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Design and rationale for the treating obstructive sleep apnea using targeted hypoglossal neurostimulation (OSPREY) trial

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Abstract

Obstructive sleep apnea (OSA) affects nearly 1 billion people worldwide, including approximately 35 million US residents. OSA has detrimental cardiovascular and neurocognitive consequences. Positive airway pressure corrects sleep disordered breathing but is not always tolerated or used sufficiently. Oral appliances and surgery provide alternatives in select populations but are variably effective.

Hypoglossal nerve stimulation can effectively treat obstructive sleep apnea. Targeted hypoglossal nerve stimulation (THN) is simpler than incumbent technology with no sensor and an easier, proximal electrode implantation. The third clinical study of THN, THN3, was the first randomized, controlled trial of hypoglossal nerve stimulation to demonstrate significant improvement of sleep disordered breathing in OSA. The present investigation reports the design of a novel trial of targeted stimulation to provide additional Level 1 evidence in moderate to severe obstructive apnea.

OSPREY is a randomized, parallel-arm, 13-month trial wherein all subjects are implanted, 2/3 are activated at Month 1 (“Treatment”) and 1/3 are activated at Month 7 (“Control”). The primary endpoint is the difference in apnea-hypopnea index response rates between Treatment and Control groups at Month 7. Secondary endpoints include quality of life and oximetry metrics.

OSPREY follows an adaptive “Goldilocks” design which optimizes the number of subjects with the need for high-confidence results. A maximum of 150 subjects is allowed, at which study power

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Declaration of Competing Interest

None.

of >95% is predicted. Interim analyses begin once 50 patients are randomized and recur after each 20 additional randomizations to detect early success or futility.

OSPREY is a unique, efficient trial that should provide high-confidence confirmation of the safety and efficacy of targeted hypoglossal nerve stimulation for moderate to severe obstructive sleep apnea.

Keywords

Obstructive sleep apnea; Randomized; Controlled trial; Adaptive design; Surgical treatment; Hypoglossal nerve; Targeted hypoglossal nerve stimulation; Neurostimulation; Sleep

1. Background

Obstructive sleep apnea (OSA) is thought to affect up to 1 billion people worldwide although the majority remain undiagnosed and untreated [2]. In the US, conservative estimates suggest that at least 35 million patients are affected [31]. Moderate to severe OSA comprises around half of the global prevalence at approximately 450 million people [2]. OSA is known to have major neurocognitive and cardiovascular sequelae although optimizing treatment to prevent complications remains problematic [14].

Nasal CPAP (continuous positive airway pressure) is first line treatment for most OSA patients supported by evidence from randomized controlled trials (RCTs) [16,32]. However, CPAP effectiveness can be limited by variable adherence to therapy. PAP therapy can provide transformative benefits for some patients and up to 87% of PAP treated patients met Medicare criteria for therapy adherence when assessed wirelessly [24]. However, epidemiologic studies indicate adherence rates closer to 70% with significant disparities between women and men, younger versus older subjects, and with long-term adherence less than 50% for women under 30 [30]. Thus, there is a need for alternative therapeutic approaches [22]. Mandibular advancement devices are an alternative, although their efficacy is variable and long-term benefits are unclear [33]. Surgical upper airway reconstruction is clinically beneficial in selected patients, although surgery usually does not usually normalize apnea-hypopnea index (AHI) and entails short term morbidity and risk [5–7,17,19,21,38]. Pharmacotherapies have been proposed although none has well-established, long-term therapeutic benefit for OSA [18,36]. Hypoglossal nerve stimulation (HGNS) has been FDA approved since 2014, although randomized trials in this context are limited to short-term, randomized withdrawal in responders [23,35].

The third clinical study of Targeted Hypoglossal Nerve stimulation (THN), THN3, was the first completed parallel-arm, randomized, controlled trial of HGNS in OSA. The trial enrolled 138 moderate to severe OSA patients (AHI 20–65 events/h) at 20 international sites. Subjects were implanted and randomized 2:1 to active or inactive therapy treatment, respectively, for 3 months beginning 1 month after surgery. All patients thereafter received active therapy and were followed for a total of 11 months after therapy activation to either 12 or 15 months post-implant. Primary efficacy endpoints were based on AHI and oxygen desaturation index (ODI) response rates, with AHI response defined by the “Sher criteria”

(≥50% reduction vs. baseline and AHI < 20 events/h) and ODI response defined as ≥25% reduction versus baseline. The four co-primary endpoints required AHI and ODI response rates to be higher for active therapy versus inactive therapy at the end of the randomization period and the pooled 11-month active therapy AHI and ODI response rates to be >50%. Secondary endpoints consisted of the Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ) and EQ-5D visual analog scale, compared between active and inactive therapy at the conclusion of the randomization period. THN3 met all primary and secondary endpoints with the exception of AHI responder rate after 11 months of therapy. For the randomized portion of the trial, AHI response rates for active and inactive therapy groups were 52% and 20%, respectively, and for ODI 63% and 41%, respectively. Pooled AHI and ODI responses following 11 months of therapy were 41% and 63%, respectively.

While THN3 established the safety profile of THN therapy as favorable, the system design was updated to improve functionality and user experience. Therefore, the purpose of the present investigation is to report the design of a confirmatory randomized, controlled trial of THN therapy with the improved system in moderate to severe OSA.

2. Methods/design

2.1. Study design

The “treating Obstructive Sleep Apnea using Targeted Hypoglossal Nerve Stimulation” (OSPREY) study is a multi-center, open-label, prospective, randomized controlled trial of THN therapy via the aura6000® System (LivaNova PLC, London, UK). The trial is sponsored and funded in its entirety by the device manufacturer. The trial has been registered with ClinicalTrials.gov (www.clinicaltrials.gov, NCT04950894). OSPREY is to be conducted in accordance with the Declaration of Helsinki, with all subjects providing informed consent prior to participating in any study-related evaluation. The institutional review board or ethics committee of each site will approve the study protocol, consent forms and other relevant materials.

OSPREY will enroll adult patients with moderate to severe obstructive sleep apnea who report intolerance of or unwillingness to use PAP. During the randomized portion of the study, objective evidence of efficacy will be examined by assessment of improvement in sleep disordered breathing between subjects with active THN therapy (Treatment) versus those with an inactive device (Control). Thereafter, therapy will be initiated in the control group in the non-randomized phase. The Treatment and Control groups will be followed on therapy for a total of 12 and 6 months, respectively, to determine overall safety and efficacy. OSPREY will enroll up to 150 subjects globally at approximately 20 sites.

2.2. Study oversight

Three independent bodies will oversee the OSPREY trial. The Steering Committee (SC), comprising three physician-experts in sleep medicine and sleep surgery, who worked with the sponsor to design the trial, will supervise its operational activities, including site

selection, quality of study conduct, enrollment and maintenance of the study protocol. The SC will also participate in analysis of trial results and lead primary publication efforts.

The Data Safety and Monitoring Board (DSMB) also consists of three members, which include a biostatistician and physician specialists in sleep medicine and otorhinolaryngology. The DSMB will be responsible for monitoring the safety and well-being of the subjects participating in the study, ensuring the scientific integrity of OSPREY and recommending action items based on safety issues, including study termination, as warranted.

The Clinical Events Committee (CEC) is composed of three physicians with specialty training in sleep surgery, sleep medicine and otorhinolaryngology. The CEC will adjudicate adverse events from the trial to determine event type, potential impact to study endpoints and relationship of events to the device, stimulation or implant procedure. In this capacity, the CEC will review site-reported unexpected adverse device effects and provide clinical input.

2.3. Study population

Subjects ≥22 years old with moderate to severe OSA (AHI 20–65 events/h in an attended, in-laboratory polysomnogram (PSG)) who have failed or are unwilling to use PAP will be screened. Hypopnea is defined as a decrease in nasal pressure flow by ≥30% of baseline lasting at least 10 s with a ≥ 4% desaturation from pre-event baseline. Subjects will have a body mass index ≤35 kg/m^2. Importantly, drug induced sleep endoscopy is not required for qualification due to the different rationale for mechanism of action of THN therapy as compared to distal hypoglossal nerve stimulation technologies [39]. Study candidates will be drawn from each site's extant and incident patient populations, referrals from collaborating institutions and direction of local, pre-screened exogenous patients to the site by third-party trial recruitment agencies. It will be a goal of the study to distribute enrollment as evenly as feasible across participating sites.

For patients already within a site's practice, screening will begin with review of medical records, followed by education about THN therapy and the trial, in person or by telephone and will conclude with clinical and home-based evaluation. External patients would first learn of the trial through online portals and undergo pre-screening by telephone interview and medical record review by healthcare professionals employed by the recruiting agencies. Once qualified, they would be referred to the appropriate site study coordinator, at which time screening would continue as with patients who originated within the site's practice.

Detailed inclusion and exclusion criteria are presented in Tables 1 and 2, respectively. Eligibility criteria derive from several core motivations: (1) selecting subjects within the target population who are willing and able to provide informed consent and fulfill trial requirements, (2) limiting participation to subjects without concomitant conditions, treatments or habits that could confound collection/interpretation of endpoints or effective titration of therapy, and (3) excluding conditions which the device has not been designed to treat or under which its ability to perform safely has not been established. Eligibility criteria also include predictive factors identified in the multicenter feasibility study of THN therapy:

BMI < 35 kg/m^2, AHI < 65 events/h, apnea index ≤30 events/h, and SpO_2 desaturations of ≥10% fewer than 15/h [13].

Having fulfilled general eligibility criteria, subjects will be screened for concomitant sleep issues that might interfere with therapy delivery. The goal is to exclude characteristics adverse to effective therapy titration, indicative of comorbid sleep pathology unrelated to OSA and/or implicated by previous studies as unfavorable to response (Table 2, items 25 and 26). All subjects will begin by completing home sleep tests (HSTs) on two nights in close succession (WatchPat, Itamar Medical, Caesarea, Israel). HSTs will be processed by the vendor, interpreted by a sleep board-certified physician and reported to the site and sponsor. HSTs will be considered valid for screening purposes when approved by the interpreting physician and total recording time is at least 4 h. To qualify as eligible, subjects must demonstrate a repeatable sleep test outcome defined as HST-estimated AHI values (using 4% desaturation criteria) within 20 events/h of one another. HST results are not used for other screening purposes (e.g., HST results are not used to formally confirm moderate to severe OSA).

Adverse events (AEs) will be collected throughout the course of the study from the time of consent until study exit. AEs will be reported by the site to the sponsor via the electronic data capture system. AE definitions are derived from ISO 14155:2020 - Clinical investigation of medical devices for human subjects.

2.4. Baseline assessment

Subjects who have completed the HSTs and other Screening assessments successfully will proceed to Baseline assessment, at which the Baseline PSG and patient-reported outcome measures (PROMs) will be collected. PROMs will include ESS, FOSQ-10, the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Index (SDI-8) and Sleep-Related Impairment (SRI-8) inventories and SF6-D (derived from SF-36) and EQ-5D-5L quality-of-life instruments. Subjects have the option to complete PROM questionnaires during baseline and endpoint visits electronically or in paper form. Paper results will be entered into the electronic data capture system by the study coordinator. PSGs will be submitted to an independent central laboratory for review and scoring using filenames generated with an undivulged code. Scoring will be conducted manually (Alice with Sleepware G3, Philips Respironics Inc., Murrysville, Pennsylvania) and adhere to the American Academy of Sleep Medicine guidelines [1,3] for scoring hypopneas based on a nasal pressure drop of 30% or greater and a desaturation of 4%. Oxygen desaturation index (ODI) will likewise be scored according to a 4% desaturation threshold. Due to the visibility of stimulation artifact in PSG recordings, it is not possible to fully blind the core laboratory scorer. Specific inclusion/exclusion criteria will be applied (Table 2, criteria 25 and 26) and subjects who fulfill all eligibility criteria will proceed to implant.

2.5. Implant

The THN therapy system may be implanted either as an inpatient or outpatient procedure. The implant process has been previously described [13]. Briefly, the implantable portion of the THN therapy system consists of two components: a multi-programmable and

rechargeable implanted pulse generator (IPG) and a hypoglossal nerve cuff electrode lead (Fig. 1). The system is implanted unilaterally, typically on the right side. The cuff portion of the lead includes six independent contacts arranged circumferentially in a helical pattern to provide multiple loci for stimulating the nerve. The cuff is implanted around the proximal hypoglossal nerve, in the submandibular region. After being secured in place and looped for strain relief, the remainder of the lead is delivered using a hollow canula subcutaneously to the pectoral pocket for the IPG. The lead is connected to the IPG, and tongue muscle activity and impedance measurements within the expected range are confirmed for each contact. The IPG is then placed in the pocket and the surgical incisions are closed. An experienced implanter completes the procedure in approximately 1–1.5 h. Didactic and practical training (cadaver laboratory and/or proctored procedures) is required for each surgeon to qualify as an implanter. In addition, a sponsor representative attends each surgery to support the procedure and perform testing of the device.

2.6. Randomization

Seven to 20 days following implant, subjects will report to the study site to assess surgical healing and to receive a randomization assignment (Fig. 2). Allocation to Treatment and Control groups will follow a 2:1 ratio to obtain greater experience with active therapy and to facilitate patient enrollment and retention. Subjects will be preferentially allocated using a process of minimization by means of an automated, computerized algorithm [8]. The process will seek to ensure balance between the two study groups in Baseline AHI, BMI and tonsil size. The procedure allocates the first subject to Treatment or Control at random. Subsequent subjects are dynamically allocated according to whichever study arm leads to better balance. That is, the allocation seeks to minimize differences in AHI, BMI and Tonsil Size. At the time of randomization, the study coordinator requests the assignment for the patient through the electronic data capture system, at which time the assignment is automatically generated by computer according to the process described above. Subject blinding is not possible as they manually control therapy and can perceive its effects.

2.7. Concomitant treatments

Following consent and during participation in OSPREY, subjects will not be allowed to use adjunct treatments for their OSA, with the exception of the control group. The control group may continue using OSA treatments (except PAP or undergoing upper airway surgery) until 14 days prior to the Month 7 PSG. Permissible treatments include oral appliances, positional therapy, supplemental oxygen, upper airway muscle exercises, weight loss and lifestyle management (e.g., abstinence from alcohol, caffeine and heavy meals before sleep).

2.8. Randomized phase

The OSPREY follow-up schedule is illustrated in Fig. 3. One month following implant, all subjects present for general examination and review of current treatments. Treatment group subjects undergo additional procedures, including evaluation of stimulation impedances and awake stimulation with each contact to determine amplitudes at which patients sense stimulation (sensory threshold) and discomfort (sensory limit). Treatment group patients will be provided with training on using the THN therapy system at home. Finally, Treatment subjects undergo PSG for activation of THN therapy and initial titration.

After Month 1, subjects assigned to both trial arms return for monthly follow-up. Control subjects return for office visits at Months 3, 5 and 7 and receive telephone follow-up at Months 2, 4 and 6. Treatment arm subjects attend office visits monthly through Month 7 and undergo PSG with the opportunity for titration at Months 2, 3 (two successive nights) and 6, while PSGs optionally occur at Months 4 and 5. The primary endpoint PSG is collected in both arms at Month 7.

Titration during PSG is guided by capture and sensory thresholds and subjective responses to stimulation from awake subjects and is based on prior clinical experience. During sleep, the process begins with evaluation of each of the 6 electrode cuff contacts to determine the potential to increase airway patency at a given stimulation intensity. Stimulation is initiated below capture threshold and gradually escalated until an effect is noted on the nasal pressure (tidal airflow) signal or the sensory limit is reached with an arousal. Contacts demonstrating the greatest increase in airflow and improvement in sleep disordered breathing without causing arousals are selected for further evaluation. Usually 2–3 of 6 contacts are included in the therapeutic regimen. Beneficial contacts are next combined in repeating sequences of stimulation. Therapy parameters (amplitude, pulse duration, frequency and contact on time) are adjusted to achieve maximum efficacy. The impact of candidate sequences on airway patency is assessed throughout sleep stages and body positions over the course of the night. If necessary, parameters are further optimized to maintain stable ventilation, oxygenation and sleep. The most beneficial sequence and stimulation parameters are selected as the chronic therapeutic program. All titrations in OSPREY are performed by trained representatives of the sponsor. Titration may occur during any PSG session except Baseline and the endpoints at Months 7 and 13.

2.9. Nonrandomized phase

Following collection of the primary efficacy data at Month 7, subjects enter the nonrandomized phase of the trial. Control subjects immediately undergo a second night of polysomnography to initiate therapy as part of their follow-up schedule, which mirrors the Treatment group schedule of from Month 1 to Month 7. For treatment arm subjects, telephone follow-up occurs at Month 8, 10 and 12 with office visits at Month 9, 11 and 13. An optional PSG with the opportunity for titration occurs at Month 9 and a mandatory PSG is performed at Month 11. All subjects have a final endpoint PSG performed at Month 13 and thereafter exit the study.

2.10. Objectives

The primary objective of OSPREY is to demonstrate the safety and effectiveness of the THN therapy system in ameliorating sleep disordered breathing associated with OSA after 6 months of stimulation compared to a control group with no stimulation.

2.11. Outcomes

The primary safety endpoint is a descriptive evaluation of all reported serious adverse device/procedure related events through Month 7 for the Treatment and Control groups. Relationship to procedure, device and study will be adjudicated by the CEC.

The primary efficacy endpoint is to demonstrate that the AHI responder rate of subjects with active device stimulation (Treatment Group) is statistically significantly higher than subjects with the inactive device (Control Group) at Month 7. Responder status is defined as reduction in AHI from Baseline of at least 50% and an AHI of less than 20 events/h.

Secondary endpoints include measurements of improvement in the Treatment group from Baseline to Month 7 in ODI, ESS, FOSQ, PROMIS SDI and SRI, SF-6D, EQ-5D and T90, the proportion of time per hour of sleep spent with arterial blood oxygen saturation less than 90%. THN therapy compliance will also be reported.

2.12. Statistical analysis

2.12.1. Maximum sample size—OSPREY is designed to have approximately 97% power at its maximum sample size of 150 evaluable subjects to detect a significant difference (one-sided p-value <0.025) in the AHI response rate between the Treatment and Control groups (Table 3). The sample size is based on the results of the THN3 study (NCT02263859), in which the AHI responder rate following 3 months of THN therapy in the Treatment group ($N = 88$) was 52% while the Control group ($N = 45$) responder rate was 20%. A superiority evaluation of clinically significant response rates is utilized because no criteria for minimum clinically important difference in response rate has been established.

2.12.2. Bayesian design and data analysis—OSPREY is designed according to Bayesian principles, employing a “Goldilocks” design [4] which allows optimization of enrollment accrual to predict early success or early futility with high confidence while minimizing the exposure of subjects to experimental therapy. Data analysis will consist of a series of interim analyses beginning when the number of randomized subjects reaches 50. Interim analyses are scheduled to take place after every additional 20 subjects are randomized, up to the maximum sample size of 150.

At each interim analysis, the study primary endpoint is evaluated according to intention-to-treat principles. Sher criteria are to be used to assess AHI response for subjects who have completed 7 months of follow-up and is the only parameter used for interim analyses. For subjects who have not yet reached 7 months of follow-up, a Bayesian model will be used to impute whether a patient is an AHI responder or non-responder for each follow up visit. The modeling is based on a beta-binomial distribution derived from a non-informative prior distribution which has been updated with the number of responding and non-responding subjects at each follow-up within the trial. The interim analysis involves calculation of two predictive probabilities which relate to the possibility of trial success. The predictive probability of trial success with the present subjects randomized (PP_n) is defined as the predictive probability that the Treatment group AHI responder rate will be significantly higher than the Control group if the trial stops accrual immediately and all enrolled subjects complete the Month 7 follow-up. PP_n is calculated by applying the Bayesian modeling framework thousands of times. The proportion of imputed complete datasets that achieve statistical significance for the primary efficacy endpoint is the predictive probability of trial success. Early success is declared if PP_n exceeds a size-dependent (number of patients randomized) threshold which conservatively restricts the potential of a false positive result

(Table 3). The predictive probability of trial success at the maximum sample size, PP_{max}, is defined as the predictive probability that the AHI responder rate of the Treatment group will be significantly higher than the Control group if the study randomizes the maximum sample size of 150 evaluable subjects. Futility is declared if PP_{max} is less than a size-dependent threshold that restricts the potential for a false negative trial result. Interim analyses will be conducted by an independent statistician and the results reported to the DSMB for review and sponsor notification.

In the final analysis, the primary efficacy endpoint will be analyzed on an intention-to-treat basis using the one-sided Fisher's exact test (test of Treatment vs. Control AHI response rate superiority) at the $\alpha = 0.025$ significance level. For other efficacy endpoints, changes from Baseline in the Treatment group and treatment effect differences between the Treatment and Control arms, together with two-tailed 95% confidence intervals, will be generated and reported with relevant *p*-values. Secondary endpoints are not individually powered and no corrections are planned for multiple comparisons. However, they will be hierarchically evaluated in the order previously listed. Month 13 efficacy outcomes will be reported relative to Baseline to provide evidence of long-term, sustained therapeutic benefit. Likewise, AE data to Month 13 will establish the long-term safety profile of THN therapy. Results of the trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) and the adaptive designs CONSORT extension.

3. Discussion

We view the OSPREY study as an important advance for the treatment of OSA for several reasons. First, the study design is unique for HGNS trials since it is based on a parallel group randomized controlled trial with an adaptive design. In contrast, the current literature is primarily focused on single arm treatment trials, observational studies and patient registries and various responder analyses [15,35,37]. Second, we have produced an efficient design that should allow enrollment of patients and a relatively rapid definitive conclusion. Third, our design will minimize the exposure of patients to experimental therapies through a 6 month randomized phase in accordance with precedent and expert consensus [11,26].

The optimal study design for alternative therapies for OSA is under debate. Based on existing literature, some have argued that withholding of CPAP may be unethical. However, controlled studies of CPAP have failed to show benefits in many cases, perhaps due to suboptimal therapy adherence in relatively asymptomatic patients [20,27]. Thus, surgical therapies which do not require treatment compliance may be helpful given the limitations of existing therapy [21,38]. One study design could include a head-to-head comparison of HGNS vs. CPAP with the assumption that CPAP may have good efficacy but limited effectiveness based on adherence to treatment. Although comparative effectiveness studies would clearly have value [10], we do not view HGNS as competitive with CPAP but rather a useful alternative for select patients. As a result, we have designed OSPREY to target patients who cannot or will not tolerate PAP therapy to facilitate rescue approaches in the future.

The STAR trial of HGNS was published in 2014 [35]. The authors reported a prospective observational case series in which improvements in AHI were observed in association with HGNS. The investigators performed a randomized withdrawal study in which patients who responded to HGNS were randomized to continued therapy versus discontinuation of HGNS. The results provided compelling evidence for HGNS use in some patients but the design of the randomized withdrawal is limited to assessments in the 'responder' group. Longitudinal observational studies can also be limited by changes over time such as those secondary to diet and exercise or other health behaviors. The Hawthorne effect can likewise be relevant where health outcomes can improve in the context of a clinical study when participants are aware that their health status is being assessed. Although observational studies have value, randomized trials such as OSPREY may better handle certain biases or confounding factors and may allow drawing of causal inferences [28,29].

Despite the strengths of OSPREY, we acknowledge a number of limitations. First, it is not powered or of sufficient duration for clinical outcomes such as myocardial infarction or cerebrovascular events [34]. However, the endpoints include important objective and subjective outcomes which would provide compelling rationale for future studies. We recognize the limitations of the AHI [25] and AHI responder rate, but they are required metrics for regulatory approval and comparison with other HGNS trials. Second, given that HGNS is FDA approved, one cannot be confident that OSPREY is without selection bias by the candidates or investigators since some candidates may opt for commercially available HGNS treatment rather than enrolling in the study. However, since the benefits of HGNS are still debated, as is the cost versus benefit, further evidence will be useful. Third, there are additional HGNS approaches under investigation, a fact that may be important to consider in the context of the OSPREY results [12]. Since head-to-head comparisons with other HGNS devices or with pharmacotherapy is not being performed in OSPREY, future comparative effectiveness studies would be needed to draw rigorous conclusions [9]. Finally, as with other trials of HGNS, restrictive eligibility criteria will result in substantial attrition in the patient funnel but are important to reduce heterogeneity that would confound assessment of outcomes. Despite these limitations, we view OSPREY as well designed and likely to yield important conclusions.

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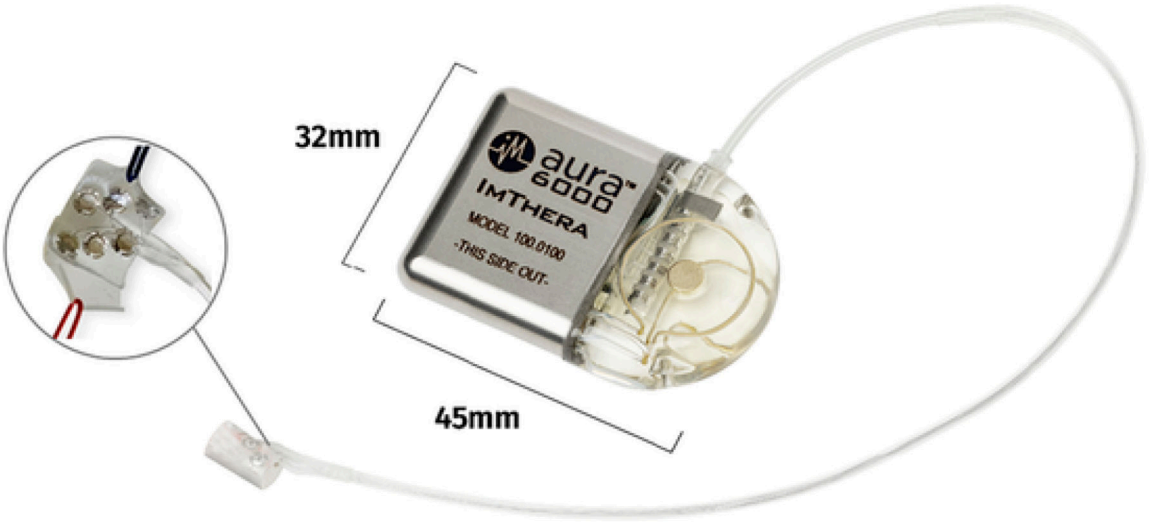

Fig. 1.
The Aura6000® targeted hypoglossal nerve (THN) therapy system with inset image detailing arrangement of electrode contacts.

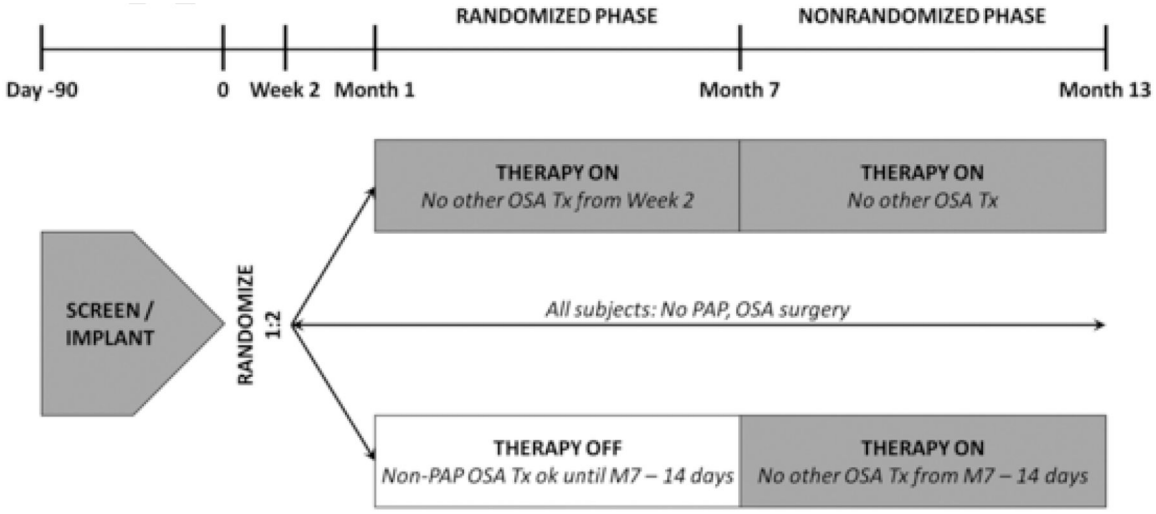

Fig. 2.

OSPREY trial schematic. Positive airway pressure therapies are not allowed at any time during the study. During the majority of the randomization period, the control group may continue using oral appliances, positional therapy, supplemental oxygen, upper airway exercises and lifestyle management strategies.

Randomized Phase	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
Treatment	🏢 🛏 ⚡	🏢 🛏	🏢 🛏 x2	🏢 🛏 *	🏢 🛏 *	🏢 🛏	🏢 🛏 ⚠
Control	🏢	☎	🏢	☎	🏢	☎	🏢 🛏 ⚠
Nonrandomized Phase	**Month 7 + 1 Day**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**Month 13**
Treatment	✕	☎	🏢 🛏 *	☎	🏢 🛏	☎	🏢 🛏 ⚠
Control	🏢 🛏 ⚡	🏢 🛏	🏢 🛏 x2	🏢 🛏 *	🏢 🛏 *	🏢 🛏	🏢 🛏 ⚠

Symbol	Meaning
🏢	Office visit
☎	Phone call
✕	No follow-up
🛏	Polysomnogram
⚡	Therapy activation
⚠	Endpoint
x2	2 successive nights
*	Optional

Fig. 3.
OSPREY time and events schedule.

Table 1

General inclusion criteria.

1	The patient is willing and capable of providing informed consent.
2	The patient is at least 22 years of age.
3	The patient is willing and capable of: • Using the remote control and charger to activate the therapy and charge the implant (assessed by the site), and • Completing all questionnaires.
4	The patient is willing and capable of returning for all follow-up evaluations and sleep studies for the duration of the study.
5	The patient has documented diagnosis of moderate to severe OSA with an AHI of at least 20 using the AASM guideline for scoring hypopneas based a nasal pressure drop of 30% or greater and a desaturation of 4%.
6	The patient declines to use or does not tolerate PAP therapy.
7	The patient expresses no difficulty with sleeping in unfamiliar environments and can do so without the use of drugs or medications.

Table 2

General exclusion criteria.

1	The patient is implanted with another active implantable device that could experience an unintended interaction with the aura6000® System.
2	The patient is enrolled in another clinical study that may confound the endpoint of this study.
3	The patient is dependent on or frequently taking medications (such as opioids, narcotics, or stimulants) that significantly alter consciousness, the pattern of respiration, sleep architecture, or with known effect on sleep-wake function or alertness.
4	The patient has difficulty falling asleep and/or uses a hypnotic for insomnia more than twice a month.
5	The patient has moderate to severe (or poorly controlled) respiratory disease (e.g. COPD such as emphysema, TB, chest wall disease, uncontrolled asthma, allergic rhinitis, etc.), or is on supplemental oxygen therapy for any reason.
6	The patient has one or more of the following: moderate to severe heart failure, in the assessment of the investigator, [NOTE: NYHA Class II or above], or a history of persistent atrial fibrillation, unstable angina, recent history of MI (<6 m), severe cardiac arrhythmias, or uncontrolled systemic or pulmonary hypertension.
7	The patient has neurological, neuromuscular, or neurodegenerative disorders (e.g. TIA, CVA, Parkinson's, Multiple Sclerosis, Muscular Dystrophy, epilepsy, diagnosed memory dysfunction, etc.).
8	The patient has other sleep disorders that, in the opinion of the Investigator, could confound functional assessment of sleepiness (e.g. narcolepsy, insomnia, etc.) or sleep movement disorders (e.g. restless leg syndrome (RLS), periodic limb movement (PLM) disorder), or that may cause sleep disturbances unrelated to OSA.
9	The patient has an active psychiatric condition that might, in the opinion of the investigator, interfere with the patient's compliance with the protocol, or effect endpoints' assessment (e.g., severe depression, schizophrenia, bipolar disorder, etc.)
10	The patient has an active systemic infection.
11	The patient has been institutionalized for treatment of alcohol, tobacco, or recreational drug use within the last 12 months and/or has a history of habitual binge drinking. Must also be willing to refrain from alcohol use on the day of ALL PSGs.
12	The patient is unwilling or unable to refrain from other OSA treatments including PAP, oral appliances, surgery, or medications, from enrollment (consent) through the completion of the M13 visit. (guidelines for the Control group are found in Section 6.3.2).
13	The patient has sleep hygiene behavior(s) that would substantially interfere with the study or its outcome assessment (e.g. shift work, sleeps less than 5 h a night, psychophysiological insomnia, etc.).
14	The patient has a BMI > 35 kg/m^2.
15	The patient exhibits clinical evidence of renal insufficiency, acute or chronic renal failure, or undergoing or expected to undergo dialysis in the future.
16	The patient has a condition likely to require future MRI, diathermy or other procedure producing strong radio frequency (RF) fields.
17	The patient is pregnant or planning to become pregnant between consent and the final M13 visit, must also be willing to use a contraception method during this time (pre-menopausal women only).
18	The patient has another reason the Investigator feels (s)he is a poor candidate for participation in the study (e.g. prior radiation therapy for cancer treatment, pre-existing hypoglossal nerve damage, various palsies, cranio-facial or bony trauma, etc.).
19	The patient requires the use of aspirin, NSAIDS or anti-coagulant medications that cannot be safely stopped at least 7 days prior to the scheduled implant.
20	The patient has conditions causing chronic pain that may affect the subject's ability to sleep comfortably in the sleep lab (e.g. herniated discs, degenerative disc disease, sciatic nerve pain, etc.).
21	The patient whose upper airway exam has a palatine or lingual tonsil grading system of 3 or 4, or HGN palsy.
22	The patient has obstructive upper airway lesions (e.g. tumors, polyps, etc.), or severe septal deviation.
23	The patient exhibits evidence of Cheyne-Stokes or periodic breathing.
24	The patient has been diagnosed with central sleep apnea per the ICSD-3 definition.
25	Inability to attain a repeatable AHI baseline value (e.g., high variability in AHI > 20) between screening HST tests.
26	The Subject meets one or more of the following sleep study criteria as assessed by the Baseline PSG:
	a. An AHI < 20 or > 65
	b. Apnea Index (AI) > 30 events per hour
	c. > 25% mixed or central apnea events as a proportion of the sum of apnea and hypopnea events per hour
	d. Positional OSA as defined by non-supine AHI <10

e. Predominantly REM OSA (ratio between the AHI in REM and AHI in NREM >2)

f. Indication of a sleep disorder or poor sleep hygiene that could confound functional assessments of sleepiness such as a poor sleep efficiency (e.g. < 85%)

Table 3

Statistical properties of trial design.

Fixed Sample Size Estimated Primary Endpoint Statistical Power						
Assumes Previous Trial Response Rates: 52% (Treatment) vs. 20% (Control) – Observed Response Rates Determine Actual Power						
Primary endpoint power	49.2%	65.9%	79.3%	88.2%	92.7%	96.7%
No. Randomized Subjects	50	70	90	110	130	150
Bayesian Operational Characteristics						
Size-dependent Thresholds for Early Success and Futility						
Early success if $PP_n >$	0.990	0.990	0.975	0.975	0.950	0.950
Early futility if $PP_{max} <$	0.005	0.005	0.010	0.010	0.025	0.025