI)**
Heart Rate (bpm) Mean (SD), N Median (Q1, Q3)	 76.3 (11.2), 137 76.0 (68.0 to 82.0)	 77.4 (12.0), 128 74.0 (68.5 to 87.5)	0.098 (-0.077, 0.277)	0.461 (0.374, 0.547)
Systolic Blood Pressure (mmHg) Mean (SD), N Median (Q1, Q3)	 130.8 (12.1), 138 130.0 (123.0 to 140.0)	 128.8 (12.7), 129 128.0 (120.0 to 136.0)	-0.177 (-0.380, 0.018)	0.566 (0.481, 0.647)
Diastolic Blood Pressure (mmHg) Mean (SD), N Median (Q1, Q3)	 83.1 (9.1), 138 83.5 (78.0 to 89.0)	 81.9 (8.8), 129 81.0 (75.0 to 88.0)	-0.130 (-0.336, 0.066)	0.558 (0.473, 0.640)
BMI (kg/m^2) Mean (SD), N Median (Q1, Q3)	 29.8 (3.0), 138 30.0 (27.7 to 32.1)	 30.0 (3.4), 130 29.9 (27.6 to 32.4)	0.085 (0.009, 0.163)	0.454 (0.369, 0.538)

Heart rate, blood pressure and body mass index (BMI) are reported for Baseline (pre-implant) and 12/15-month time points, as well as for the change between time points, for the pooled Treatment and Control groups. SD, standard deviation; IQR, interquartile range.

Table e9. Responses in Secondary Outcomes to Targeted Hypoglossal Nerve Stimulation between baseline and 12/15-month time points by responder status (Responders vs. Non-responders)

eTable 9. Responses in Secondary Outcomes to Targeted Hypoglossal Nerve Stimulation between baseline and 12/15-month time points by responder status (Responders vs. Non-responders)				
Endpoint	**Baseline**	**Month 12/15**	**Standardized Mean Difference (95% CI)**	**Probability of Superiority (95% CI)**
Responders, N = 57				
ESS Mean (SD), N Median (Q1, Q3)	11.7 (4.9), 56 12.0 (8.0 to 16.0)	6.7 (4.5), 57 5.0 (4.0 to 10.0)	-1.047 (-1.458, -0.742)	0.848 (0.759, 0.929)
FOSQ Mean (SD), N Median (Q1, Q3)	14.7 (3.5), 56 15.6 (12.1 to 17.3)	18.0 (2.2), 57 18.7 (16.7 to 19.7)	1.103 (0.823, 1.454)	0.857 (0.759, 0.938)
Systolic Blood Pressure (mmHg) Mean (SD), N Median (Q1, Q3)	129.7 (11.5), 57 130.0 (122.0 to 136.0)	126.8 (12.9), 55 124.0 (118.0 to 135.0)	-0.286 (-0.595, -0.008)	0.636 (0.509, 0.755)
Diastolic Blood Pressure (mmHg) Mean (SD), N Median (Q1, Q3)	82.5 (8.0), 57 84.0 (79.0 to 88.0)	80.4 (8.2), 55 80.0 (74.0 to 86.0)	-0.270 (-0.631, 0.037)	0.664 (0.545, 0.782)
BMI (kg/m^2) Mean (SD), N Median (Q1, Q3)	29.3 (3.2), 57 29.6 (27.2 to 31.5)	29.3 (3.4), 55 29.6 (27.0 to 31.6)	0.014 (-0.074, 0.106)	0.536 (0.409, 0.664)
Non-Responders, N = 77				
ESS Mean (SD), N Median (Q1, Q3)	11.2 (4.7), 76 11.0 (8.0 to 15.0)	6.5 (4.4), 76 6.0 (3.0 to 8.0)	-1.024 (-1.372, -0.763)	0.873 (0.800, 0.940)
FOSQ Mean (SD), N Median (Q1, Q3)	15.1 (3.0), 75 15.0 (12.7 to 17.5)	18.0 (2.2), 76 18.8 (17.0 to 19.7)	1.121 (0.837, 1.481)	0.872 (0.791, 0.939)
Systolic Blood Pressure (mmHg) Mean (SD), N Median (Q1, Q3)	131.2 (12.7), 77 130.0 (125.0 to 140.0)	130.2 (12.5), 74 130.5 (122.0 to 138.0)	-0.100 (-0.380, 0.179)	0.514 (0.399, 0.622)

* Change from Baseline to 12/15 Months. ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; BMI, body mass index.

Figure e1: Patient Flow Diagram.

Between May 2015 and June 2018, 138 patients were enrolled and implanted at 20 centers in the United States, Europe and Israel. Completion of enrollment required screening of 1,289 patients. The leading (≥5% of all exclusions) documented, non-mutually exclusive reasons for screen failure were AHI < 20 (17.9%), positional OSA (12.9%), REM OSA (10.6%), Friedman tongue position IV (6.0%), SaO_2 10% falls index > 15 (5.5%) and apnea index > 30 (5.1%).

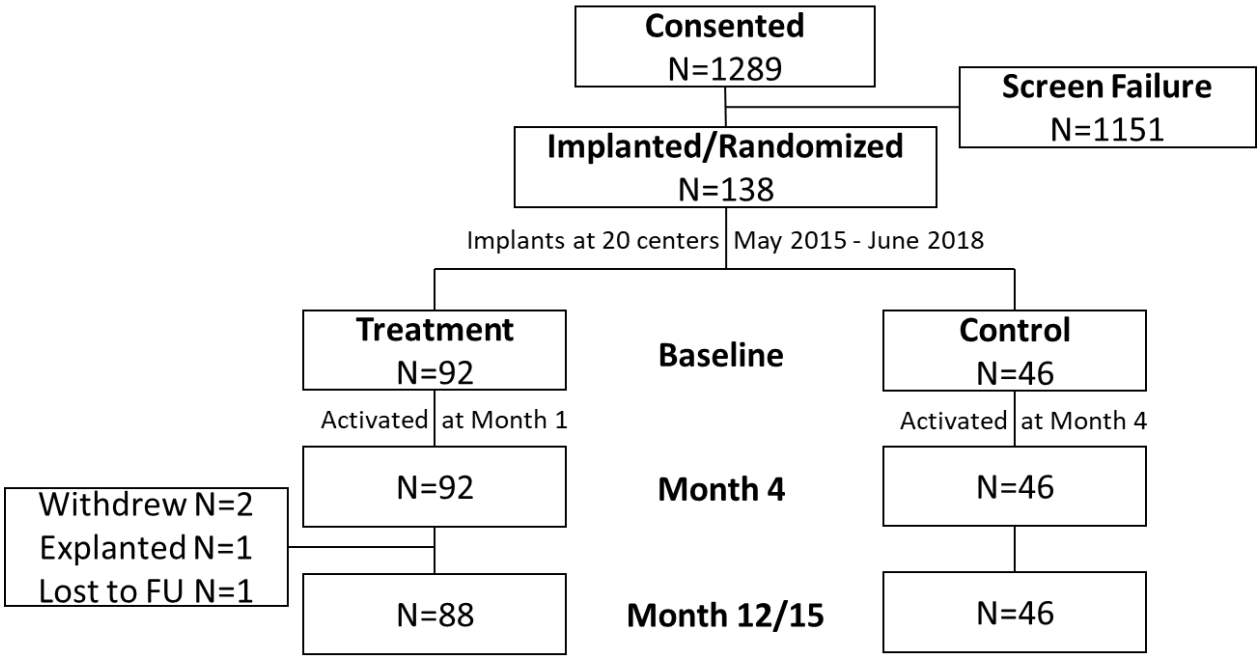


Figure e2. Trial Developments and Core Laboratory Cross-Validation

During the course of the trial, three developments occurred that were relevant to the study results. First, a conflict of interest was identified with the core laboratory charged with scoring the co-primary efficacy endpoints. This issue was resolved by engaging another core laboratory, which provided the polysomnographic results presented herein. Results of the two core laboratories were nonetheless comparable as assessed with Passing-Bablok regression. A representative example of the comparison is provided below for AHI at Month 4 for the Treatment and Control groups. Second. minor updates and improvements were made to the THN system's implanted pulse generator, remote control and charging antenna, resulting in two variants of each in the study. Third, accumulated experience with contact selection and stimulus titration led to greater standardization of the protocols used to optimize THN therapy (as illustrated in **Figure e3** below).

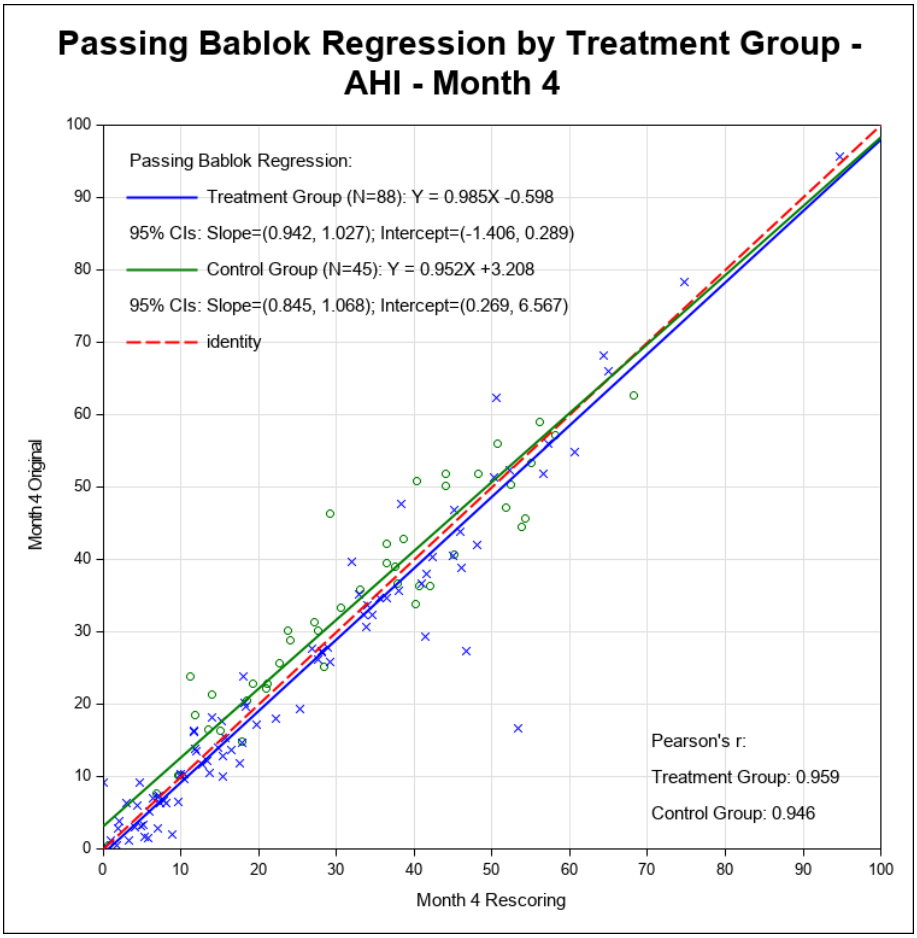
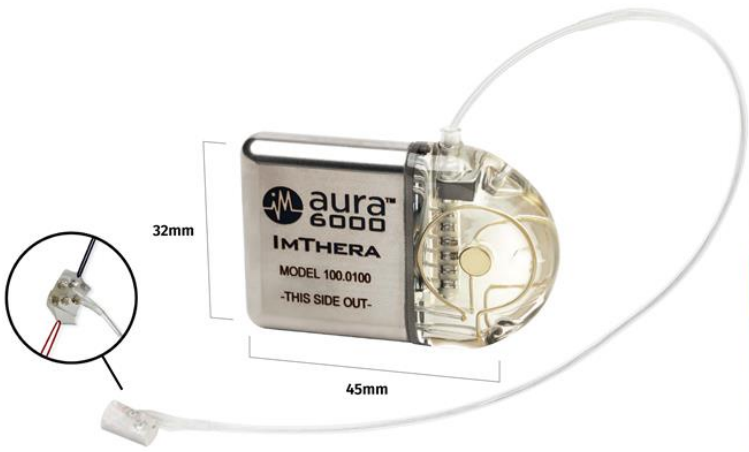


Figure e3. Targeted Hypoglossal Nerve Stimulation (THN) System

The THN System consisted of a combination of implanted and external components. A multi-contact circumferential lead was implanted around the proximal hypoglossal nerve and was connected to a rechargeable pulse generator implanted subcutaneously below the clavicle. External components enabled recharging and programming of the implanted pulse generator, consisting of a remote control with charging antenna and a laptop computer with a customized application program (not shown).



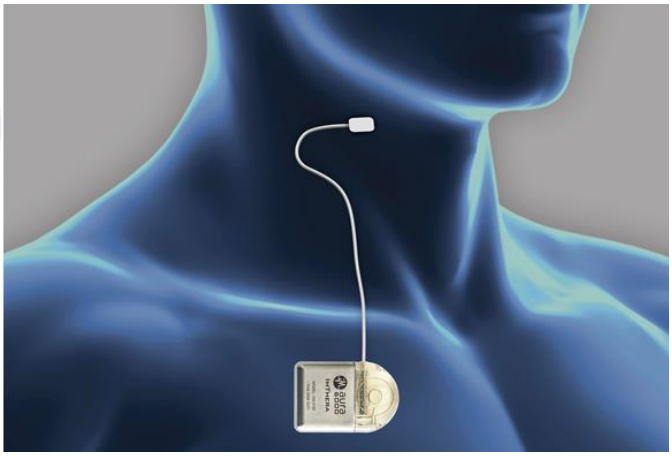
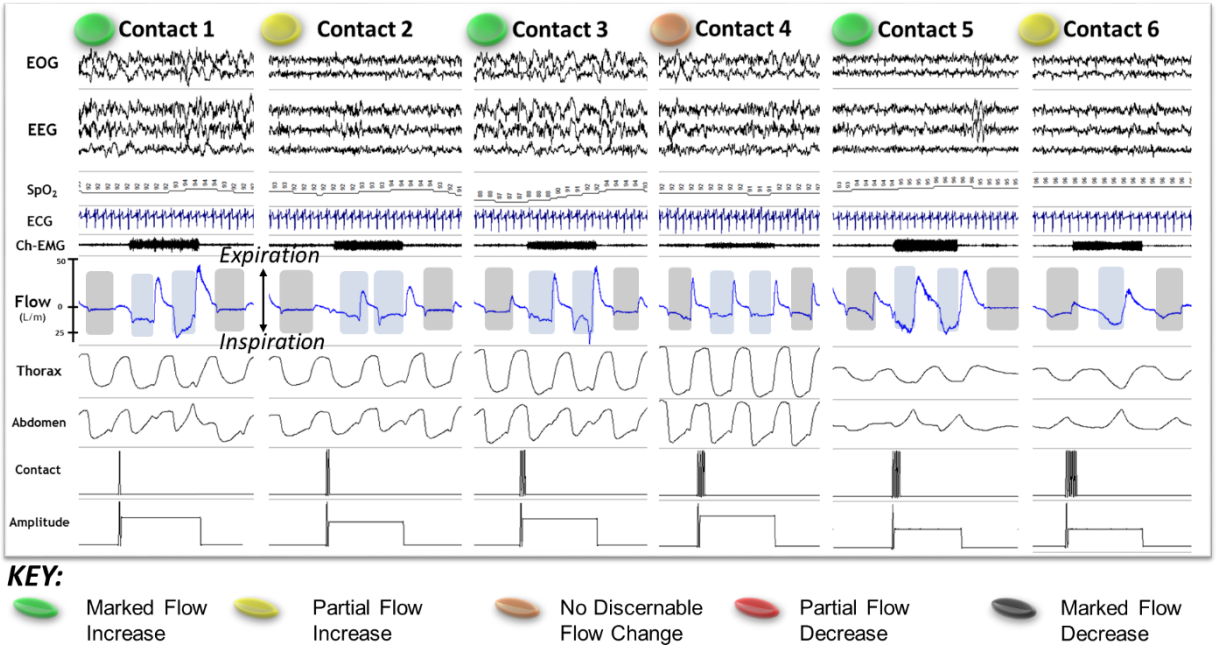
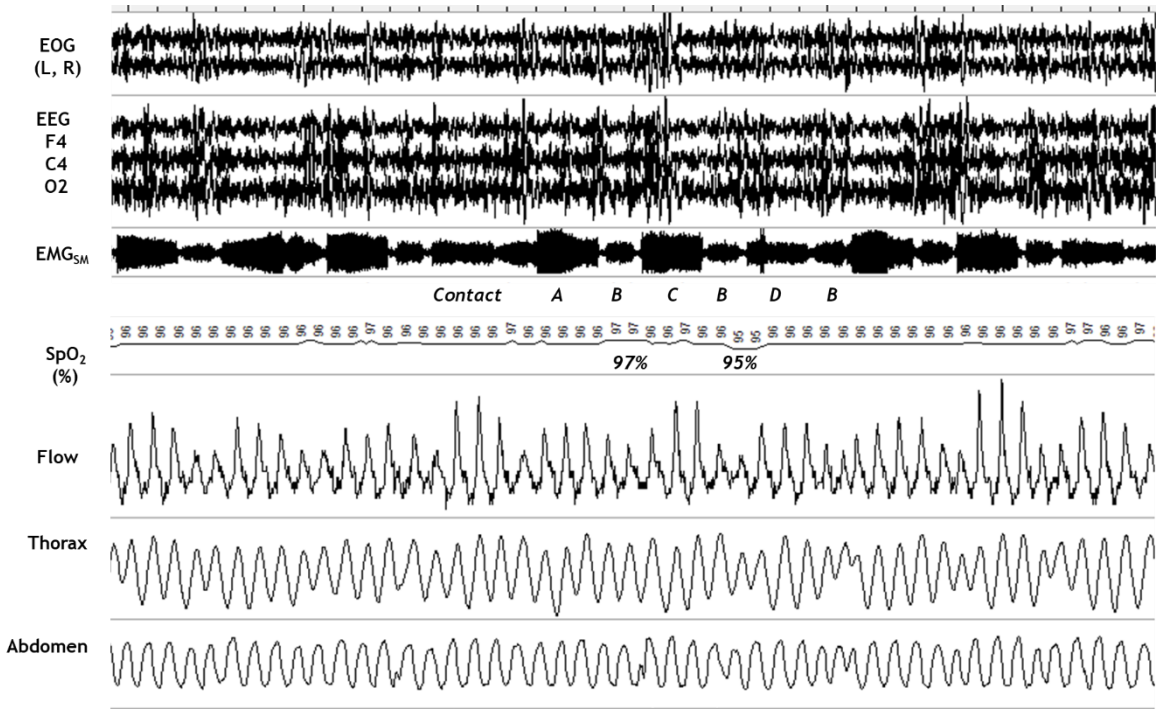


Figure e4: Polysomnographic Recording Examples illustrate approach to identifying potential therapeutic contacts (top) and assembling a multi-contact therapeutic regimen (bottom)



Polysomnographic recording examples contrasting flow responses to stimulating each contact separately during continuous non-REM sleep. Stimulation bursts appear as ~5s increases in EMG_{SM}. Stimulated inspirations are denoted with light blue-gray shading on flow tracing. Unstimulated inspirations are shaded gray. Stimulation results in variable changes in inspiratory airflow from increased to decreased levels of flow compared to adjacent breaths (see KEY at bottom of figure). After characterizing breath-wise responses in each electrode, two to three of the electrodes that generated robust increases in airflow (pharyngeal patency) were stimulated for several seconds in alternating fashion to evaluate therapeutic efficacy in the remainder of the night. Inspiratory airflow is represented by downward signal deflection. EOG, electrooculogram; EEG, electroencephalogram; SpO_2, pulse oximetry; ECG, electrocardiogram, EMG_{SM}, submental electromyogram; Flow, nasal airflow (inspiration down); Thorax and Abdomen, piezoelectric effort belts. Contact number and stimulation amplitude and duration are illustrated in bottom two channels.



3-minute polysomnographic recording example during multi-contact stimulation: EMG_{SM} stimulation bursts of a given duration were applied to four contacts in rotating order (A→B→C→B→D→B), separated by short intervening gaps off stimulation. Stimulation stabilized airflow, respiratory effort, oxygenation and sleep. Note variability in flow responses to stimulating specific contacts with somewhat greater levels of tidal airflow when stimulating contacts A, C and D compared to contact B. EOG, electrooculogram; EEG, electroencephalogram; SpO2, pulse oximetry; EMG_{SM}, submental electromyogram; Flow, nasal airflow; Thorax and Abdomen, piezoelectric effort belts.

Figure e5. Table and Box and Whisker Plots of Outcome Measures at Baseline and after Long-term Therapy in Treatment and Control Groups Combined

Clinically meaningful improvements in AHI, ODI, FOSQ and ESS following 11 months of treatment (follow up months 12 and 15 for Treatment and Control, respectively) were observed (all p<0.0001 for mean and median changes). Mean EQ-5D VAS and EQ-5D Index improved following 11 months of treatment with p-values of 0.0001 and 0.0072, respectively. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; FOSQ, Functional Outcomes of Sleep Questionnaire; ESS, Epworth Sleepiness Scale; EQ-5D VAS, Euro Quality of Life 5-Dimensions Visual Analog Scale; EQ-5D Index, US weighting of Euro Quality of Life 5-Dimensions scale.

Long Term Outcomes				
Endpoint	**Baseline**	**Month 12/15**	**Standardized Mean Difference (95% CI)**	**Probability of Superiority (95% CI)**
AHI (events/hr) Mean ± SD Median (Q1, Q3)	 37.9 ± 9.81 36.5 (31.0 to 44.9)	 27.6 ± 21.14 19.6 (11.4 to 41.0)	-0.614 (-0.906, -0.368)	0.709 (0.627, 0.784)
ODI (events/hr) Mean ± SD Median (Q1, Q3)	 37.3 ± 9.91 35.1 (31.2 to 44.6)	 27.2 ± 20.69 19.7 (11.9 to 39.8)	-0.612 (-0.897, -0.369)	0.739 (0.664, 0.813)
FOSQ-10 Mean ± SD Median (Q1, Q3)	 15.0 ± 3.17 15.0 (12.7 to 17.5)	 18.0 ± 2.20 18.8 (17.0 to 19.7)	1.114 (0.909, 1.353)	0.865 (0.804, 0.919)
ESS Mean ± SD Median (Q1, Q3)	 11.2 ± 4.83 11.0 (8.0 to 15.0)	 6.6 ± 4.44 6.0 (3.0 to 9.0)	-1.037 (-1.286, -0.833)	0.863 (0.805, 0.916)
EQ-5D VAS Mean ± SD Median (Q1, Q3)	 78.3 ± 14.82 80.0 (70.0 to 90.0)	 82.4 ± 11.19 85.0 (75.0 to 90.0)	0.326 (0.178, 0.479)	0.645 (0.569, 0.718)
EQ-5D Index Mean ± SD Median (Q1, Q3)	 0.90 ± 0.154 0.94 (0.84 to 1.00)	 0.92 ± 0.114 0.94 (0.88 to 1.00)	0.190 (0.030, 0.346)	0.550 (0.481, 0.615)

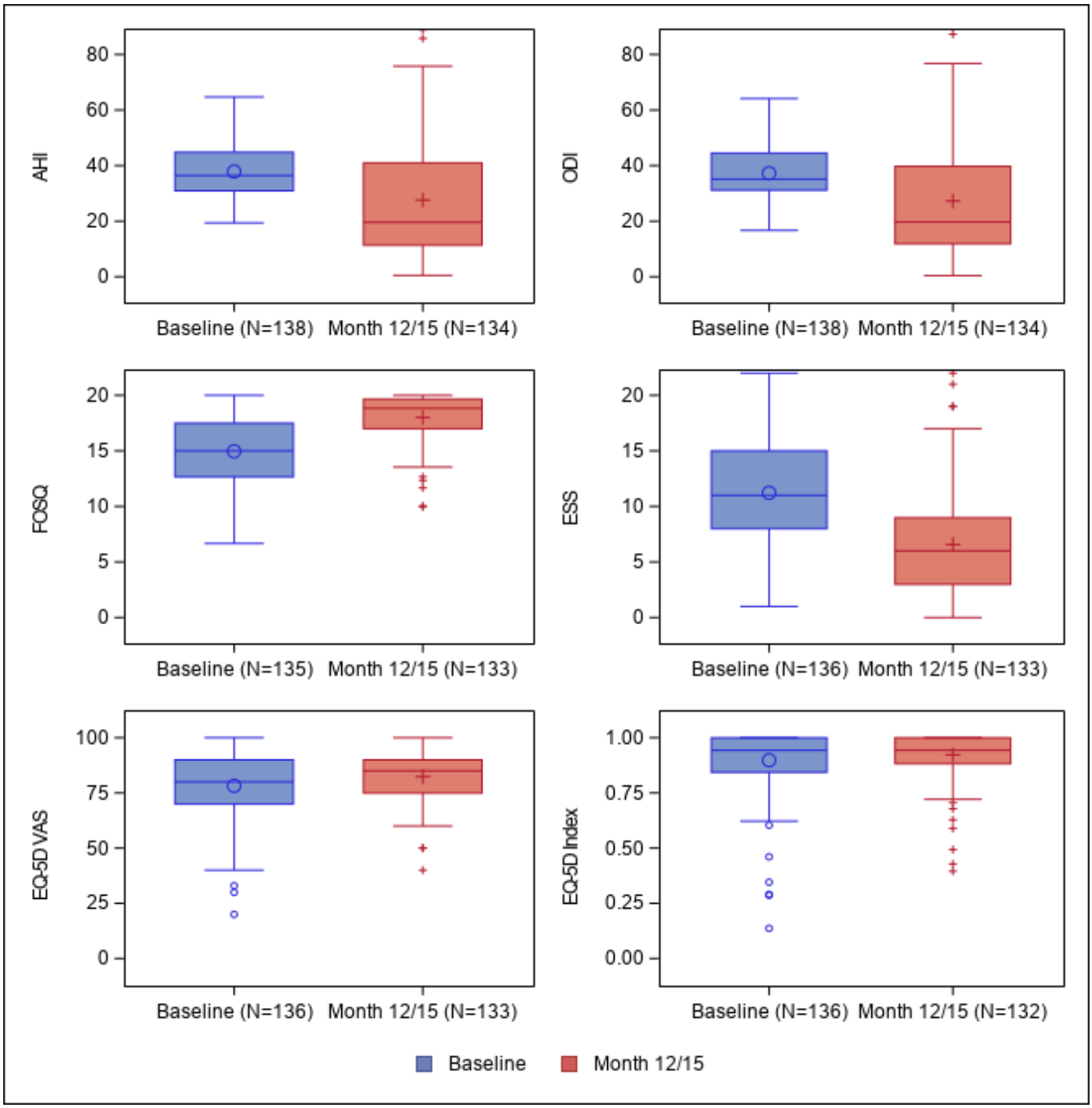
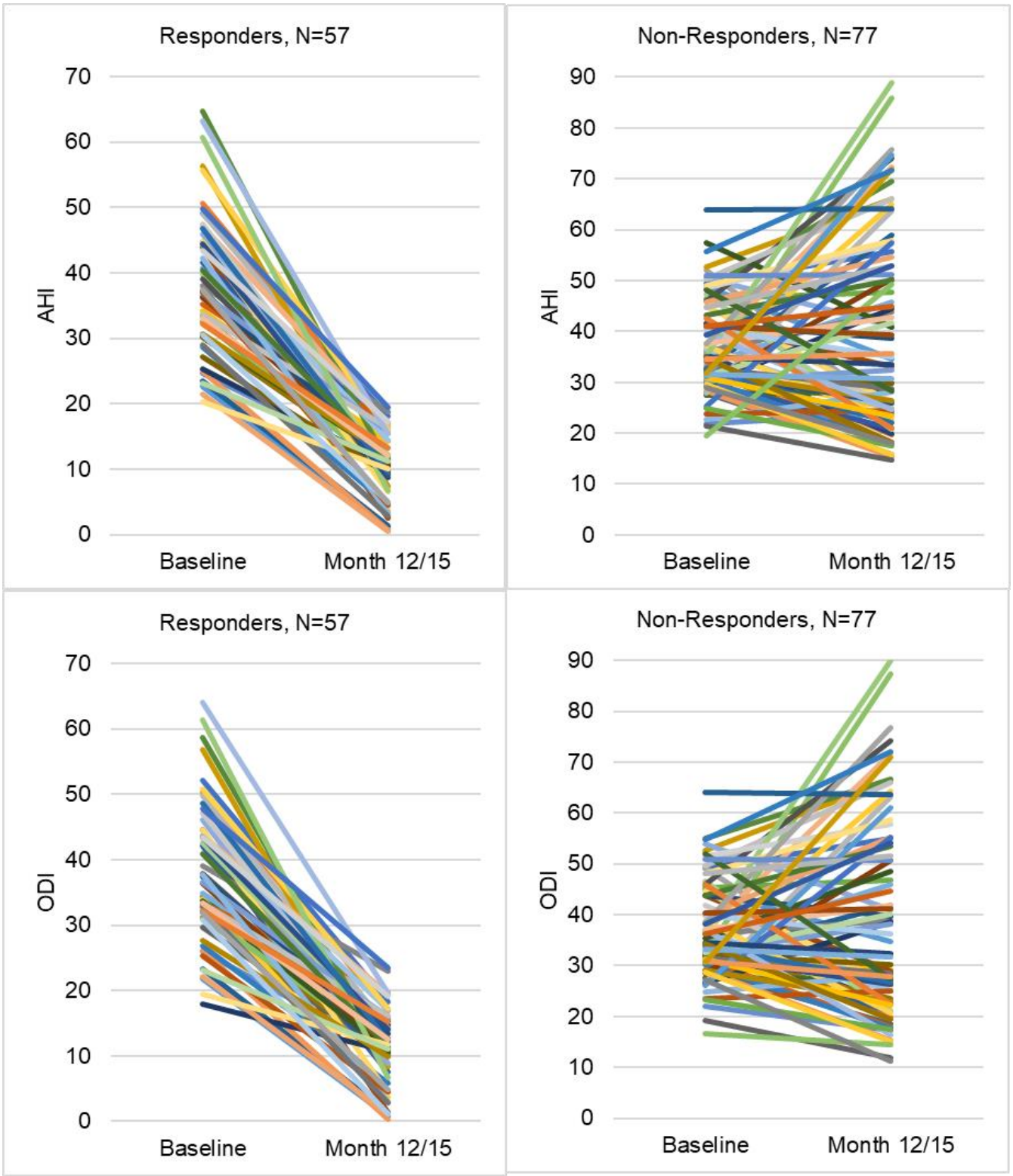


Figure e6. Changes in Sleep Apnea Indices in AHI Responders and Non-responders



AHI, apnea-hypopnea index; ODI, oxygen desaturation index.

References

1. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 2007.

2. Friedman M, Jacobowitz O, Hwang MS, et al. Targeted hypoglossal nerve stimulation for the treatment of obstructive sleep apnea: Six-month results. Laryngoscope 2016;126(11):2618–23.

3. Vargha A, Delaney HD. A Critique and Improvement of the CL Common Language Effect Size Statistics of McGraw and Wong. Journal of Educational and Behavioral Statistics 2016;25(2):101–32.

4. Strollo PJ Jr, Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. NEJM 2014;370(2):139–49.

5. Eastwood PR, Barnes M, MacKay SG, et al. Bilateral hypoglossal nerve stimulation for treatment of adult obstructive sleep apnoea. Eur Respir J 2020;55(1):1901320.

6. Eastwood PR, McEvoy D, Wheatley J, et al. Hypoglossal Nerve Stimulation Therapy to Treat Obstructive Sleep Apnea: Interim Feasibilty Trial Results. 2011;183:A2726.

7. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. Value Health 2019;22(8):931–41.

8. Op de Beeck S, Wellman A, Dieltjens M, et al. Endotypic mechanisms of successful hypoglossal nerve stimulation for obstructive sleep apnea. Am J Respir Crit Care Med 2021;203(6):746–55.