ONLINE DATA SUPPLEMENT

Title

Bilateral Hypoglossal Nerve Stimulation for Treatment of Obstructive Sleep Apnea

Authors

Peter R. Eastwood, PhD[1,2], Maree Barnes, MD[3,4], Stuart G. MacKay, MD[5,6,7,8], John R. Wheatley, MD[9,10,11], David R Hillman, MD[1,2], Xuân-Lan Nguyên, MD[12.13], Richard Lewis, MD[14, 15], Matthew C Campbell, MD[3,4], Boris Pételle, MD[16], Jennifer H Walsh, PhD[1,2], Andrew C Jones, MD[5,6,7], Carsten E Palme, MD[10,17], Alain Bizon, MD[18], Nicole Meslier, MD[19,20], Chloé Bertolus, MD[21,22], Kathleen J Maddison, PhD[1,2], Laurent Laccourreye, MD[18], Guillaume Raux, PhD[23], Katleen Denoncin, PhD[23], Valérie Attali, MD[13,21], Frédéric Gagnadoux, MD[19,20], Sandrine H Launois, MD[12.13].

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 S1)*.

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 S1. 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 S2. 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 S3. 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 S4. 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 S5. 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 S6. 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

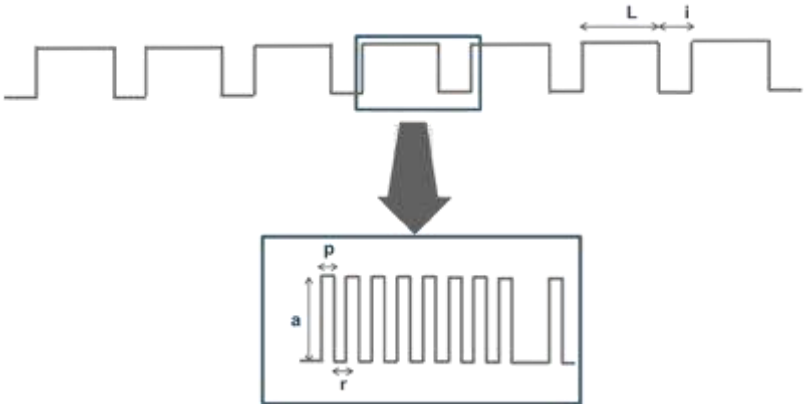
AHI=apnea hypopnea index unless otherwise specified. AHI=apnea hypopnea index; ODI=4% oxygen desaturation index; SaO_2<90%=proportion of the night spent at an oxygen saturation below 90%; AI=apnea index; HI=hypopnea index; ESS=Epworth Sleepiness Scale; FOSQ10=the 10-item Functional Outcomes of Sleep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

Supplementary Table S7. Snoring scoring report at baseline vs 6-Month Visit

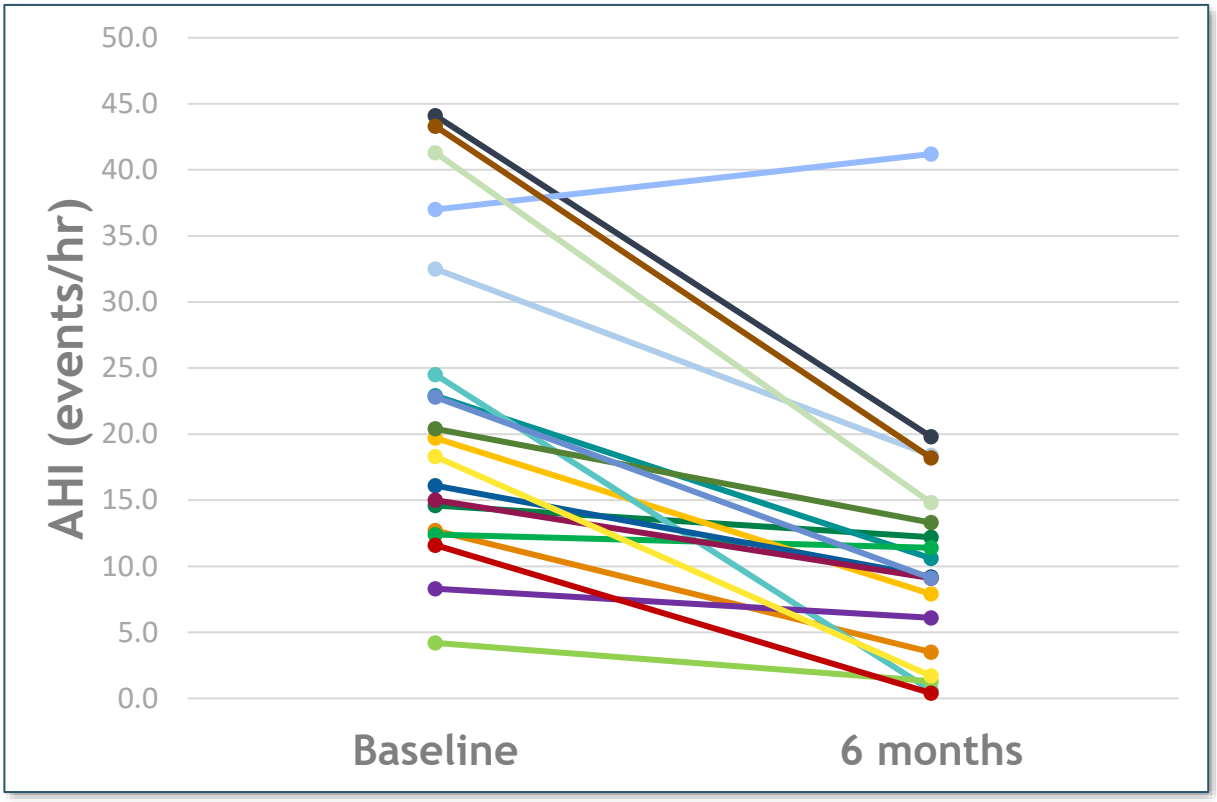
Snoring scale	Baseline (N=24)	6-Month Visit (N=20)
No snoring	0%	10%
Soft snoring	4.2%	55%
Loud snoring	45.8%	20%
Very intense snoring	29.2%	0%
Bed partner/patient leaves room due to snoring	20.8%	15%

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.

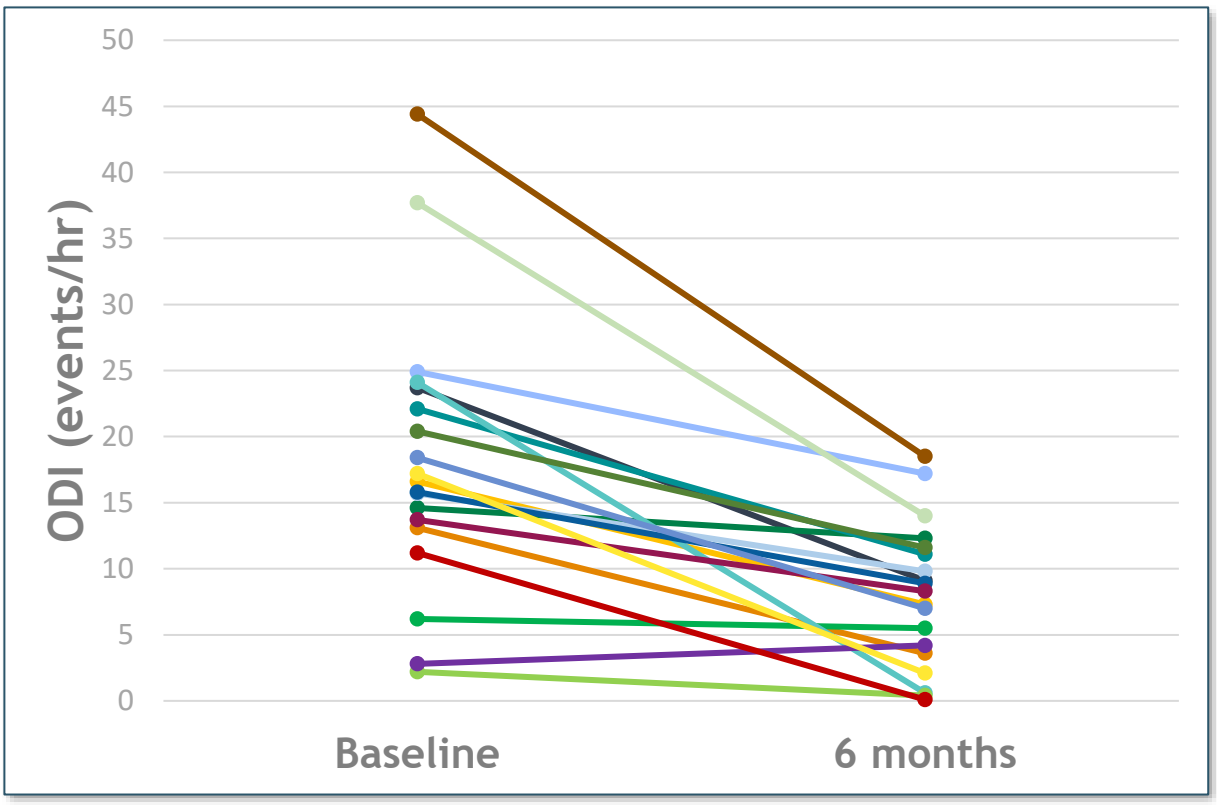
Supplementary Figure S1. Disposable patch and activation unit



Supplementary Figure S2. 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 S3. 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 S4. 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).