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Early View

Original article

Bilateral Hypoglossal Nerve Stimulation for Treatment of Adult Obstructive Sleep Apnea

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TITLE PAGE

Title

Bilateral Hypoglossal Nerve Stimulation for Treatment of Adult Obstructive Sleep Apnea

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Summary Take Home Message

This new method of hypoglossal nerve stimulation to treat sleep apnea does so bilaterally via an implanted neuro stimulator activated externally. Its simplicity and relative non-invasiveness have not compromised its effectiveness relative to older methods.

ABSTRACT

Background and Aim: Hypoglossal Nerve Stimulation (HNS) decreases Obstructive Sleep Apnea (OSA) severity via genioglossus muscle activation and decreased upper airway collapsibility. This study assessed the safety and effectiveness at 6 months post-implantation of a novel device delivering bilateral HNS via a small implanted electrode activated by a unit worn externally, to treat OSA: the Genio™ system.

Methods: This prospective, open-label, non-randomized, single arm treatment study was conducted at eight centres in three countries (Australia, France, UK). Primary outcomes were incidence of device-related Serious Adverse Events (SAEs) and change in the Apnea-Hypopnea Index (AHI). The secondary outcome was the change in the 4% Oxygen Desaturation Index (ODI). Additional outcomes included measures of sleepiness, quality of life, snoring, and device use. This trial was registered with ClinicalTrials.gov, number NCT03048604.

Results: From 27 implanted participants (63% male, aged 55.9±12.0 years, BMI 27.4±3.0 kg/m^2), 22 completed the protocol. At 6 months BMI was unchanged (p=0.85), AHI decreased from 23.7±12.2 to 12.9±10.1 events/hr, a mean change of 10.8 events/hr (p<0.001); ODI decreased from 19.1±11.2 to 9.8±6.9 events/hr, a mean change of 9.3 events/hr (p<0.001). Daytime sleepiness (ESS, p=0.01) and sleep-related quality of life (FOSQ-10, p=0.02) both significantly improved. The number of bed partners reporting loud, very intense snoring, or leaving the bedroom due to participant snoring decreased from 96% to 35%. Ninety-one percent of participants reported device use >5 days per week, and 77% reported use for >5 hours per night. No device-related SAE occurred during the 6-months post-implantation period.

Conclusions: Bilateral HNS using the Genio™ system reduces OSA severity and improve quality of life without device related complication. The results are comparable with previously published HNS systems despite minimal implanted components and a simple stimulation algorithm.

Key words: implantable neuro stimulator; bilateral stimulation; quality of life; snoring; safety; oxygen desaturation; arousals; intention to treat.

INTRODUCTION

Obstructive Sleep Apnea (OSA) is a disorder characterized by recurrent episodes of decreased (hypopnea) or absent (apnea) inspiratory airflow during sleep. The primary mechanism underlying these events is a sleep-related decrease in pharyngeal muscle activity which causes narrowing and collapse of the airway in predisposed individuals. The resultant intermittent episodes of arterial oxygen desaturation and repeated disruption of sleep cause excessive daytime sleepiness and other medical co-morbidities such as hypertension, depression and stroke [1, 2].

The goal of OSA treatment is to prevent airway narrowing and/or collapse in order to maintain optimal breathing during sleep, to reduce co-morbidities and to relieve associated symptoms. Positive Airway Pressure (PAP) is recognized as the primary treatment for patients with moderate-to-severe OSA. PAP involves the delivery of air under pressure to the pharynx via a well-fitting mask. This pressure acts as a pneumatic splint, holding the airway open and preventing its collapse. Although a highly efficacious treatment, patients are often uncomfortable using the device and adherence to therapy remains problematic [3, 4]. For this reason, there is substantial interest in developing alternate treatments for OSA. These include Hypoglossal Nerve Stimulation (HNS), which modulates upper airway collapsibility through neural stimulation of the genioglossus muscle [5].

Since the first successful use of a HNS system to treat OSA was reported in 2001 [6], three HNS systems have been CE-marked. Apnex Medical published the first feasibility study in 2011, reporting a significant decrease in OSA severity and symptoms following implantation

with their system [7], but this device did not enter clinical practice because a pivotal study failed to show a between-group difference in the reduction of sleep apnea, owing to major unanticipated improvements in the control group (ClinicalTrials.gov number, NCT01446601) [8]. Inspire Medical Systems currently manufactures the only United States Food and Drug Administration-approved HNS device for OSA. This device is an implantable, pacemaker-like pulse-generator with a sensing lead placed between the external and internal intercostal muscles to detect breathing effort, and a stimulation lead connected to a cuff electrode wrapped around one (unilateral) hypoglossal nerve [9]. A 60-month outcome study, the STAR trial, reported a significant decrease in OSA severity and symptoms [10]. ImThera Medical has developed the aura6000™ system, another HNS device. This system does not include a sensing lead and stimulates the hypoglossal nerve with 6 electrodes at a more proximal location, co-activating the tongue protrusors and retractors (using different stimulation vectors) to stiffen the posterior aspect of the tongue and pharyngeal walls to open the airway [11]. Improvements in OSA severity and symptoms have been reported at 6-months following implantation [12].

This manuscript presents the results of a multicentre, prospective, open-label, non-randomized, single arm OSA treatment study of a novel HNS device, the Genio™ system. It differs favourably from previous HNS devices as it does not require any leads (connective wires between the sensor/cuff electrodes and the pulse generator) and only one incision is required without any tunneling. Further, stimulation is delivered bilaterally and controlled from an externally worn unit that activates a small implanted battery-free submental stimulator at a predetermined, adjustable rate and duty cycle. This study, the BLAST OSA study (**B**i**LA**teral Hypoglossal Nerve **S**timulation for **T**reatment of **O**bstructive **S**leep **A**pnea),

was undertaken to evaluate the safety, and effectiveness of the Genio™ system over a period of 6 months in adult participants with moderate-to-severe OSA.

METHODS

Participants

Participants were recruited from Sleep Clinics and Otolaryngology practices, and were eligible for implantation if they met the following criteria: 21-75 years old; BMI ≤ 32 kg/m^2; obstructive Apnea-Hypopnea Index (AHI) of 20-60 events/hr and combined central and mixed AHI of fewer than 10 events/hr; no positional OSA (defined as non-supine-AHI < 10 events/hr and supine-AHI ≥ non-supine-AHI x 2); absence of soft palate Complete Concentric Collapse (CCC) during Drug Induced Sleep Endoscopy (DISE) [13]; and had not tolerated or accepted PAP treatments (see footnote). *For a complete list of inclusion and exclusion criteria see Supplementary Table 1.*

Study overview and design

The study design was a multicentre, prospective, open-label, non-randomized, single arm treatment study. Potential participants were provided with information about the study. If they agreed to take part, they underwent testing to confirm full eligibility during an 8-week period, during which baseline measurements (including baseline polysomnography, PSG) were obtained. If eligibility was confirmed, participants were surgically implanted with the Genio™ system (Nyxoah SA, Mont-Saint-Guibert, Belgium) under general anaesthesia. The procedure required making a small incision above the hyoid bone and dissecting through the platysma, mylohyoid and geniohyoid muscles to the genioglossus muscle. The

hypoglossal nerve branches were then identified and the stimulation unit (Figure 2A) sutured in place (see below, *Study Device*, for more detail). The device was activated 4 to 6 weeks after implantation, titrated (optimized) at follow-up visits at 2, 3, and 4 months, and outcome measurements obtained at a 6-month follow-up visit (Figure 1) with fixed therapeutic settings on full-night PSG.

Outcomes

The primary outcome measures were the incidence of device-related Serious Adverse Events (SAE) and the change in AHI. The secondary outcome measure was the change in the 4% Oxygen Desaturation Index (ODI). Additional outcome measures were changes in: time spent at an oxygen desaturation below 90%; sleep efficiency; sleep fragmentation using the Arousal Index (ArI); daytime sleepiness using the Epworth Sleepiness Scale (ESS); sleep-related quality of life using the Functional Outcomes of Sleep Questionnaire (FOSQ-10); partner-reported snoring; and the number of participants considered 'responders' to the therapy, defined using the established standard for similar studies of surgical outcomes in OSA of at least a 50% reduction in mean AHI and an AHI of less than 20 events/hr [7, 10, 12, 14]. An objective measurement of the time spent using the device each night could not be obtained with the current generation of the device. For this reason, nightly usage of the Genio™ system was evaluated through a usability questionnaire completed by the participants at 6 months of the number of hours used per night and the number of nights used per week.

Study device

The Genio™ system consists of a stimulation unit (Figure 2A) surgically implanted in the submental region, positioned over the genioglossi muscles with its stimulating electrodes proximate to both the left and right hypoglossal nerve branches. This electrode positioning was adjusted with the aid of a nerve integrity monitor system. In order to stimulate the nerves, the implanted stimulation unit receives energy pulses transmitted transdermally from an external activation unit which is attachable to an adhesive disposable patch and which is placed under the chin by the participant prior to going to sleep (Figure 2B). These are removed by the participant in the morning, the disposable patch is discarded, and the activation unit recharged for its next use *(Supplementary Figure 1)*.

The activation unit holds participant-specific stimulation parameters that are pre-programmed and are adjusted wirelessly. Device programming and adjustments occurred during awake titrations as well as in-lab PSG studies performed prior to the 6-month endpoint visit. During PSG studies stimulation parameters were refined until settings were obtained that did not wake the participant and maintained upper airway patency and oxyhaemoglobin saturation. Stimulation ON time (train length) and stimulation OFF time (train interval) was pre-programmed based on each participant's breathing frequency measured during unobstructed breathing when asleep *(Supplementary Figure 2)*. The device is a constant voltage source with intensity of the stimulation is mainly controlled by the pulse amplitude, represented by the percentage of the maximal amount of energy that can be delivered to the nerve by the implanted stimulator considering its relative position and the impedance between the electrodes and the nerve *(see Supplementary Table 2)*. Most

participants needed time to reach tolerance of stimulation therapy levels, hence optimization took up to 4 months.

Sleep recordings and scoring

All PSG results in this publication were generated from sleep studies scored by an independent core laboratory (Registered Sleepers Inc., North Carolina, USA). Participants were included in the trial based on 2014 AASM recommended scoring guidelines [15]. However, to permit more direct comparison with available literature [9], all results presented in this paper are based on the 2014 AASM acceptable scoring guidelines [15] *(see online data supplement for additional detail)*.

Statistical analysis

In order to detect a clinically meaningful reduction of at least 15/hour in AHI with 90% power at a 5% level of significance, and assuming a standard deviation of 20/hour, a total sample size of 21 subjects was required to test the null hypothesis. Allowing for a 15% drop-out, 25 subjects were included.

The changes from baseline to 6 months after surgery in AHI, ODI, the ESS and FOSQ-10 were calculated for each participant. P-values from a paired t-test were provided for the different measures and all data were presented as mean (SD) unless otherwise stated. Safety-related analyses were performed on an intention-to-treat basis and included all participants who underwent study procedures with data available for analysis (n=27). Modified intention-to-treat analyses were performed on all other measures by excluding two participants in whom no titration was performed (*i.e.,* no PSG data available post-implant) and 3 participants who

withdrew prior to the 6-month PSG study (*i.e.,* n=22). Analyses were also undertaken on a per protocol basis in participants without any major protocol deviation and good compliance with the therapy (n=19) *(see online data supplement for additional detail)*.

Study oversight and approvals

A Clinical Events Committee (CEC) independently reviewed any Adverse Events (AEs). The CEC consisted of three experienced and recognized ENT surgeons and sleep medicine specialists. All individuals provided written, informed consent prior to participation in the study which was conducted in compliance with ISO14155:2011 and approved by the Ethics Committees at all centres. ClinicalTrials.gov Identifier: NCT03048604 *(see online data supplement for additional detail)*.

RESULTS

Participant characteristics

Between April 2017 and February 2018, seven centres in France and Australia screened 93 participants into the study (one centre was activated in the UK but did not enrol any participants) (*Supplementary Table 3*). A total of 66 participants failed the screening after consent and did not receive an implant (*Supplementary Table 4*). The most common reasons for this were CCC at the soft palate and participant AHI results outside of the allowed screening range (based on full night PSG). Twenty-seven (27) participants were implanted with the Genio™ system (Figure 1).

Among the 27 implanted participants, 22 reached the 6-month follow-up visit (Figure 1). Two participants exited the study prior to the first post-implant PSG due to procedure-related infections. One participant was withdrawn from the study due to non-study related behavioural issues. Another one should not have been implanted since only limited hypoglossal nerve stimulation response was observed during the surgery and was subsequently withdrawn from the study. Finally, one participant was withdrawn as they failed to return for the 6-month endpoint visit despite numerous attempts from the centre to re-establish contact with the participant.

The demographics of the 27 participants implanted with the Genio™ system are presented in Table 1. Their mean age was 55.9±12.0 years, mean BMI 27.4±3.0 kg/m^2, 63.0% (17/27) were male and 88.9% (24/27) were Caucasian. In the 22 who reached the 6-month follow-up visit, BMI was unchanged when compared to baseline, being 27.73 and 27.67 kg/m^2, respectively (p=0.85).

Primary outcomes

No device-related SAEs occurred during the 6-months post-implantation. Three out of the 27 implanted participants experienced 4 SAEs related to the surgical procedure: 3 were local infections at the surgical site including 2 participants at the same centre necessitating explantation of the devices at 2 and 3 months after implantation. The corresponding SAEs were resolved without further sequelae. The fourth procedure-related SAE was impaired swallowing which led to a 1-day prolongation of implantation-related hospitalization. This SAE spontaneously resolved without further sequelae. The most frequent procedure-related non-serious AEs that occurred in implanted participants were impairment or painful

swallowing (30% of participants), dysarthria (26% of participants), hematoma (19% of participants), and swelling or bruising around the incision site (19% of participants). Among the device-related non-serious AEs, 30% of participants experienced local skin irritation due to the disposable patch, which resolved in all cases except one that remained present at the 6-month visit. The events of skin irritation were resolved without any treatment or with topical medication and, in two cases, temporarily suspending use of the disposable patch. Other non-serious device-related AEs included tongue abrasion (11% of participants), tongue fasciculations (11% of participants) and discomfort due to electrical stimulation (11% of participants) (*Supplementary Table 5*). There were no instances of extrusion of the stimulation unit or the sutures used to hold it in place.

Mean AHI decreased from baseline to the 6-month PSG from 23.7±12.2 to 12.9±10.1 events/hr, $p<0.0001$ (Table 2 and Figure 3); the mean individual percent decrease was 47.3% (median=48.6%). When examined using a per protocol analysis (n=19) the mean AHI decreased from 22.2±12.0 to 11.0±9.5 events/hr, respectively, $p<0.0001$ (*Supplementary Table 6 and Supplementary Figure 3*); the mean individual percent decrease was 51.4% (median=55.1%). The responder rate was 50.0% (11 of 22) for the modified intention-to-treat analysis and 57.9% (11 of 19) for the per protocol analysis. Additionally, the therapy resulted in 11 participants with a residual AHI below 15 events/hr, 4 participants below 10 events/hr and 3 participants below 5 events/hr.

Secondary outcome

Mean ODI decreased from baseline to the 6-month PSG from 19.1±11.2 to 9.8±6.9 events/hr, p<0.0001 (Table 2 and Figure 4); the mean individual percent decrease was 43.3% (median=47.2%). Using the per protocol analysis (n=19) the mean ODI decreased from 18.2±10.4 to 8.0±5.4 events/hr, respectively, p<0.0001 (*Supplementary Table 6 and Supplementary Figure 4*); the mean individual percent decrease was 50.6% (median=56.0%).

Additional outcomes

The ESS decreased from 11.0±5.3 to 8.0±5.4, a mean change of 3.3 units [95% CI 0.8-5.7, p=0.0113] (median=1.0 units) whereas the FOSQ-10 score increased from 15.3±3.3 to 17.2±3.0, a mean change of 1.9 units [95% CI 0.4-3.4, p=0.0157] (median=1.0 units) (Table 2). The apnea index, hypopnea index, arousal index and time spent with a $SaO_2 \leq 90\%$ significantly decreased (all p<0.05, Table 2). Sleep efficiency increased, the proportion of the night spent in non-rapid-eye movement (NREM) stage 1 and NREM stage 3 sleep decreased and the proportion of the night spent in NREM stage 2 and rapid-eye movement (REM) sleep increased (all p<0.05, Table 2). Bed partners reporting loud, very intense snoring, or leaving the bedroom due to partner snoring decreased from 96% at baseline to 35% at 6-months post implantation (*Supplementary Table 7*). Finally, at 6 months post-implantation 91% of participants reported using the Genio™ system more than 5 days a week and 77% reported a nightly use of more than 5 hours a night.

DISCUSSION

The safety profile of the Genio™ system was favourable given the absence of any device-related SAEs over the course of the study. The four procedure-related SAEs were resolved

without further sequelae. This procedure-related SAE occurrence compares favourably with other HNS device reports [8, 11]. The two local infections requiring explantation of the device occurred at the one centre and were judged by the Clinical Events Committee to be related to the surgical procedure rather than the device itself. The non-serious procedure-related AEs were anticipated with the type of upper airway surgery performed under general anaesthesia. All non-serious device-related AEs, including local skin irritation due to the disposable patch, were resolved except one where irritation remained evident at the 6-month visit. Stimulation could be initially experienced as uncomfortable to some participants, but often resolved with simple device parameter adjustments. Despite these minor side-effects, usage of the therapy was high with 91% of participants using the system more than 5 days a week and 77% reporting using it more than 5 hours a night. This exceeds most reports of adherence to PAP, with patient compliance ranging from 29-83% [3, 16-18], although recent data from patients undergoing standard clinical care but using current PAP technology suggests that short-term (90 day) adherence rates are approximately 75% in individuals who accept PAP therapy [19].

There were improvements in the primary and secondary performance endpoints at 6 months post implantation. The mean individual percent decrease in these measures was 47.3% and 43.3%, respectively for the modified intention-to-treat analyses (n=22) and 51.4% and 50.6% for the per protocol analyses (n=19), respectively. The magnitude of change is similar to that reported by studies using other HNS devices, which range from 52% to 62% decrease in AHI and 45% to 52% decrease in ODI [7, 9, 20-22]. The number of overnight titration visits to achieve these results is similar to that reported for other available HNS systems [23].

The improvements in objective measures of OSA severity were accompanied by improvements in symptoms. Specifically, the mean ESS score at the 6-month visit was below the threshold of 10 defined in the literature as being equivalent to a normal population [24]. In addition, although the 1.9 point increase in the FOSQ-10 score just failed to meet the 2-point standard threshold for a clinically meaningful improvement quality of life [25] in the modified intention-to-treat analysis, the per protocol analysis showed an increase of 2.5 points. This clinically significant improvement in quality of life is similar to improvements reported with other device use [7, 9, 22, 26]. These changes were accompanied by decreases in partner-reported snoring intensity and improvements in sleep architecture, specifically an increase in sleep efficiency and REM sleep and a decrease in stage 1 sleep and in the number of arousals. Such changes are generally consistent with those reported in studies with other devices [7, 27].

Compared to other implantable HNS devices the Genio™ system has four main differences. Firstly, rather than the unilateral stimulation offered by previous systems, the Genio™ system delivers bilateral HNS. This is achieved by the implantable stimulation unit that sits like “a saddle on a horse” over the genioglossi muscles near their insertion on the mandible, such that its stimulating electrodes face both the left and the right distal (medial) hypoglossal nerve branches. This approach, using paddle electrodes, differs from other systems which are based on unilateral stimulation of the hypoglossal nerve as the cuff electrode is positioned around only one hypoglossal nerve branch, usually the right [7, 9, 12]. While no studies have directly compared the effects on airway patency of bilateral versus unilateral HNS several findings support the notion that bilateral stimulation might

result in an improved response. For example, studies using unilateral HNS have reported that when tongue protrusion occurs in a more anterior motion (*i.e.,* bilateral movement) rather than to the left or right, a better outcome is achieved [28, 29]. The improved response could be due to a number of factors including the difference in type of electrodes (paddle versus cuff), the applicable location of the cuff electrode on the hypoglossal nerve and resultant activation of different sets of pharyngeal muscles[30]; recruitment of genioglossus muscle fibres that receive innervation from the hypoglossal nerve on the contralateral side (i.e. cross-talk from right to left) [31]; or greater movement of the soft palate with forward motion of the tongue as a consequence of improved coupling of the palatoglossus muscle in the soft palate with the muscles of the lateral tongue body [32, 33]. The more symmetrical muscle activation provided by the bilateral nature of the HNS delivered by the system has positive implications for patient comfort and functionality. Notably, as with other HNS devices, this device is designed to stimulate the hypoglossal nerve rather than the muscle directly. Indeed, the energy delivered by the device is insufficient to generate muscle activation through direct stimulation.

A second difference between the Genio™ system and other HNS devices it that it stimulates only the genioglossus muscle, as a result of positioning the stimulating paddle electrodes close to the insertion of the distal hypoglossal nerve into the genioglossus muscle. In contrast, other systems use cuff electrodes placed around more proximal segments of the hypoglossal nerve resulting in stimulation of additional upper airway muscles with a consequent variety of movement patterns of the upper airway structures, including the tongue [28, 33-35]. Despite these differences in approach the magnitude of therapeutic response appears to be similar [7, 9, 20-22], possibly reflecting the central importance of

genioglossus stimulation and the favourable functional effects of the bilateral stimulation offered by the Genio™ system, as discussed in the previous paragraph.

The third unique feature of the Genio™ system is that the small stimulation unit, incorporating electrodes and a receiver, is the only implanted component and is battery-less. It is implanted via a short midline submental incision and positioned proximate to the distal hypoglossal nerves. This electrode is activated transdermally by an activation unit that is worn externally. This differs from other devices which require surgical implantation of a unilateral cuff electrode around the hypoglossal nerve via a lateral submandibular incision which, in turn, are connected by at least one lead, which is tunnelled subcutaneously, to the implanted stimulator powered by an internal non-rechargeable battery and, in some of the HNS systems, to implanted respiratory sensing leads [7, 9, 12]. While no direct comparisons between systems have yet been made, it is possible that patients undergoing HNS using the Genio™ system will have relatively shorter surgery time, smaller and less incisions, faster healing time and less procedure-related postoperative pain. The external stimulation unit of the Genio™ system can be readily serviced, while servicing of the implanted stimulators of all these other systems (for example, for battery or system malfunction or device or firmware upgrade) would require explantation of the unit.

The fourth difference between the Genio™ system compared to others is that it delivers intermittent stimulation at a pre-programmed adjustable rate and duty cycle. Specifically, the system is programmed to deliver stimulation at a fixed rate, adjusted to be near the participant's own breathing frequency during unobstructed breathing when asleep. Stimulation duration is fully adjustable, but in the present trial was maintained at 70% of the

total respiratory cycle time for most participants. This lengthy duty cycle was adopted in the knowledge that the participant's own rate would vary overnight, but still ensure stimulation for at least part of each inspiration. The cyclical pauses between stimulations were provided to allow for rest periods between muscle contractions. As such, stimulation is not systematically synchronized with the participant's breathing frequency, with stimulation occurring at variable periods in the respiratory cycle depending on the breathing frequency at any given time. This differs from other devices which deliver intermittent stimulation synchronized with inspiration as detected by respiration sensing leads [7, 9] or by delivering near-constant stimulation by cycling stimulation between multiple electrode combinations [12]. Advantages of the dispensation with inspiratory synchronization by the Genio™ system via its predetermined adjustable rate and duty cycle approach is removal of the need for implanted respiratory effort sensing leads which add complexity, invasiveness and vulnerability to failure.

Despite the marked difference in modes of delivery of HNS, the magnitude of therapeutic response between these different devices appears to be similar [7, 9, 20-22]. This may appear surprising given the common belief that the pharyngeal airway is most vulnerable to collapse at end-expiration when the calibre of airway is thought to be at its smallest [36-39]. However, this pattern is not always observed and several studies have reported substantial inter and intra-subject variability in the relationship of pharyngeal cross sectional area to phase of respiration [36, 37, 40]. It is likely that the specific relationship between airway size, collapsibility and respiratory phase is a consequence of the relative contributions of a number of factors including transmural pressure gradients; pharyngeal muscle recruitment;

lung volume; airway anatomy; head, neck and body posture; and sleep state [37, 39, 41, 42], which will vary between and within individuals.

The study has several limitations. By design the study was observational and did not have a control group. However, given the promising results to date, the next step would be to undertake a larger trial with possible control group and longer-term follow up to confirm the findings of the current study. While the study did not reach its pre-defined target AHI reduction of 15 events per hour used to compute the study sample size, it should be noted this was used only for estimate statistical power and the study achieved a statistically significant reduction in AHI.

In conclusion, the BLAST OSA study has demonstrated the safety and performance of the Genio™ system, associated with high adherence in participants with moderate-to-severe OSA and who have either not tolerated, failed or refused PAP therapy. The study showed significant reduction of OSA severity and improvement of sleepiness and quality of life, while keeping an acceptable safety profile. These results are consistent with previously published HNS systems from which the Genio™ system offers distinct, potentially advantageous differences. These include: (a) bilateral rather than unilateral HNS; (b) minimal implanted components which are battery-less with the activation unit worn externally; and (c) stimulation provided at a predetermined, adjustable rate and duty cycle rather than requiring inspiratory synchronisation with attendant implanted sensing leads. All these changes act to decrease the complexity and invasiveness of HNS application and simplify and facilitate maintenance of the system. Our findings suggest that these simplifications have been made without compromising safety or effectiveness.

Given the results of this study, the limitations of the existing treatment options, and the negative health and wellbeing consequences of leaving significant OSA untreated, the Genio™ system may be considered as a valid treatment option to treat OSA in a targeted population.

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FIGURE LEGENDS

Figure 1. Flow diagram showing study enrolment and participant progress PSG=polysomnography. DISE=drug induced sleep endoscopy.

Figure 2. Submental musculature showing (A) the implanted stimulator straddling the genioglossus muscles and hypoglossal nerve branches bilaterally and (B) the disposable patch and activation unit. The images are for illustrational purposes only and it should be noted that the surgical anatomy might differ from person to person thereby requiring adjustment to the specific placement of the implanted stimulator over the hypoglossal nerves.

Figure 3. Change in Apnea-Hypopnea Index (AHI) for each participant from baseline to 6 months post-implantation. Each colored line represents an individual participant using modified intention-to-treat analyses (n=22).

Figure 4. Change in 4% Oxygen Desaturation Index (ODI) for each participant from baseline to 6 months post-implantation. Each colored line represents an individual participant using modified intention-to-treat analyses (n=22).

FOOTNOTES

[1] An additional inclusion criterion for French sites only was *participants who do not tolerate mandibular advancement devices.*

TABLES

Table 1. Demographic and baseline characteristics

Demographic Outcomes	Mean (SD) / %(n/N) (N = 27)	Median [Min, Max]
Age, year	55.9 (12.0)	58.5 [32.5; 74.7]
Male, gender	63% (17/27)	
Body Mass Index, kg/m^2	27.4 (3.0)	28.1 [20.7; 32.3]
BP Systolic, mmHg	130.4 (17.5)	130.0 [86.0; 177.0]
BP Diastolic, mmHg	78.1 (6.6)	78.0 [61.0; 90.0]
Neck Circumference, cm	39.0 (4.2) (N = 24)	39.5 [32.0; 48.0]
Race: Caucasian	88.9% (24/27)	
Race: Hispanic	11.1% (3/27)	

Data are mean (SD) or otherwise specified. BP=blood pressure.

Table 2. Outcome measures for modified intention-to-treat analyses.

Outcome	Baseline (N=22)	6 months (N=22)	Mean Difference (95% CI)	P-value
Sleep Disordered Breathing				
AHI, events/hr	23.7 (12.2)	12.9 (10.1)	10.8 (14.6 to 7.0)	<0.0001
ODI, events/hr	19.1 (11.2)	9.8 (6.9)	9.3 (13.1 to 5.5)	<0.0001
SaO_2<90%, % time	5.0 (6.0)	2.1 (3.0)	2.9 (4.6 to 1.3)	0.0015
AI, events/hr	10.1 (10.2)	5.6 (8.4)	4.8 (9.2 to 0.4)	0.0334
HI, events/hr	12.5 (8.9)	7.6 (6.2)	4.9 (8.1 to 1.7)	0.0049
Symptoms				
ESS	11.0 (5.3)*	8.0 (5.4)	3.0 (5.7 to 0.8)	0.0113
FOSQ-10	15.3 (3.3)	17.2 (3.0)	1.9 (0.4 to 3.4)	0.0157
Sleep Architecture				
Sleep Efficiency, %	84.0 (10.8)	87.3 (8.9)	3.2 (0.01 to 6.4)	0.0494
NREM Stage 1, %	13.1 (7.9)	8.2 (4.0)	5.0 (8.3 to 1.7)	0.0053
NREM Stage 2, %	60.9 (8.7)	67.6 (9.5)	6.7 (2.2 to 11.3)	0.0058
NREM Stage 3, %	8.2 (6.9)	3.5 (4.3)	4.7 (6.6 to 2.7)	<0.001
REM, %	17.8 (6.4)	20.7 (7.3)	2.9 (-0.3 to 6.2)	0.0782
ArI, events/hr	28.7 (11.5)	16.0 (8.0)	12.7 (16.6 to 8.9)	<0.0001

Data are mean (SD) unless otherwise specified. AHI=apnea hypopnea index; ODI=4% oxygen desaturation index; SaO_2<90%=proportion of the night spent at an oxygen saturation below 90%; AI=apnea index; HI=hypopnea index; ESS=Epworth Sleepiness Scale; FOSQ10=the 10-item Functional Outcomes of Sleep Questionnaire; NREM sleep=non rapid-eye movement; REM sleep=rapid eye movement; ArI=arousal index. *N=21.

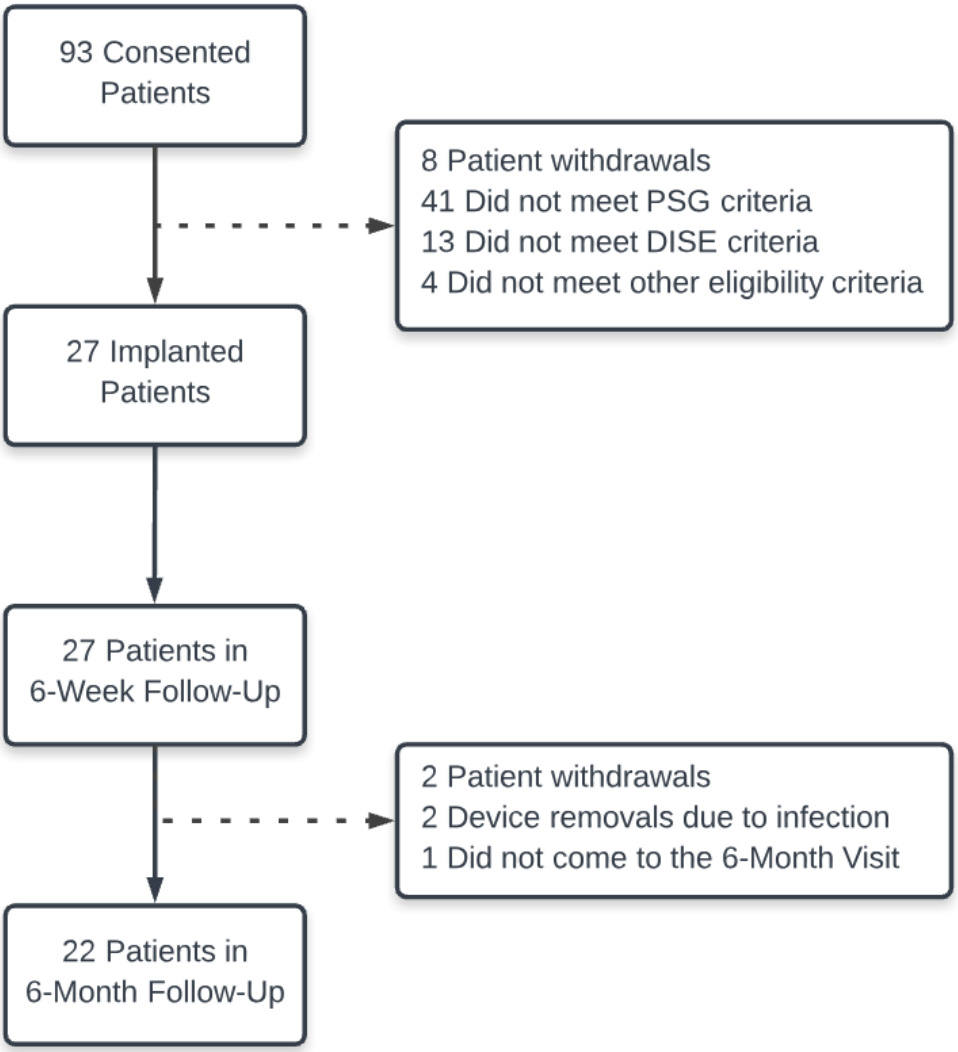

Figure 1. Flow diagram showing study enrolment and participant progress

PSG=polysomnography; DISE=drug induced sleep endoscopy.

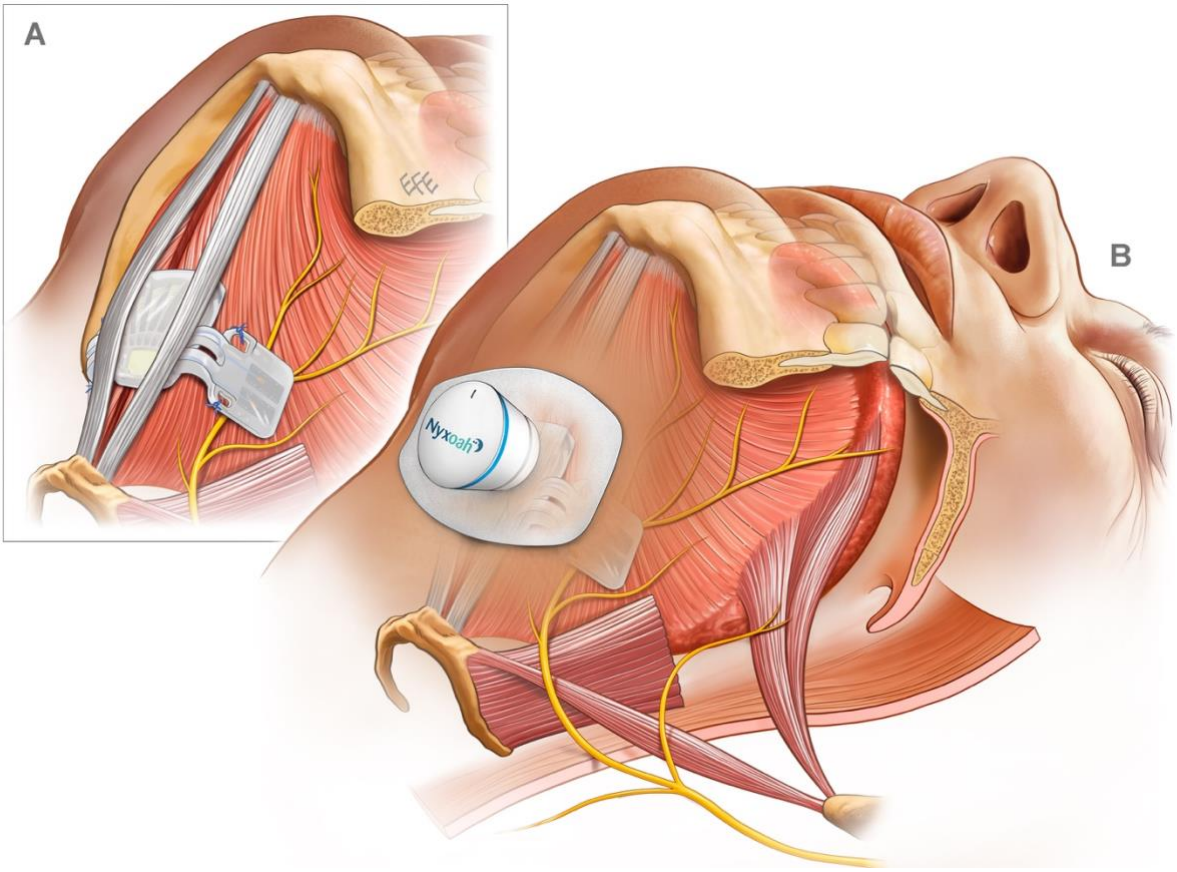

Figure 2. Submental musculature showing (A) the implanted stimulator straddling the genioglossus muscles and hypoglossal nerve branches bilaterally and (B) the disposable patch and activation unit. The images are for illustrational purposes only and it should be noted that the surgical anatomy might differ from person to person thereby requiring adjustment to the specific placement of the implanted stimulator over the hypoglossal nerves.

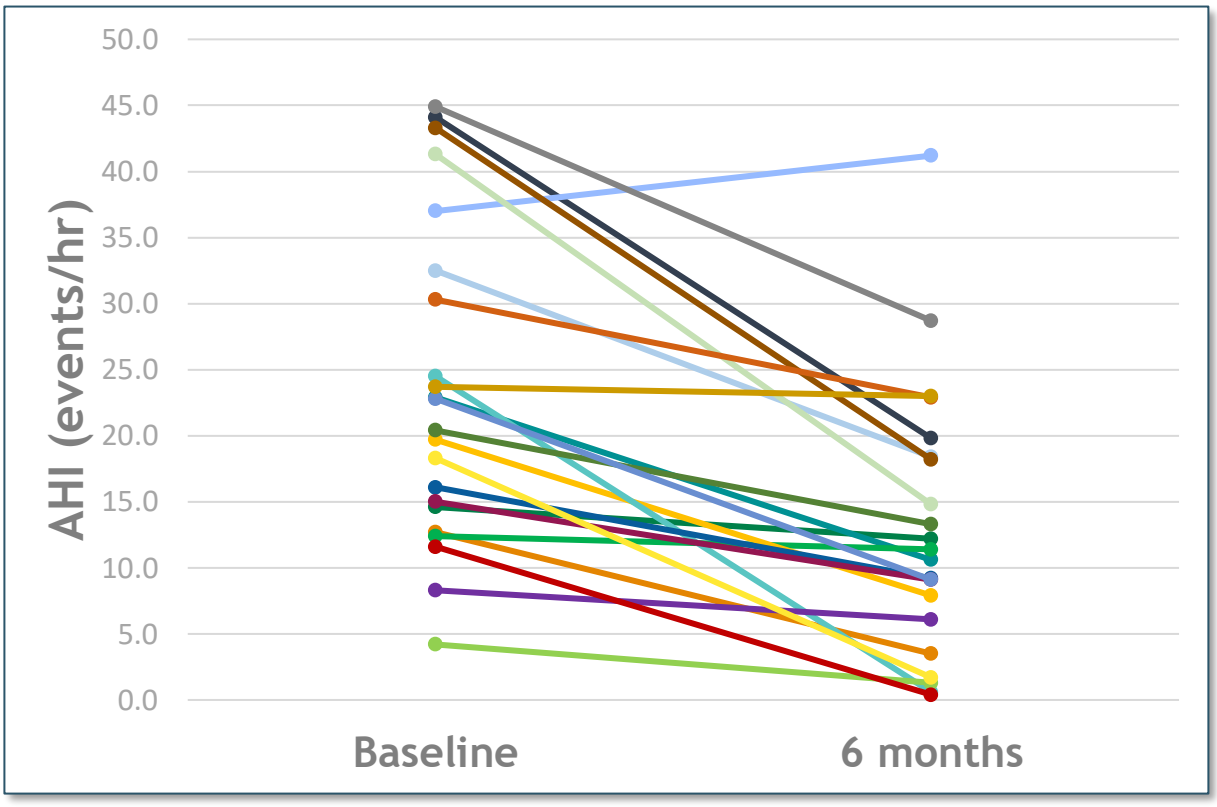

Figure 3. Change in Apnea-Hypopnea Index (AHI) for each participant from baseline to 6 months post-implantation. Each coloured line represents an individual participant using modified intention-to-treat analyses (n=22).

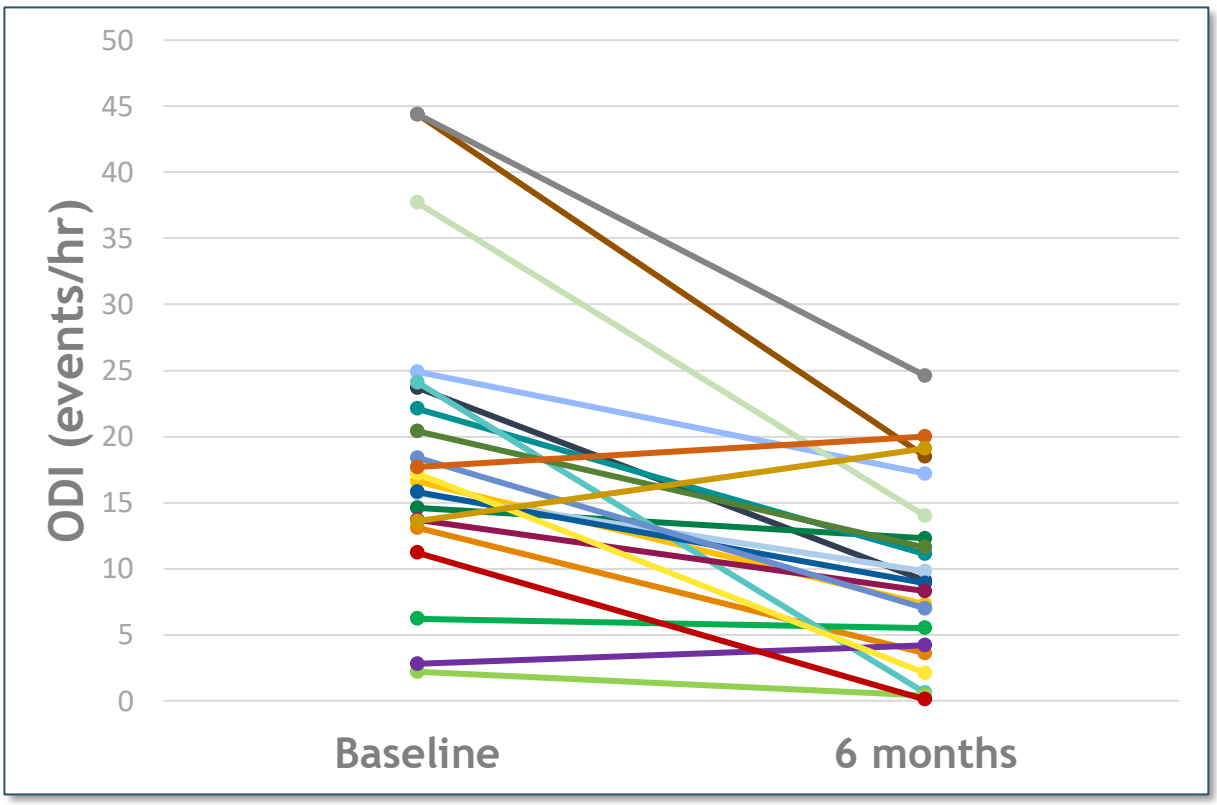

Figure 4. Change in 4% Oxygen Desaturation Index (ODI) for each participant from baseline to 6 months post-implantation. Each coloured line represents an individual participant using modified intention-to-treat analyses (n=22).

ONLINE DATA SUPPLEMENT

Title

Bilateral Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnea

Authors

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Supplementary Text – Methods

METHODS

Participants

Participants were eligible for implantation if they met the following criteria: 21-75 years old; BMI ≤ 32 kg/m^2; obstructive Apnea-Hypopnea Index (AHI) of 20-60 events/hr and combined central and mixed AHI of fewer than 10 events/hr; no positional OSA (defined as non-supine-AHI < 10 events/hr and supine-AHI ≥ non-supine-AHI x 2); absence of Complete Concentric Collapse (CCC) at the soft palate observed during a Drug Induced Sleep Endoscopy (DISE) (8); and had not tolerated or accepted PAP treatments (see footnote). *For a complete list of inclusion and exclusion criteria see supplementary Table 1.*

Study overview and design

The study design was a multicentre, prospective, open-label, non-randomized, single arm treatment study. Potential participants were provided with information about the study. If they agreed to take part, they underwent testing to confirm full eligibility during an 8-week period, during which baseline measurements (including baseline PSG) were obtained. If eligibility was confirmed, participants were implanted with the Genio™ system under general anaesthesia. The Genio™ system was activated 4 to 6 weeks after implantation, titrated (optimized) at follow-up visits at 2, 3, and 4 months, and outcome measurements obtained at a 6-month follow-up visit (Figure 1) with fixed therapeutic settings on full-night PSG.

Outcomes

The primary outcome measures were the incidence of device-related Serious Adverse Events (SAE) and the change in AHI. The secondary outcome measure was the change in the 4% Oxygen Desaturation Index (ODI). Additional outcome measures were the changes in the following: time

spent at an oxygen desaturation below 90%; sleep efficiency; sleep fragmentation using the Arousal Index (ArI); daytime sleepiness using the Epworth Sleepiness Scale (ESS); sleep-related quality of life using the Functional Outcomes of Sleep Questionnaire (FOSQ-10); partner-reported snoring and the number of participants who responded to the therapy, where a 'responder' was defined using the established standard of at least a 50% reduction in mean AHI and an AHI of less than 20 events/hr (9). Nightly usage of the Genio™ system was evaluated through a usability questionnaire completed by the participants at 6 months of the number of hours used per night and the number of nights used per week.

Study device

The Genio™ system consists of a stimulation unit (Figure 2A) implanted in the submental region via a surgical procedure and positioned over the genioglossus muscle with its stimulating electrodes proximate to both the left and right hypoglossal nerve branches. In order to stimulate the nerves, the implanted stimulation unit receives energy pulses transmitted transdermally from an external activation unit which is attachable to an adhesive disposable patch and which is placed under the chin by the participant prior to going to sleep (Figure 2B). These are removed by the participant in the morning, the disposable patch is then discarded, and the activation unit recharged for its next use *(Supplementary Figure 1)*.

The activation unit holds participant-specific stimulation parameters that are pre-programmed and are adjusted wirelessly. Stimulation is performed with a duty cycle (the ON/OFF stimulation cycle reproduces itself all night) and not synchronized with the participant's respiratory cycle.

Sleep recordings and scoring

All PSG results in this publication were generated from sleep studies scored by an independent core laboratory (Registered Sleepers Inc., North Carolina, USA). Participants were included in the trial based on 2014 AASM recommended scoring guidelines (10). However, to permit more direct

comparison with available literature (4), all results presented in this paper are based on the 2014 AASM acceptable scoring guidelines in which an apnea is defined as a ≥ 90% airflow decrease lasting 10 seconds or more and a hypopnea as an airflow decrease of at least 30% for 10 seconds or more accompanied by a 4% reduction in oxygen saturation (10).

Statistical analysis

We estimated that a sample of 21 participants would provide 90% power to detect a clinically meaningful reduction of at least 15 events/hr for the primary outcome (with a standard deviation of 20 events/hr) at a two-sided significance level of 0.05. Allowing for a 15% drop-out, 25 successfully implanted participants were required to obtain performance data. Finally, 27 participants were implanted with the Genio™ system. The changes from baseline to 6 months after surgery in AHI, ODI, the ESS and FOSQ-10 were calculated for each participant. P values from a paired t-test were provided for the different measures and all data were presented as mean (SD) unless otherwise stated.

Safety-related analyses were performed on an intention-to-treat basis and included all participants who underwent study procedures with data available for analysis (n=27). Modified intention-to-treat analyses were performed on all other measures by excluding two participants in whom no titration was performed (*i.e.,* no PSG data available post-implant) and 3 participants who withdrew prior to the 6-month PSG study (*i.e.,* n=22). Analyses were also undertaken on a per protocol basis in those participants who completed the study with baseline and 6-month PSG data without any major protocol deviation and good compliance with the therapy (n=19).

Study oversight and approvals

A Clinical Events Committee (CEC) was established to independently review any Adverse Events (AEs). The CEC consisted of three experienced and recognized ENT surgeons and sleep medicine specialists. All individuals provided written, informed consent prior to participation in the study

which was conducted in compliance with ISO14155:2011 Clinical investigation of medical devices for human subjects – Good Clinical Practice. The trial was approved by the Ethics Committees at all centres. ClinicalTrials.gov Identifier: NCT03048604.

Supplementary Table 1. Complete list of inclusion and exclusion criteria

Inclusion Criteria (complete list)

A participant had to have met the following inclusion criteria to be eligible for inclusion in the study:

1. Man or woman between 21 and 75 years of age
2. BMI ≤ 32 kg/m^2
3. Obstructive AHI of 20-60 events/hr and combined central and mixed apnea-hypopnea index of < 10 events/hr documented by at least one PSG performed during the screening phase
4. Absence of positional OSA (defined as non-supine-AHI < 10 events/hr and supine-AHI ≥ non-supine-AHI x 2)
5. Participants who do not tolerate or do not accept PAP treatments and MAD[1]. PAP intolerance is defined as:
   a) inability to use PAP after having tried to use it for a period of minimum 2 months[2] (less than 5 nights per week of usage; usage defined as 4 hours or more of use per night); or
   b) unwillingness to continue to use PAP after having tried to use it for a period of minimum 2 months[3] (for example, a patient returns the PAP system after attempting to use it).
6. Absence of untreated or incompletely-treated sleep disorders other than OSA, such as chronic insomnia, narcolepsy, restless legs syndrome, REM behaviour disorder, etc.
7. Small or absent tonsils (0, 1+, or 2+ according to the Brodsky Classification)
8. Absence of major craniofacial abnormalities narrowing the airway or the implantation site
9. Stable medications for at least 1 month
10. Absence of known moderate-to-severe neurologic, cardiac, pulmonary, renal, or hepatic disorders
11. Absence of psychiatric problems except for treated depression or mild anxiety
12. No acute illness or infection
13. Participant agrees to refrain from alcoholic beverages 24 hours prior to each of the sleep study exams conducted during the study

Exclusion Criteria (complete list)

Patients meeting any of the following criteria were excluded from the study:

1. Participants with chemical abuse history within the previous 3 years
2. Unable or incapable of providing informed written consent
3. Unwilling or incapable of returning to all follow-up visits and sleep studies, including evaluation procedures and filling out questionnaires
4. Presence of another AIMD, specifically pacemaker, or Implantable Cardioverter-Defibrillator (ICD)
5. Participants that are or have been implanted with a hypoglossal nerve stimulation device

6. Diagnosed coagulopathy or taking anticoagulant medications (warfarin, ASA (Aspirin), Clopidogrel (Plavix) or similar) that cannot be temporarily be bridged (by heparin) or stopped to allow surgery to take place
7. Shift workers
8. Pregnant or plan to become pregnant within the next 12 months or breastfeeding
9. Patient with life expectancy < 12 months
10. Surgical resection or radiation therapy for cancer or congenital malformations in the larynx, tongue, or throat (Note that some prior surgeries, such as Uvulopalatopharyngoplasty (UPPP), tonsillectomy or adenoidectomy, to remove obstructions related to obstructive sleep apnea are allowed)
11. Hypoglossal nerve palsy (obvious limited tongue movement, such as inability to protrude tongue, or unintended lateral deviation of the tongue when protruding), or patients with degenerative neurological disorder (i.e. Parkinson's, Alzheimer's)
12. Previous surgery on the soft tissue of the upper airway (e.g., uvula, soft palate or tonsils) performed within 12 weeks of scheduled implant
13. Obvious fixed upper airway obstructions (tumours, polyps or nasal obstruction)
14. Any chronic medical illness or condition that contraindicates a surgical procedure under general anaesthesia as judged by the investigators
15. Participants with prior surgery to the mandible and/or maxilla, other than dental treatments
16. Participants included in another clinical study (excluding registries)
17. Use of any investigational drug or procedure within 30 days of screening visit
18. The presence of CCC of the soft palate on endoscopy
19. Any functional or structural problem that would impair the ability of a hypoglossal nerve stimulator to treat OSA
20. Participants taking medications such as opiates that may affect sleep, alertness or breathing

[1]Mandibular advancement device was only part of the protocol used in France.

[2]The minimum period of 2 months was only part of the protocol used in France.

[3]The minimum period of 2 months was only part of the protocol used in France.

Supplementary Table 2. Distribution of stimulation parameters

Stimulation Parameters at 6-month visit		% (N = 22)
Constant Voltage Device (max 12V)		
Stimulation Amplitude (%)	<10	13.6%
	10-30	45.5%
	35-50	31.8%
	55-75	9.1%
	80-100	0%
Stimulation Frequency (Hz)	30	4.5%
	35	77.3%
	40	13.6%
	45	4.5%
Stimulation Pulse Duration (µsec)	50-90	59.1%
	100-150	31.8%
	160-200	9.1%
	>200	

Device programming and adjustments occurred during awake titrations and in-lab PSGs at study visits prior to the 6-month endpoint visit. The most commonly configured parameters in order of importance were the stimulation amplitude (%), the pulse duration (µsec) and the pulse frequency (Hz).

Supplementary Table 3. Summary of centre enrolment

Site	Enrolled (N)	Screening Failures (N)	Implanted (N)
AU-01	23	18	5
AU-02	8	5	3
AU-03	22	15	7
AU-04	16	14	2
FR-01	3	2	1
FR-02	13	9	4
FR-03	8	3	5
Total	**93**	**66**	**27**

AU=Australia; FR=France

Supplementary Table 4. Reasons for screening failures

Reasons for Screening Failures	Number (% of 66)
Participants excluded after the screening PSG	40 (61%)
Due to AHI < 20 events/hr	28
Due to positional OSA	6
Due to AHI > 60 events/hr	3
Due to combined central/mixed AHI > 10 events/hr	3
Participants excluded due to a BMI > 32 kg/m^2	2 (3%)
Participants excluded after the surgical consultation	3 (4%)
Due to large tonsil size	2
Due to congenital malformation	1
Participants excluded after DISE due to CCC	12 (18%)
Participants excluded for other reasons	9 (14%)
Withdrawal of consent	7
Shift worker	1
Intake of medications that affect sleep, alertness or breathing	1
Total number of screen failed participants	**66 (out of 93)**

PSG=polysomnography; AHI=apnea hypopnea index; OSA=obstructive sleep apnea; BMI=body mass index; DISE=drug induced sleep endoscopy; CCC=complete concentric collapse.

Supplementary Table 5. Most frequent device-related adverse events (AEs)

Description of AE	#AEs	# of Participants	Fully Resolved	Partially Resolved	Ongoing
Local skin irritation	9	8	8	0	1
Abnormal scarring	5	3	5	0	0
Tongue abrasion	4	3	4	0	0
Tongue fasciculations	4	3	4	0	0
Discomfort due to electrical stimulation	3	3	2	0	1

Supplementary Table 6. Outcome measures for per protocol analyses.

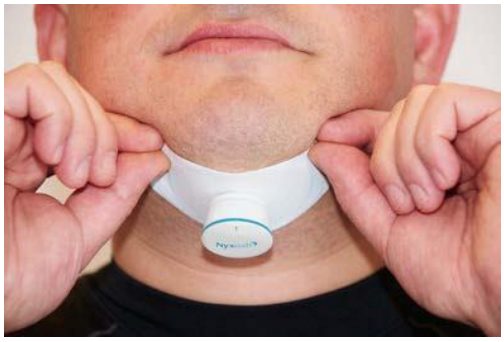
Outcome	Baseline (N=19)	6 months (N=19)	Mean Difference (95% CI)	P-value
Sleep Disordered Breathing				
AHI, events/hr	22.2 (12.0)	11.0 (9.5)	11.2 (15.5 to 6.9)	<0.0001
ODI, events/hr	18.2 (10.4)	8.0 (5.4)	10.2 (13.9 to 6.4)	<0.0001
SaO_2<90%, % time	5.5 (6.3)	2.2 (3.2)	3.3 (5.2 to 1.4)	0.0016
AI, events/hr	9.6 (10.6)	5.0 (9.0)	4.5 (9.4 to -0.4)	0.0673
HI, events/hr	11.3 (6.4)	5.9 (4.7)	5.4 (7.8 to 3.0)	0.0002
Symptoms				
ESS	10.8 (5.3)*	7.4 (5.4)	3.7 (6.6 to 0.9)	0.0129
FOSQ-10	15.2 (3.4)	17.7 (2.4)	2.4 (0.9 to 4.0)	0.0038
Sleep Architecture				
Sleep Efficiency, %	83.7 (11.6)	87.0 (9.4)	3.3 (-0.4 to 7.1)	0.0785
NREM Stage 1, %	13.5 (8.2)	8.6 (4.1)	4.9 (8.8 to 1.1)	0.0149
NREM Stage 2, %	60.1 (9.0)	66.7 (10.0)	6.8 (1.5 to 12.1)	0.0148
NREM Stage 3, %	8.2 (7.3)	3.3 (4.6)	4.9 (7.2 to 2.6)	0.0002
REM, %	18.2 (6.7)	21.2 (7.7)	3.0 (-0.7 to 6.8)	0.1078
ArI, events/hr	25.5 (8.5)	13.9 (6.0)	11.7 (15.9 to 7.5)	<0.0001

AHI=apnea hypopnea index unless otherwise specified. AHI=apnea hypopnea index; ODI=4% oxygen desaturation index; SaO_2<90%=proportion of the night spent at an oxygen saturation below 90%; AI=apnea index; HI=hypopnea index; ESS=Epworth Sleepiness Scale; FOSQ10=the 10-item Functional Outcomes of Sleep Questionnaire; NREM sleep=non rapid-eye movement; REM sleep=rapid eye movement; ArI=arousal index. *N=18.

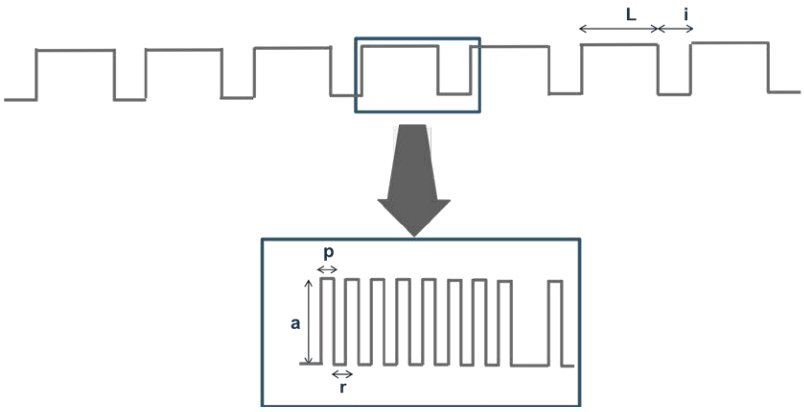
Supplementary Table 7. Snoring scoring report at baseline vs 6-Month Visit

Snoring scale	Baseline (N=24)	6-Month Visit (N=20)
No snoring	0%	10%
Soft snoring	4.2%	55%
Loud snoring	45.8%	20%
Very intense snoring	29.2%	0%
Bed partner/patient leaves room due to snoring	20.8%	15%

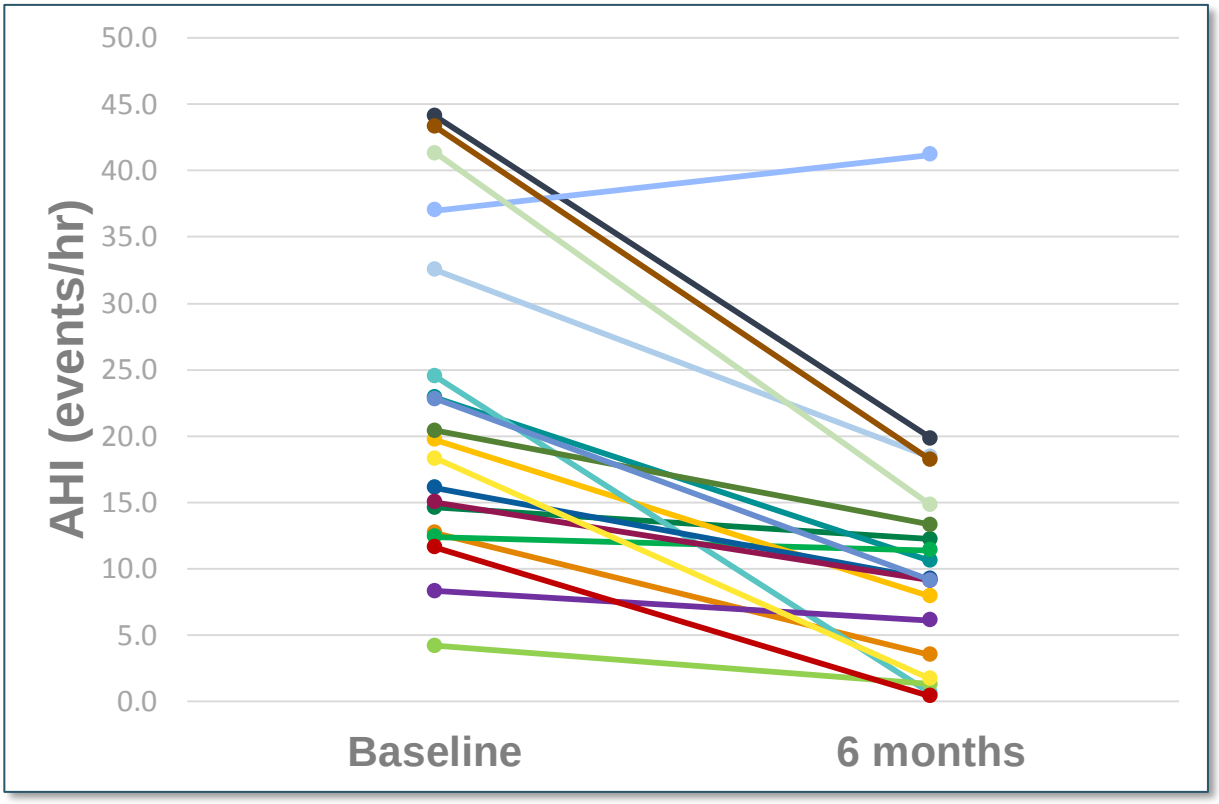
Participants were asked to assess how their bed partner scored their snoring intensity on a categorical scale (no snoring, soft snoring, loud snoring, very intense snoring, or bed partner/patient leaves room). Supplementary Table 6 provides the percentage of participants in each category at baseline (N=24) and at the 6-month visit (N=20). The reason why some participants do not appear in the baseline or 6-month data is that they either did not have a bed partner or did not reach the 6-month visit. The percentage of bed partners reporting no- or soft snoring increased from 4.2% at baseline to 65% at the 6-month visit.



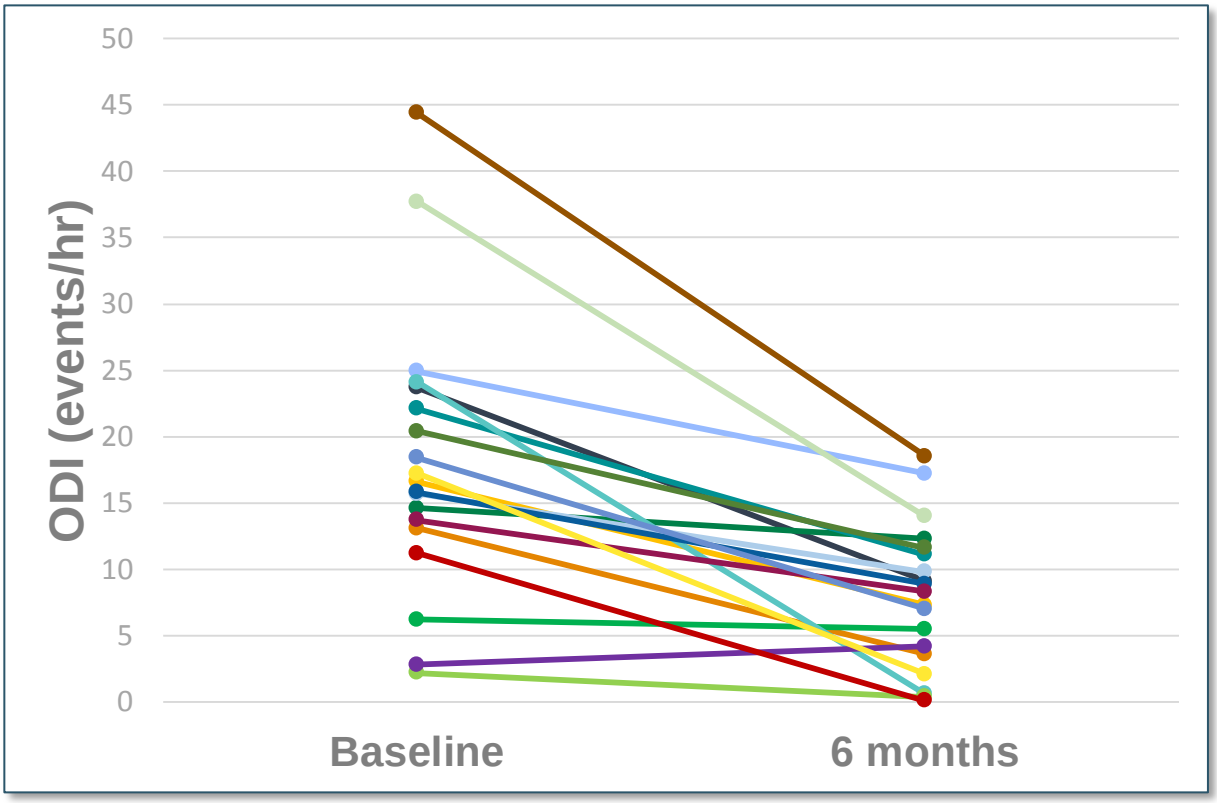
Supplementary Figure 1. Disposable patch and activation unit



Supplementary Figure 2. Stimulation parameters included stimulation ON time (train length, L); stimulation OFF time (train interval, i); stimulation amplitude (a), pulse duration (r) and the pulse frequency.



Supplementary Figure 3. Change in Apnea Hypopnea Index (AHI) for each participant from baseline to 6 months post-implantation. Each coloured line represents an individual participant using per protocol analyses (n=19).



Supplementary Figure 4. Change in 4% Oxygen Desaturation Index (ODI) for each participant from baseline to 6 months post-implantation. Each coloured line represents an individual participant using per protocol analyses (n=19).