

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NYXOAH, INC., and
NYXOAH SA,
Petitioners,

v.

INSPIRE MEDICAL SYSTEMS, INC.,
Patent Owner.

U.S. Patent No. 11,806,526

Issue Date: November 7, 2023

Title: STIMULATION FOR TREATING SLEEP DISORDERED BREATHING

Inter Partes Review No.: IPR2026-00091

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 11,806,526
UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.107**

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TABLE OF CONTENTS

	Page
I. Introduction.....	1
II. Overview.....	1
III. Grounds for Standing (37 C.F.R. §42.104(A)).....	8
IV. '526 Patent Summary	8
V. Prosecution History	11
A. Filing Date and Priority	11
B. Prosecution	11
VI. Claim Construction.....	13
VII. Person of Ordinary Skill in the Art.....	13
VIII. State of the Art.....	14
A. Neuromuscular Stimulators.....	14
B. OSA Treatment.....	15
1. Closed-Loop Systems	16
2. Open-Loop Systems.....	17
C. Duty Cycles	17
IX. Identification of Challenges.....	18
A. Challenged Claims	18
B. Statutory Grounds for Challenges	18
X. Identification of How the Challenged Claims are Unpatentable.....	20
A. Ground 1: Claims 1-8, 10-18, 21-23 are Obvious from Durand-Hoegh	20

Petition for *Inter Partes* Review of U.S. Patent No. 11,806,526

1.	Durand.....	20
2.	Hoegh	23
3.	Motivation to Combine Durand and Hoegh	23
4.	Application of Durand-Hoegh to Claims 1-8, 10-18, 21-23.....	27
a.	Claim 1.....	27
b.	Claim 2.....	34
c.	Claim 3.....	35
d.	Claim 4.....	35
e.	Claim 5.....	38
f.	Claim 6.....	39
g.	Claim 7.....	39
h.	Claim 8.....	40
i.	Claim 10.....	40
j.	Claim 11.....	41
k.	Claim 12.....	42
l.	Claim 13.....	43
m.	Claim 14.....	44
n.	Claim 15.....	45
o.	Claim 16.....	45
p.	Claim 17.....	47
q.	Claim 18.....	48
r.	Claim 21.....	49
s.	Claim 22.....	50

t.	Claim 23.....	52
B.	Ground 2: The Challenged Claims are Obvious from Headley- Tran.....	52
1.	Headley	52
2.	Tran	53
3.	Motivation to Combine Headley and Tran	56
4.	Application of Headley-Tran to the Challenged Claims	59
a.	Claim 1.....	59
b.	Claim 2.....	65
c.	Claim 3.....	66
d.	Claim 4.....	66
e.	Claim 5.....	69
f.	Claim 6.....	69
g.	Claim 7.....	70
h.	Claim 8.....	71
i.	Claim 9.....	71
j.	Claim 10.....	72
k.	Claim 11.....	73
l.	Claim 12.....	73
m.	Claim 13.....	74
n.	Claim 14.....	75
o.	Claim 15.....	76
p.	Claim 16.....	76

Petition for *Inter Partes* Review of U.S. Patent No. 11,806,526

q.	Claim 17.....	78
r.	Claim 18.....	78
s.	Claim 19.....	79
t.	Claim 20.....	80
u.	Claim 21.....	80
v.	Claim 22.....	81
w.	Claim 23.....	82
XI.	Mandatory Notices Under 37 C.F.R. § 42.8.....	82
A.	Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)).....	82
B.	Related Matters (37 C.F.R. § 42.8(b)(2)).....	83
1.	Judicial Matters	83
2.	Administrative Matters	83
3.	Related Patents.....	83
C.	Lead/Back-up Counsel (37 C.F.R. § 42.8(b)(3)):	83
D.	Notice of Service Information (37 C.F.R. § 42.8(b)(4)):.....	84
XII.	Conclusion	84

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35 U.S.C. §103	1, 18
----------------------	-------

35 U.S.C. §§ 311 <i>et seq.</i>	1
---------------------------------------	---

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37 C.F.R. § 42.8	82
------------------------	----

37 C.F.R. § 42.8(b)(1)	82
------------------------------	----

37 C.F.R. § 42.8(b)(2)	83
------------------------------	----

37 C.F.R. § 42.8(b)(3)	83
------------------------------	----

37 C.F.R. § 42.104(A)	8
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37 C.F.R. § 42.106(a)	8
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37 C.F.R. § 42.108	1
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Petitioners' Exhibit List

<i>Exhibit #</i>	<i>Description</i>
1001	U.S. Patent No. 11,806,526 (the "'526 Patent")
1002	Select portions of the prosecution history of the '526 Patent ("File History")
1003	Declaration of Petitioners' Expert Dr. Gerald Loeb
1004	Declaration of Petitioners' Expert Dr. Ingrid Hsieh-Yee
1005	International Patent Application Publication No. WO 2016/149344
1006	U.S. Patent Application Publication No. 2006/0224211 ("Durand")
1007	U.S. Patent Application Publication No. 2015/0094962 ("Hoegh")
1008	International Patent Application Publication No. WO 2010/006218 ("Headley")
1009	Tran et al., "Development of Asynchronous, Intralingual Electrical Stimulation to Treat Obstructive Sleep Apnea," Proceedings of the 25th Annual International Conference of the IEEE EMBS, Cancun, Mexico (September 17-21, 2003) ("Tran-I")
1010	Tran et al., "First Subject Evaluated with Simulated BION™ Treatment in Posterior Genioglossus to Prevent Obstructive Sleep Apnea," Proceedings of the 26th Annual International Conference of the IEEE EMBS, San Francisco, CA (September 1-5, 2004) ("Tran-II")
1011	U.S. Patent No. 5,944,680 ("Christopherson")
1012	U.S. Patent Application Publication No. 2014/0228905 ("Bolea")
1013	Mortimer, "Electrical Excitation of Nerve," Neural Prostheses – Fundamental Studies, Chapter 3 (1990) ("Mortimer")
1014	Anagnostopoulos, et al., "Electronic Pacemakers of the Heart, Gastrointestinal Tract, Phrenic Nerve, Bladder, and Carotid Sinus: Current Status," Surgery 60:2, 480-494 (August 1966) ("Anagnostopoulos")
1015	Glenn et al., "Electrical Stimulation of Excitable Tissue by Radio-Frequency Transmission," Annals of Surgery 160:3, 338-350 (1964) ("Glenn")
1016	Judson et al., "Radio-Frequency Electrophrenic Respiration – Long-Term Application to a Patient with Primary Hypoventilation," JAMA 203:12, 1033-1037 (March 18, 1968) ("Judson")

<i>Exhibit #</i>	<i>Description</i>
1017	Singh, et al., “Recruitment Properties of Intramuscular and Nerve-Trunk Stimulating Electrodes,” IEEE Transactions on Rehabilitation Engineering, 8:3, 276-285 (September 2000) (“Singh”)
1018	Richmond et al., “Tactical Application of Sensorimotor Prosthetic Technology,” Proceedings of the 25th Annual International Conference of the IEEE EMBS, Cancun, Mexico (September 17-21, 2003) (“Richmond”)
1019	Edmonds, et al., “The Effects of Transcutaneous Electrical Stimulation During Wakefulness and Sleep in Patients with Obstructive Sleep Apnea,” Am Rev Respir Dis, 146:1030-1036 (1992) (“Edmonds”)
1020	Miki et al., “Effects of Submental Electrical Stimulation During Sleep on Upper Airway Patency in Patients with Obstructive Sleep Apnea,” Am Rev Respir Dis 140:1285-1289 (1989) (“Miki”)
1021	Decker et al., “Functional Electrical Stimulation and Respiration During Sleep,” Journal of Applied Physiology, 75(3): 1053-1061 (1993) (“Decker”)
1022	Eisele et al., “Direct Hypoglossal Nerve Stimulation,” Arch. Otolaryngol Head Neck Surg., 123:57-61 (1997) (“Eisele1997”)
1023	Fuller et al., “Effect of Co-Activation of Tongue Protrudor and Retractor Muscles on Tongue Movements and Pharyngeal Airflow Mechanics in the Rat,” Journal of Physiology 519, 2, 601-613 (1999) (“Fuller”)
1024	U.S. Patent No. 6,572,543 (“Christopherson ’543”)
1025	Schwartz et al., “Electrical Stimulation of the Lingual Musculature in Obstructive Sleep Apnea,” J Appl Physiol. (81(2):643-652 (1996) (“Schwartz1996”)
1026	Goding et al., “Relief of Upper Airway Obstruction With Hypoglossal Nerve Stimulation in the Canine,” Laryngoscope, 108:162-169 (1998) (“Goding”)
1027	U.S. Patent No. 4,830,008 (“Meer”)
1028	Yoo et al., “Selective Stimulation of the Hypoglossal Nerve: A FINE Approach to Treating Obstructive Sleep Apnea,” Proceedings of the Second Joint EMBS/BMES Conference, 2049-2050 (October 23-26, 2002) (“Yoo”)
1029	Fairbanks et al., “Neurostimulation for Obstructive Sleep Apnea,” ENT Journal (January 1993) (“Fairbanks”)

<i>Exhibit #</i>	<i>Description</i>
1030	Schwartz et al., “Therapeutic Electrical Stimulation of the Hypoglossal Nerve in Obstructive Sleep Apnea,” Arch Otolaryngol Head Neck Surg., Vol. 127 (Oct. 2001) (“Schwartz2001”)
1031	Oliven, “Treating Obstructive Sleep Apnea with Hypoglossal Nerve Stimulation,” Current Opinion in Pulmonary Medicine 17:419-424 (2011) (“Oliven”)
1032	Mwenge et al., “Targeted Hypoglossal Neurostimulation for Obstructive Sleep Apnoea: a 1-Year Pilot Study,” Eur Respir J. 41:360-367 (2013) (“Mwenge”)
1033	Zaidi et al., “Tongue Anatomy and Physiology, the Scientific Basis for a Novel Targeted Neurostimulation System Designed for the Treatment of Obstructive Sleep Apnea,” Neuromodulation; 16:376-386 (2013) (“Zaidi”)
1034	Steier et al., “Continuous Transcutaneous Submental Electrical Stimulation in Obstructive Sleep Apnea,” Chest 140:998-1007 (2011) (“Steier”)
1035	Agnew et al., “Considerations for Safety with Chronically Implanted Nerve Electrodes,” Epilepsia, 31 (Suppl. 2): S27-32 (1990) (“Agnew”)
1036	U.S. Patent No. 7,277,749 (“Gordon”)
1037	Meadows et al., “Effective of Targeted Activation of Tongue Muscles on Oropharyngeal Patency in the Rat,” Journal of the Neurological Sciences, 346:178-193 (August 2014) (“Meadows”)
1038	Eastwood et al., “Treating Obstructive Sleep Apnea with Hypoglossal Nerve Stimulation,” SLEEP, 34:11, 1479-1486C (2011) (“Eastwood”)
1039	Sinha et al., “Safety of Microstimulator During Radiation Therapy – A Preliminary Study on Head and Neck Cancer Patients,” J. Nucl. Med. Radiat. Ther. 5:4 (2014) (“Sinha”)
1040	Kaplan et al., “Preventing ischial pressure ulcers: III. Clinical pilot study of chronic neuromuscular electrical stimulation,” Applied Bionics and Biomechanics 8, 345359 (2011) (“Kaplan”)
1041	Bailey et al., “Anatomic consequences of intrinsic tongue muscle activation,” J Appl Physiol 101:1377-1385 (2006) (“Bailey”)
1042	Brennick et al., “MRI study of pharyngeal airway changes during stimulation of the hypoglossal nerve branches in rats,” J Appl Physiol 90:1373-1384 (2001) (“Brennick”)

Petition for *Inter Partes* Review of U.S. Patent No. 11,806,526

<i>Exhibit #</i>	<i>Description</i>
1043	Oliven et al., “Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea,” J Appl Physiol 95:2023-2029 (2003) (“Oliven2003”)
1044	Oliven et al., “Effect of coactivation of tongue protrusor and retractor muscles on pharyngeal lumen and airflow in sleep apnea patients,” J Appl Physiol 103:1662-1668 (2007) (“Oliven2007”)

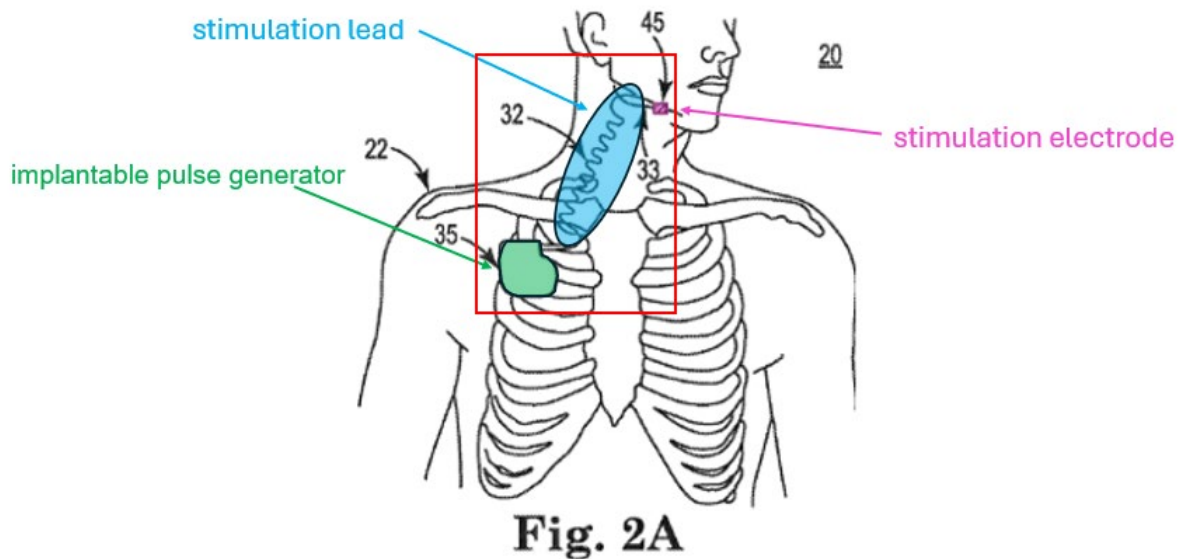
I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311 *et seq.* and 37 C.F.R. §§ 42.1 *et seq.*, Nyxoah, Inc. and Nyxoah SA (“Petitioners”) hereby petition for *inter partes* review of U.S. Patent No. 11,806,526 (“’526 Patent”). Claims 1-23 (the “Challenged Claims”) of the ’526 Patent are unpatentable under 35 U.S.C. §103 in view of the prior art references discussed herein. This Petition demonstrates by a preponderance of the evidence that there is a reasonable likelihood that Petitioners will prevail with respect to at least one of the Challenged Claims. Institution of *inter partes* review of the ’526 Patent pursuant to 37 C.F.R. § 42.108 is requested respectfully.

II. OVERVIEW

The Challenged Claims are unpatentable as obvious over the prior art, as they do nothing more than claim conventional devices (neurostimulators) operating in a known way (asynchronously) to treat obstructive sleep apnea (“OSA”). The Challenged Claims recite a device for treating OSA including a non-cardiac stimulation means for stimulating an upper airway patency-related nerve using a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods that are asynchronous to (i.e., not synchronized with) a patient’s breathing. The non-cardiac stimulation means includes an implantable electrode and/or an implantable pulse generator.

Annotated FIG. 2A of the '526 Patent shows a device having **electrode portion 45**, electrically coupled to **implantable pulse generator 35** via **stimulation lead 32**, which engages and stimulates the hypoglossal nerve (“HGN”).

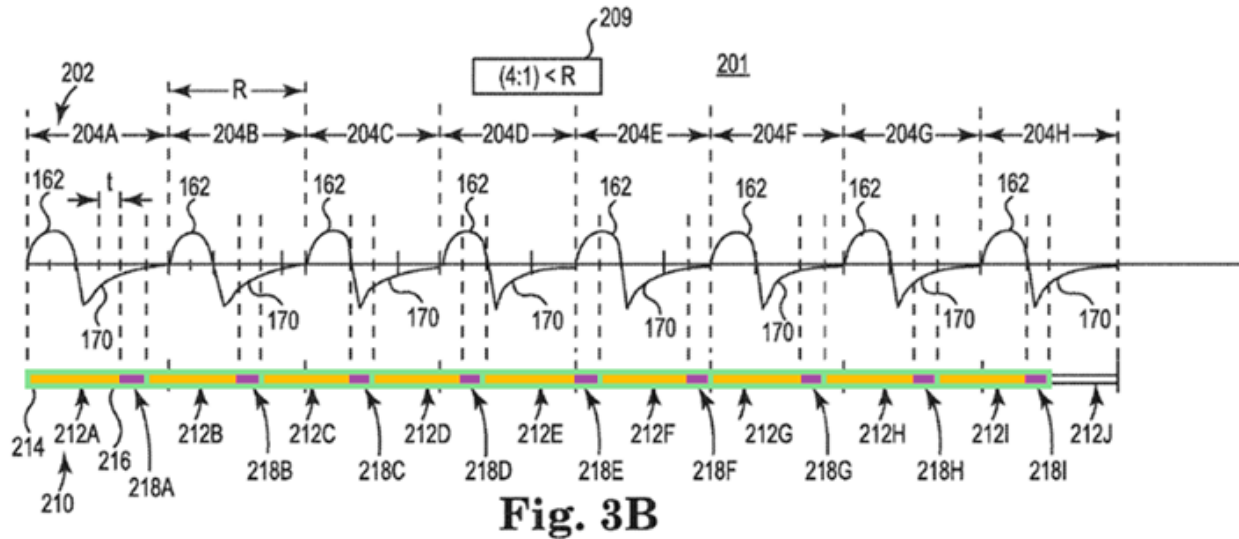
EX-1001 FIG. 2.¹

The '526 Patent acknowledges neurostimulation devices for treating OSA, which included non-cardiac stimulation means, were well-known and widely implemented prior to March 2015. EX-1001 9:3-10:10.

The purported novelty of the '526 Patent is treating OSA using asynchronous stimulation (i.e., stimulation based on a stimulation cycle not

¹ All colored annotations added unless otherwise stated.

synchronized to actively-sensed respiration) in which the stimulation periods 212 are greater than respective non-stimulation periods 218.



EX-1001 FIG. 3B, 12:637-13:9, 13:28-35.

Treatment of OSA using asynchronous stimulation was not new, having been disclosed over a decade before the priority date of the '526 Patent. For example, each of Durand, Hoegh, Headley, and Tran discloses treating OSA by repeatedly stimulating the HGN asynchronously (i.e., without using actively sensed breathing for timing).

Ground 1 demonstrates the Challenged Claims are obvious over the combination of Durand and Hoegh. Durand discloses the identical architecture of the '526 Patent for treating OSA.

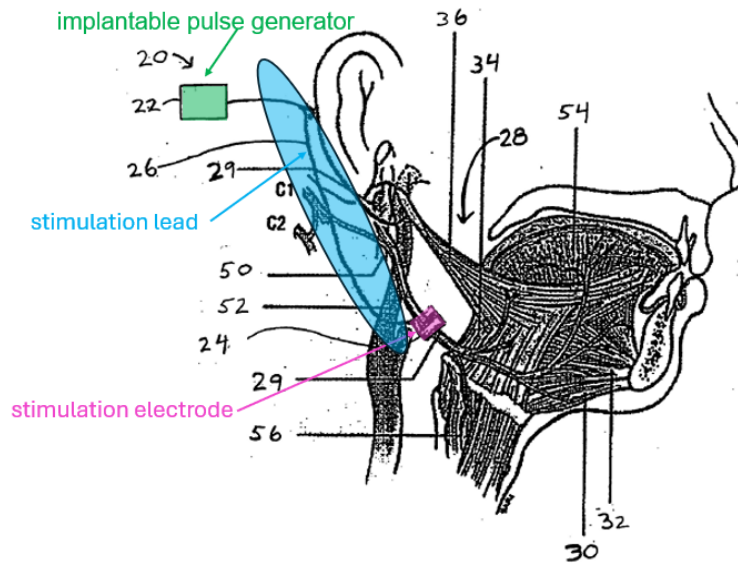


FIG. 1

EX-1006 FIG. 1.

Durand discloses apparatus 20 including **implantable pulse generator** 22 for generating the desired electrical stimulus via **stimulus lead** 26 connected to **stimulation electrode** 24, which is further connected to the HGN. EX-1006 ¶14.

Durand further discloses that **intermittent electrical stimulation** at controlled intervals (predetermined based on the patient's resting nighttime metabolism by observing the nighttime respiratory rate) avoids "the added complexity of closed-loop feedback," e.g., the added complexity of synchronous stimulation. EX-1006 ¶¶4, 25.

Durand discloses **applying a stimulation signal** for about 2-3 seconds with a **wait** of at least 2-3 seconds between the **pulse trains**. Durand does not expressly

disclose basing the duration of the **stimulation period** on a reference respiratory-related parameter, but Hoegh discloses that “[t]he hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire respiratory phase” and “[t]o mimic this natural physiology, stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms.” EX-1007 ¶¶92. Hoegh further discloses “the maximum stimulation duty cycle may be set from 41% to 69% in 3% increments,” which includes the **stimulation period** having a duration that exceeds the duration of the **non-stimulation period**. EX-1007 ¶¶98, 114.

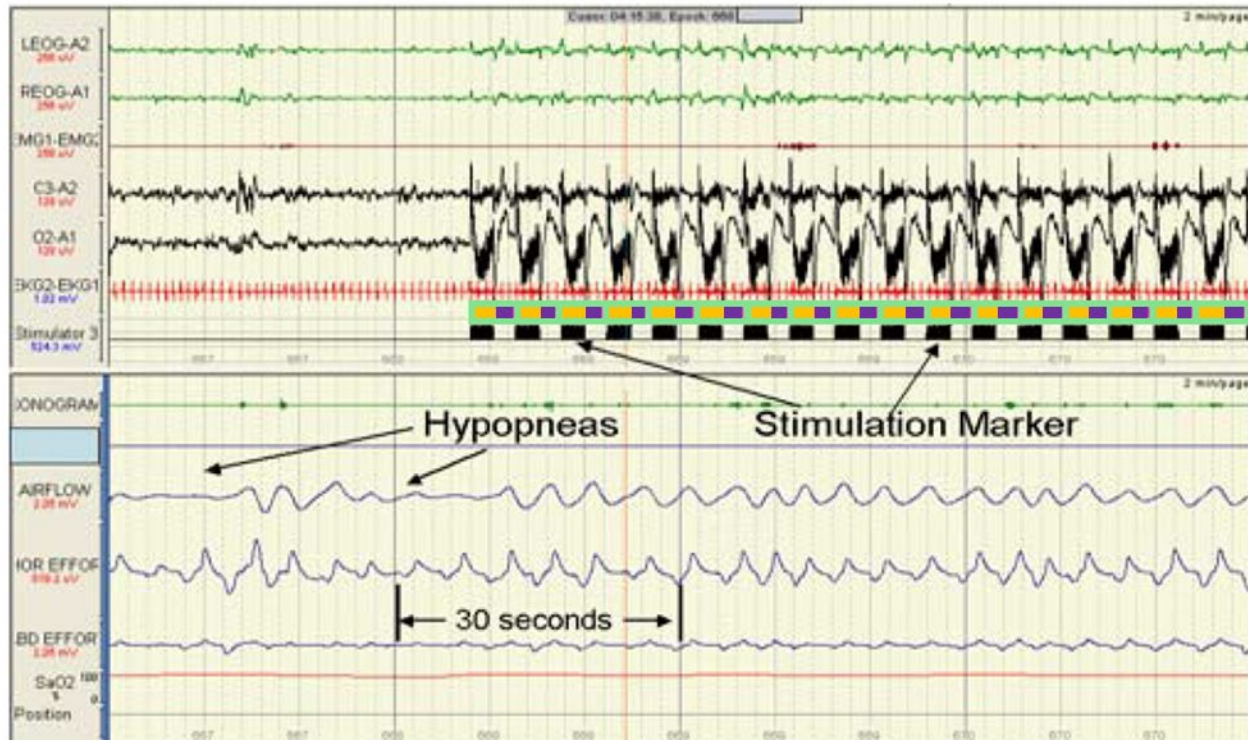
A POSITA understood the teachings of Durand and Hoegh could be combined given the two references disclose the same type of devices for treating OSA and use the same technique, i.e., asynchronously stimulating the HGN. EX-1003 ¶¶95-99. A POSITA would have been motivated to combine the teachings of Durand and Hoegh to provide a device that avoids the complexity of a sensing lead while providing stimulation that mimics the patient’s natural physiology and that covers the entire inspiratory phase of the patient’s natural respiratory cycle. EX-1003 ¶¶106, 110-113, 116-120. Accordingly, Challenged Claims 1-8, 10-18, and 21-23 are obvious from Durand and Hoegh.

With respect to Ground 2, Headley discloses an implantable device that stimulates the genioglossus (“GG”) asynchronously to treat OSA. The device

includes a receiver having a pulse generator and a stimulating electrode. EX-1008 ¶¶29-30. Headley also discloses providing an alternating on/off treatment in which the tissue is stimulated for a given period then allowed to rest for a given period before being stimulated again. EX-1008 ¶48. Although Headley expressly a stimulation period duration that is greater than a non-stimulation period duration, Headley does not expressly disclose using a reference respiratory-related parameter.

Tran discloses a device for treating OSA similar to the device disclosed by Headley that is implanted in the tongue in close proximity to where the HGN branches to the GG. EX-1009 p.376. The device recruits the motor units stimulated by the HGN to open a patient's airway. *Id.* Brief trains of stimulation pulses are applied "at intervals close to the respiratory cycle of the patient" to synchronize the patient "spontaneously with the resulting intermittent periods of patency in the airway." EX-1009 p.377.

Annotated FIG. 4 of Tran-II below illustrates an asynchronous stimulation cycle with a stimulation period (ON period) of 3 seconds and a non-stimulation period (OFF period) of 2 seconds.



EX-1010 FIG. 4; EX-1009, p.377.

A POSITA would have been motivated to combine the teachings of Headley and Tran to provide a device for treating OSA that provides stimulation based on the patient's respiratory rate in order to have the patient spontaneously synchronize with the intermittent periods of patency in the airway. EX-1003 ¶¶239-244.

Advantageously, the combination of the references would provide a device that obviates the need for a sensor to synchronize stimulation with breathing while effectively improving airway patency. EX-1010, p.4288; EX-1003 ¶¶239-240.

The references used in the Grounds below demonstrate that the purported invention of the Challenged Claims was well-known at the time of the '526 Patent and unpatentable.

EX-1001 FIG. 2A.

In another embodiment, system 80 includes nerve-coupling electrode portion 82 and pulse generator 84. Electrode portion 82 may be mechanically and electrically coupled to or placed in close proximity to nerve 72 to enable electrical coupling of electrode portion 82 to nerve 72. Pulse generator 84 includes internal components 90 and may include external components 92. EX-1001 11:60-12:22.

FIG. 3A illustrates normal breathing pattern 150 in which respiratory cycle 160 includes inspiratory phase 162 and expiratory phase 170. Inspiratory phase 162 includes initial portion 164, intermediate portion 165, and end portion 166. Expiratory phase 170 includes initial portion 174, intermediate portion 175, end portion 176, and expiratory peak 177. EX-1001 12:43-56.

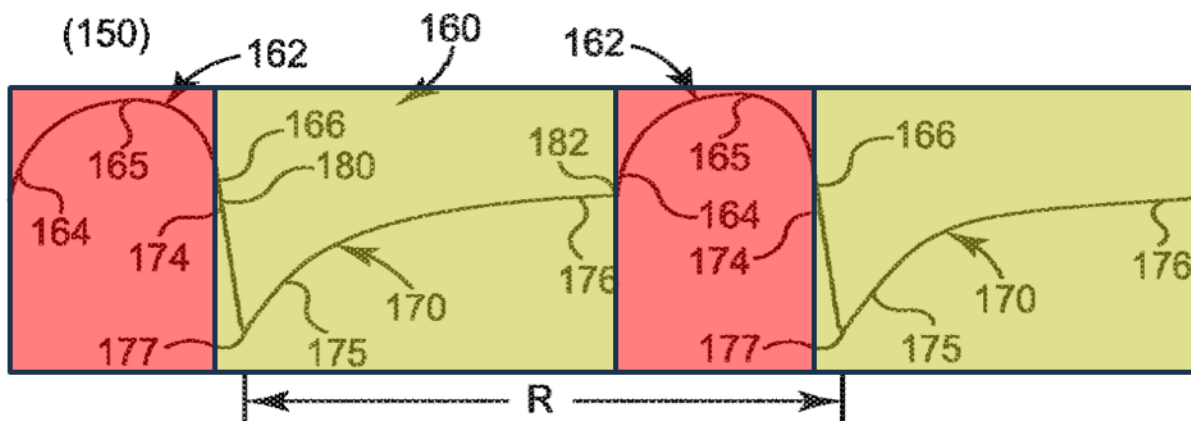
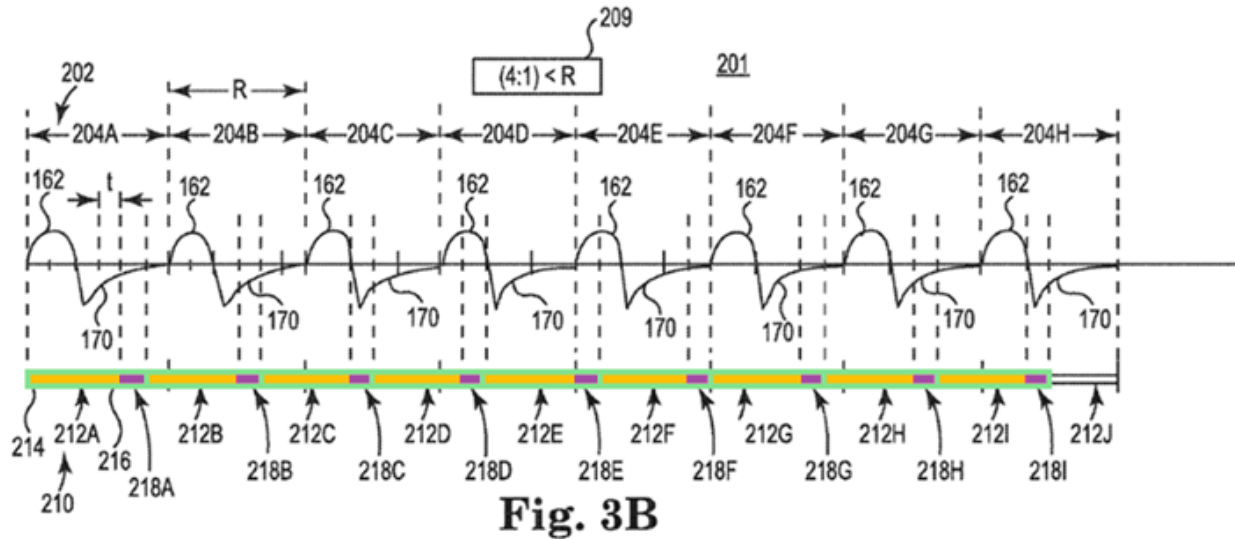


Fig. 3A

EX-1001 FIG. 3A.

FIG. 3B illustrates stimulation protocol 210 along with respiratory pattern 202 including a series of reference respiratory cycles 204A-204H each having

duration R. Respiratory pattern 202 represents stable respiration and is based on a historical patient-specific and/or multi-patient average respiratory cycle. EX-1001 12:57-13:45.



EX-1001 FIG. 3B.

Stimulation protocol 210 includes a series of **stimulation periods** 212A-212J spaced apart by **non-stimulation periods** 218A-218I such that duration R is divided into six time units. For some patients, the duration of the respiratory cycle is about 3-6 seconds, corresponding to a rate of 10-18 breaths/minute. Stimulation protocol 210 operates according to a **stimulation cycle** having a duration less than duration R and a **stimulation period** duration exceeding a **non-stimulation period** duration by a factor of 3. EX-1001 13:21-14:2.

According to the '526 Patent, because the overall duration of the **stimulation cycle** does not match duration R, stimulation protocol 210 ensures that each

successive stimulation period will fall along a different portion of successive respiratory cycles, overlapping with a portion of the inspiratory phase. EX-1001 14:56-15:2. FIGS. 3C-3D respectively illustrate a stimulation protocol 220 that operates according to a stimulation cycle having a duration greater than duration R and a stimulation cycle that has a variable duty cycle for each stimulation cycle. EX-1001 16:39-51.

V. PROSECUTION HISTORY

A. Filing Date and Priority

The application that issued as the '526 Patent ("’481 Application") was filed September 4, 2020 as a continuation of U.S. Application No. 15/562,714, filed September 28, 2017 as a national phase entry of International Application No. PCT/US2016/022611, filed March 16, 2016, claiming priority to U.S. Provisional Application No. 62/135,305 ("Provisional"), filed March 19, 2015. For this Petition, Petitioners assume the '526 Patent's earliest-claimed priority date—March 19, 2015—is the priority date.

B. Prosecution

The '481 Application was filed with 24 claims, including independent claims 1, 17, and 23. EX-1002 01561-1564. During prosecution, all of the pending claims were rejected as obvious over Bolea (EX-1012). EX-1002 00155-163.

In response, Applicant amended the independent claims to recite “a first stimulation therapy protocol.” EX-1002 00129-133. Applicant also argued that Bolea only discloses using an asynchronous or fixed mode during daytime familiarization and not as a therapy for sleep apnea. EX-1002 0134-136.

The Examiner, having been incorrectly persuaded by Applicant’s arguments and apparently misapprehending or overlooking certain disclosures in Bolea, issued a Notice of Allowance (“NOA_1”) on July 6, 2023. EX-1002 0088; EX-1003 ¶¶58-64.

NOA-1 included an examiner’s amendment amending each independent claim to require the non-cardiac stimulation means comprise an implantable electrode and/or an implantable pulse generator. EX-1002 0093-94. A corrected Notice of Allowance (“NOA-2”) was mailed on July 21, 2023 moving the prior examiner’s amendment to the end of the independent claims. EX-1002 0079-81. The ’526 Patent issued with the language presented in NOA-1, and a certificate of correction was issued on March 25, 2025, to correct the claim language to match that of NOA-2. EX-1002 0002. Independent claim 1 as corrected recites:

1.pre	<i>A device for treating obstructive sleep apnea, comprising:</i>
1.a1	<i>a non-cardiac stimulation means for stimulating an upper airway patency-related nerve,</i>
1.a2	<i>according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in</i>

	<i>which a timing of the stimulation periods is asynchronous relative to patient breathing,</i>
1.b	<i>wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and</i>
1.c	<i>wherein the duration of each respective stimulation period is based on a reference respiration-related parameter,</i>
1.d	<i>wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.</i>

VI. CLAIM CONSTRUCTION

Each claim term in the Challenged Claims should be given its plain and ordinary meaning in this proceeding, and no specific construction of any claim term is required because the prior art relied on in this Petition meets each of the claim terms under any reasonable construction.

VII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (“POSITA”) at the time of the ’526 Patent would have at least a bachelor’s degree in Electrical Engineering, Biomedical Engineering, or a related field and at least five years of training or additional work experience in neurostimulators or a related field. Through this formal education and/or training, a POSITA understood neuromuscular anatomy and physiology. Additional hands-on and design experience could compensate for less formal education and vice versa. EX-1003 ¶¶24-27.

VIII. STATE OF THE ART

The prior art references and the knowledge of a POSITA provide factual support for the state of the art at the time of the invention and provide additional motivation to modify and/or combine references. Accordingly, these references should be considered by the Board.

A. Neuromuscular Stimulators

Nerves can be excited by an applied electrical impulse that changes concentrations of potassium ions inside an axon and sodium ions outside, providing a fundamental principle behind clinical neuromuscular stimulators beginning in the mid-1900s. EX-1013, p.68; EX-1014, pp.480-482, 488; EX-1015, pp.339-346; EX-1016, p.1033. Muscle fibers are innervated (stimulated) by large diameter motor axons that originate in the central nervous system (typically brainstem or spinal cord). EX-1015, pp.338, 343-348; EX-1017, pp.276-277; EX-1018, p.2015. These axons are sensitive to electrical stimulation, which may be applied anywhere along their length. EX-1017, pp.276-277; EX-1003 ¶¶29-31.

Typical stimulation electrodes include nerve cuff electrodes wrapped around peripheral nerve trunks or branches; patch electrodes sutured onto the connective tissue of a nerve, muscles, or fascia, and intramuscular wire electrodes implanted near the terminal branches of the motor axons. EX-1014, pp.481-482; EX-1019, p.1031; EX-1017, pp.276-277; EX-1020, pp.1285-1286. Because electrical

excitation of an axon spreads throughout the branches of that axon regardless of where excitation was initiated, the effects on the muscle are the same for different electrode locations and types. EX-1003 ¶32.

Pulse generators for stimulating muscles were known and frequently used in laboratory and clinical settings. EX-1021, p.1055; EX-1019, p.1031; EX-1022, p.58; EX-1023, p.603; EX-1024 16:13-23. These stimulators, which could be external or implanted, included a processor and memory that allowed adjustments of voltage amplitude, pulse width, and/or frequency at which stimulation was applied, the length of the burst durations, and the intervals between bursts. EX-1006 ¶15; EX-1012 ¶462; EX-1021 p.1055; EX-1019 p.1031; EX-1022 p.58; EX-1023 p.603; EX-1024 16:13-23; EX-1003 ¶32.

B. OSA Treatment

OSA is caused by obstruction of the upper airway during sleep. EX-1020, p.1285. During sleep, the tongue prolapses due to diminished neuromuscular activity of the genioglossus (“GG”), causing pharyngeal occlusion. EX-1025, p.643; EX-1020, p.1285; EX-1026, pp.162-163; EX-1027 1:47-52; EX-1012 ¶6; EX-1028, p.2049. By the 1990s, stimulation of the HGN/GG was being investigated for OSA treatment due to low patient compliance with continuous positive airway pressure (“CPAP”) devices. EX-1020, p. 1285; EX-1027 2:67-3:5, 4:16-25; EX-1019, p.1031; EX-1025, pp.643-644; EX-1029, pp.52-53; EX-1021,

p.1053; EX-1022, p.58; EX-1026, pp.166-167; EX-1023, p.601. The development of neurostimulation therapies for OSA progressed to clinical systems by the early 2000s, including closed-loop systems and open-loop systems. EX-1030, p.1217; EX-1031, pp.337-339; EX-1038, p.1480; EX-1003 ¶¶33-35.

Regardless of the type of therapy system (e.g., open loop or closed loop), titration was a typical step in providing the treatment and was done after implantation of the device. EX-1012 ¶¶ 536-537, 556-592; EX-1031, p.422; EX-1032, pp.361-362. Titration typically involved applying stimulation to a patient under observation and varying one or more stimulation parameters (e.g., pulse width, amplitude, frequency, and duty cycle). EX-1012 ¶¶556-592. The goal of titration was to identify the optimal stimulation settings that would provide an effective, desired response (e.g., increased airway patency) in a manner that was safe and comfortable to the patient to ensure compliance with the treatment. EX-1012 ¶¶527, 556-558. Titration and the adjustment of one or more stimulation parameters, including increasing/decreasing the stimulation duty cycle, involved nothing more than the exercise of routine skill in the art. EX-1003 ¶36.

1. Closed-Loop Systems

Clinical closed-loop systems included electrode(s), pulse generator, and sensors (such as an intrathoracic pressure sensor) for actively sensing a patient's respiration cycle to synchronize stimulation. EX-1030, p.1217; EX-1038, p.1480.

The stimulation parameters (e.g., voltage or current amplitude, pulse width, and pulse frequency) and the duration during which the stimulation was provided were configured specifically for each patient. EX-1030, p.1217; EX-1038, pp.1480-81; EX-1003 ¶37.

2. Open-Loop Systems

Clinical open-loop systems similarly included a pulse generator and an electrode, but differed in that they did not require the use of a sensor. EX-1032, pp.361-362; EX-1033, p.384. Instead, these systems relied on either continuous (e.g., constantly pulsed) or intermittent (e.g., periodically pulsed) asynchronous stimulation to treat OSA. EX-1034, p.999; EX-1033, p. 384; EX-1003 ¶38.

C. Duty Cycles

Duty cycles (e.g., the proportion of time stimulation is applied during a given period) were known and used to provide recovery time and avoid neural damage and muscle fatigue. EX-1035, pp. S27, S29; EX-1026, p.167; EX-1033, pp. 382, 384; EX-1037, p.191; EX-1036, 10:1-29. Both open-loop and closed-loop systems for treating OSA utilized duty cycles. EX-1033, p.384; EX-1026, p.163; EX-1030, p.1217. The duty cycle of an open-loop system typically was fixed based on a patient's historical average of sleeping respiratory rate. EX-1012 ¶266; EX-1026, p.163; EX-1030, p.1217; EX-1033, p.384; EX-1003 ¶¶39-40.

Stimulation of the HGN causes the tongue to protrude, increasing the size of the upper airway and resisting collapse during inspiration. EX-1012 ¶162; EX-1018, pp.2017-2018; EX-1036, 7:20-28, 8:61-9:15. Stimulation of the HGN was targeted to the inspiratory phase of a patient's respiratory cycle. EX-1026, p.168; EX-1030, p.1221; EX-1038, p.1480 . To ensure open-loop systems applied stimulation during the inspiratory phase, duty cycles of greater than 50% were used. EX-1012 ¶473; EX-1018, p.2019; EX-1009, p.377; EX-1010, p.4288; EX-1003 ¶41.

IX. IDENTIFICATION OF CHALLENGES

A. Challenged Claims

Claims 1-23 of the '526 Patent are challenged in this Petition.

B. Statutory Grounds for Challenges

The Challenges are set forth in detail below and summarized as follows:

Ground	Claims	Basis	References
1	1-8, 10-18, 21-23	§103	Durand, either alone or in view of Hoegh
2	1-23	§103	Headley in view of Tran

Ground 1: Claims 1-8, 10-18, and 21-23 are obvious over U.S. Patent Application Publication 2006/0224211 (EX-1006, “Durand”) in combination with U.S. Patent Application Publication No. 2015/0094962 (EX-1007, “Hoegh”).²

Durand published on October 5, 2006 and qualifies as prior art under §102(a)(1)(AIA). The patent corresponding to Durand was one of over 350 references cited in an IDS filed on January 23, 2018 (EX-1003 ¶¶67), but was not applied by the Office during prosecution.

Hoegh is the pre-grant publication of U.S. Patent Application 14/505,151, filed on October 2, 2014, claiming priority to U.S. Provisional Applications 61/885,991, filed October 2, 2013, and 62/058,914, filed October 2, 2014. Hoegh qualifies as prior art under §102(a)(2)(AIA). Hoegh was not cited or applied by the Office during prosecution.

Ground 2: Claims 1-23 are obvious over International Patent Application Publication WO 2010/006218 (EX-1008, “Headley”) in combination with two works of Tran, et al. (Tran et al., “Development of Asynchronous, Intralingual Electrical Stimulation to Treat Obstructive Sleep Apnea,” Proceedings of the 25th Annual International Conference of the IEEE EMBS, September 17-21, 2003 (EX-1009, “Tran-I”), and Tran et al., “First Subject Evaluated with Simulated BION™

² Referred to herein as “Durand-Hoegh.”

Treatment in Posterior Genioglossus to Prevent Obstructive Sleep Apnea,”
Proceedings of the 26th Annual International Conference of the IEEE EMBS,
September 1-5, 2004 (EX-1010, “Tran-II”), which cites and builds on Tran-I)
(collectively “Tran”).³

Headley published on January 14, 2010 and qualifies as prior art under
§102(a)(1)(AIA). Headley was not cited or applied by the Office during
prosecution.

Tran-I was publicly accessible no later than February 2004, EX-1004 ¶¶48-
50, and thus qualifies as prior art under at least §102(a)(1)(AIA). Tran-II was
publicly accessible no later than November 2004, EX-1004 ¶¶86-89, and thus
qualifies as prior art under at least §102(a)(1)(AIA). Neither Tran-I nor Tran-II
was cited or applied by the Office during prosecution.

X. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground 1: Claims 1-8, 10-18, 21-23 are Obvious from Durand- Hoegh

1. Durand

Durand, titled “Method of treating obstructive sleep apnea using electrical
nerve stimulation,” is directed to methods of treating OSA using electrical nerve

³ Referred to herein as “Headley-Tran.”

stimulation. EX-1006, Title, Abstract. Durand discloses a method for treating OSA by electrically stimulating the HGN, using intermittent electrical stimulation at controlled intervals based on the patient's metabolism. EX-1006 ¶1, Abstract. Durand explains that “electrical stimulation of the hypoglossal nerve...can maintain the patency of the upper airway by activating the upper airway dilator muscles, thereby minimizing or eliminating airway collapse during sleep.” EX-1006 ¶12; EX-1003 ¶¶67-68.

FIG. 1 of Durand shows apparatus 20 for stimulating a nerve.

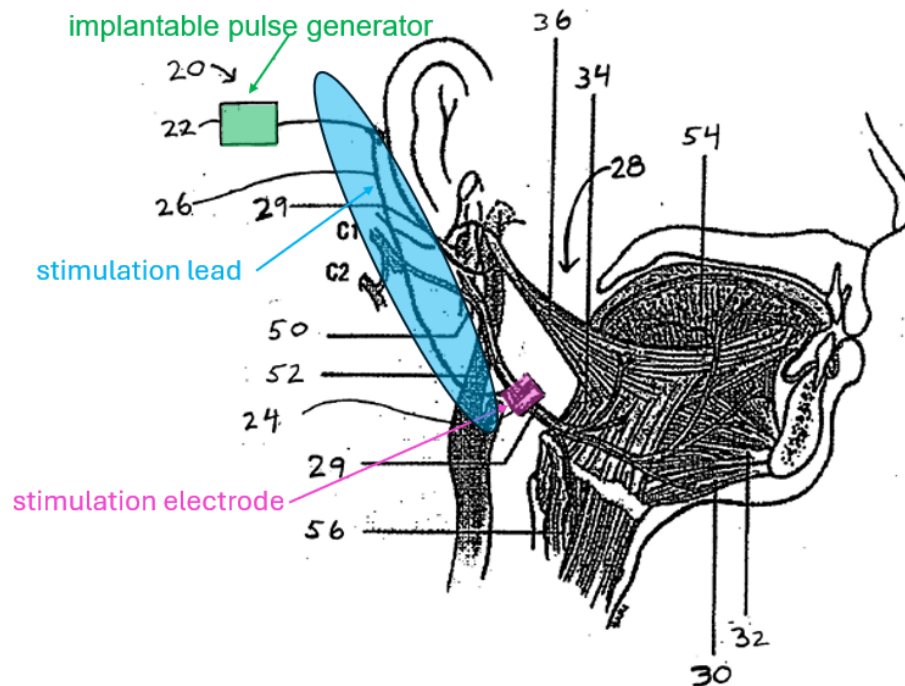


FIG. 1

EX-1006, FIG. 1; EX-1003 ¶69.

The apparatus includes **control system 22** for generating the desired electrical stimulus via **lead wire 26** and **stimulation electrode 24**, which is further connected to the HGN. EX-1006 ¶14, FIG. 1. **Control system 22** can include an IPG implanted in the body of the patient and controls application of the electrical stimulation. EX-1006 ¶16. **Lead wire 26** connects **electrode 24** to **control system 22**. EX-1006 ¶14. Durand explains that “muscles that control the upper airway 28 and are innervated by the hypoglossal nerve 29...” EX-1006 ¶19; EX-1003 ¶70.

Durand discloses both synchronous and asynchronous techniques for treating OSA. Durand’s asynchronous technique includes stimulating a nerve using “**intermittent electrical stimulation** at controlled intervals, predetermined based on the patient’s resting nighttime metabolism, determined by observing the nighttime respiratory rate, for example.” EX-1006 ¶4. **Control system 22** can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback from the nerve being stimulated. “In this method, the stimulation interval can be determined from the patient’s nighttime basal metabolism, e.g., based on the patient’s observed nighttime resting respiratory rate. The resultant timing of the stimulation closely simulates the patient’s normal nighttime respiration cycle.” EX-1006 ¶25. In one embodiment, Durand discloses a predetermined stimulation interval with **stimulus pulses** applied

for about 2-3 seconds and a wait of at least 2-3 seconds between the pulse trains.

EX-1006 ¶25; EX-1003 ¶¶71-72.

2. Hoegh

Hoegh, titled “Obstructive sleep apnea treatment screening methods,” relates to methods for treating OSA. EX-1007 ¶2, Title, Abstract. Hoegh discloses “a screening method for evaluating patient suitability for an implanted hypoglossal nerve stimulation (HGNS) device.” EX-1007 Abstract; EX-1003 ¶¶73-74.

FIG. 1 of Hoegh shows HGNS system 100 comprising internal components 1000 and external components 2000. EX-1007, FIG. 1. The HGNS system 100 treats OSA “by increasing neuromuscular activity to the genioglossus muscle via stimulation of the hypoglossal nerve (HGN)...to mitigate upper airway collapse during sleep.” EX-1007 ¶50. Hoegh further discloses that “[s]timulation may be generated by an implantable neurostimulator (INS) 1100,” EX-1007 ¶50, that may be applied in an asynchronous mode (fixed mode) having intervals set to a rate similar to a respiratory cycle. EX-1007, ¶114; EX-1003 ¶¶75-76.

3. Motivation to Combine Durand and Hoegh

Durand discloses a device including a cuff electrode and a control system for treating OSA by stimulating the HGN using trains of stimulus pulses at stimulation intervals “determined from the patient’s nighttime basal metabolism, e.g., based on the patient’s observed nighttime resting respiratory rate” such that “[t]he resultant

timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle," which avoids "the added complexity of closed-loop feedback." EX-1006 ¶25. Durand further discloses that the duration of the stimulation period (2-3 seconds) may be equal to or longer than the non-stimulation period (2-3 seconds). EX-1006 ¶25. Durand recognizes that the stimulation interval can be based on the patient normal nighttime interval, but does not provide further details including any example values for a typical respiration cycle and its relative duration compared to the stimulus interval. However, this is not surprising because, as discussed in VIII.B-VIII.C, it was well-known how to determine an effective stimulus interval based on a patient's typical respiration cycle. VIII.B-VIII.C; EX-1003 ¶¶90-91.

While Durand does not expressly disclose the duration of the stimulation period relative to the patient's inspiratory phase and provides limited disclosure about a patient's nighttime metabolism and its relationship to treating OSA, Hoegh does. Specifically, Hoegh provides a detailed discussion of the components of the OSA treatment system, surgical technique for implanting the device, and of titration. EX-1007 ¶¶53-59, 74-158, 190-213; EX-1003 ¶¶92-93.

Hoegh further discloses a detailed analysis of the patient's natural physiology, including that "[t]he hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire

respiratory phase” and “[t]o mimic this natural physiology, **stimulation** may be delivered during to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms.” EX-1007 ¶92. Hoegh further discloses that a stimulation duty cycle applied to the HGN may be used to determine the **stimulation period** as a percentage of the predicted respiratory period. EX-1007 ¶96. A duty cycle of 40% means that a **stimulus** is applied for 40% of the duration of the respiratory period. Hoegh further discloses that in one embodiment for a respiration cycle of 5 seconds, “the maximum stimulation duty cycle may be set from 41% to 69% in 3% increments,” such that **stimulation period** would have a duration that exceeds the duration of the **non-stimulation period** and the patient’s inspiratory phase to increase the probability of providing the patient with stimulus during the inspiratory phase. EX-1007 ¶¶98, 114. Thus, Hoegh’s disclosure is consistent with Durand’s disclosure. EX-1003 ¶94.

A POSITA would have been specifically motivated to modify Durand’s asynchronous stimulation method to deliver stimulation to the HGN for 300 ms longer than the inspiratory phase of a patient’s respiratory cycle, as taught by Hoegh, to mimic the patient’s natural physiology. EX-1003 ¶¶92, 94, 110-111. Hoegh discloses that mimicking the patient’s natural physiology is beneficial to “maximize stimulation coverage of actual inspiration” and to account for “variability” relating to variations in respiration rate that causes “actual inspiration

to differ from predicted inspiration.” EX-1007 ¶¶92; EX-1003 ¶¶95; *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) (explaining “any need or problem known in the field of endeavor...can provide a reason for combining the elements in the manner claimed”).

A POSITA had a reasonable expectation of success combining Durand-Hoegh for several reasons. *First*, both references disclose treating OSA using implantable devices, including a **nerve cuff** and **control system/pulse generator**, to electrically stimulate the HGN asynchronously. EX-1006 ¶¶13-16; EX-1007 ¶¶50-51; EX-1003 ¶¶96.

Second, both references disclose similar implantation locations. *Compare* EX-1006, FIG. 1 *with* EX-1007, FIG. 1; EX-1003 ¶¶97.

Third, both references disclose a duty cycle based on a typical respiration cycle for a patient, with the only difference being that Hoegh provides more details of a typical respiration cycle and its relative duration compared to the stimulus interval. EX-1006 ¶¶25; EX-1007 ¶¶98, 114; EX-1003 ¶¶98.

A POSITA recognized that such modification was well within the routine skill in the art as demonstrated in VIII.B, as it merely required simple software modifications to the IPG, which was typically performed during the titration process after device implantation. EX-1007 ¶¶134-137, 190-213; VIII.B; EX-1003 ¶¶99; *KSR*, 550 U.S. at 415-16.

4. Application of Durand-Hoegh to Claims 1-8, 10-18, 21-23

a. Claim 1

- i. [1.pre] *A device for treating obstructive sleep apnea, comprising:*

To the extent the preamble is limiting, FIG. 1 of Durand illustrates an apparatus [*device*] for treating OSA. EX-1006 ¶¶11-12, FIG. 1; EX-1003 ¶100.

Durand discloses [1.pre]. EX-1003 ¶101.

- ii. [1.a1] **a non-cardiac stimulation means for stimulating an upper airway patency-related nerve,**

Durand discloses the apparatus includes control system 22 and cuff electrode [*non-cardiac stimulation means for stimulating*] that is connected to the HGN [*upper-airway-patency-related nerve*] to provide electrical stimulation.

In the case of *obstructive sleep apnea, electrical stimulation of the hypoglossal nerve*, for example, *can maintain the patency of the upper airway* by activating the upper airway dilator muscles, thereby minimizing or eliminating airway collapse during sleep.

EX-1006 ¶12.

The apparatus 20 includes a control system 22 (shown schematically) for generating the desired electrical stimulus, and an electrode 24 connected to the nerve to transmit the electrical stimulus to the nerve.

The electrode 24 preferably is a cuff electrode that provides an *intimate connection to the nerve*.

EX-1006 ¶14; EX-1003 ¶102.

Durand discloses [1.a1]. EX-1003 ¶103.

- iii. [1.a2] *according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,*

Durand discloses that control system 22 generates intermittent electrical stimulation at controlled intervals [*first stimulation therapy protocol including alternating periods of stimulation and non-stimulation*].

More particularly, a method provided in accordance with the invention includes *controlling the patency of a patient's airway by stimulating a nerve using at least one of the following techniques:...*

(c) *intermittently electrically stimulating a nerve at controlled intervals, predetermined based on the patient's resting nighttime metabolism, which can be determined from the patient's observed respiratory rate,* for example.

EX-1006 ¶13; EX-1003 ¶104.

Durand further discloses that controls system 22 does not detect a physical process or require feedback from the nerve being stimulated because the rate is predetermined [*a timing of the stimulation periods is asynchronous relative to patient breathing*].

In a third embodiment of the method, *the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback*

from the nerve being stimulated. In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate... In this embodiment, *the stimulation is provided at predetermined rate or pace without the added complexity of closed-loop feedback.*

EX-1006 ¶25; EX-1003 ¶¶105-106.

Durand discloses [1.a2]. EX-1003 ¶¶106-107.

- iv. [1.b] *wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and*

Durand discloses a stimulation pulse train of 2-3 seconds [*a duration of each respective stimulation period*] and a wait period of 2-3 seconds between pulse trains.

The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, *a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains.*

EX-1006 ¶25; EX-1003 ¶108.

Durand expressly discloses a two-second wait period [*a duration of each respective non-stimulation period*], which has a duration that is less than a 2½

second train of stimulation pulses that closely simulates the patient's normal nighttime respiratory cycle. EX-1003 ¶109.

To the extent PO argues that Durand does not expressly disclose this claim element, a POSITA would have modified Durand's teachings to include Hoegh's teaching of stimulating the HGN for at least 300 ms longer than the inspiratory phase of the patient [*a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period*]:

To mimic this natural physiology, ***stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms.***

EX-1007 ¶92; EX-1003 ¶¶110-111.

Hoegh further discloses increasing the stimulation duty cycle [*stimulation period*] when operating asynchronously to increase the likelihood the stimulation overlapping the patient's inspiratory period.

The stimulation duty cycle may be fixed or adaptive. In the fixed mode, the stimulation duty cycle may be set using the programmer system 2100 to designate a fixed percentage value. ***This fixed value may be increased when the respiratory period signal is lost, increasing the likelihood of aligning with actual inspiration...*** Thus, in some instances, ***the stimulation duty cycle may run above normal (e.g., above 50% to 60%) to achieve a better likelihood of covering the inspiratory phase.***

EX-1007 ¶97; EX-1003 ¶112.

Thus, Durand-Hoegh discloses that a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period. Hoegh further provides an express teaching and motivation for increasing the duration of the stimulation period relative to the non-stimulation period. EX-1007 ¶97; EX-1003 ¶113. A POSITA would have been motivated to provide a stimulation period with a duration that exceeds the duration of the non-stimulation period to mimic the patient's natural physiology and to increase the likelihood of the stimulation period overlapping the patient's inspiratory phase. EX-1003 ¶113.

Durand-Hoegh discloses [1.b]. EX-1003 ¶¶113-114.

- v. ***[1.c] wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter,***

Durand discloses that a timing of stimulation pulse trains [*duration of each respective stimulation period*] is based on a patient's observed nighttime resting respiratory rate [*based on a reference respiratory-related parameter*].

In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., ***based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains*** will closely simulate the patient's normal nighttime respiration cycle.

EX-1006 ¶25; EX-1003 ¶115.

A POSITA understood that by simulating the patient's observed nighttime resting respiratory rate [*reference respiratory-related parameter*], application of the train of stimulation pulses [*duration of each respective stimulation period*], as taught by Durand (and Hoegh), would ensure that the upper airway remains open during sleep. EX-1006 ¶20; EX-1007 ¶¶92-93, 114, 127; EX-1003 ¶¶116-120.

Durand discloses [1.c], either alone or in combination with Hoegh. EX-1003 ¶¶120-121.

- vi. [1.d] *wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.*

Durand discloses the non-cardiac stimulation means includes cuff electrode 24 [*implantable electrode*] and control system 22 [*implantable pulse generator*] connected to electrode 24 by lead wire 26 [*electrically connectable to the implantable electrode*].

The apparatus 20 includes a control system 22 (shown schematically) for generating the desired electrical stimulus, and an electrode 24 connected to the nerve to transmit the electrical stimulus to the nerve. The electrode 24 preferably is a cuff electrode that provides an intimate connection to the nerve.

EX-1006 ¶14.

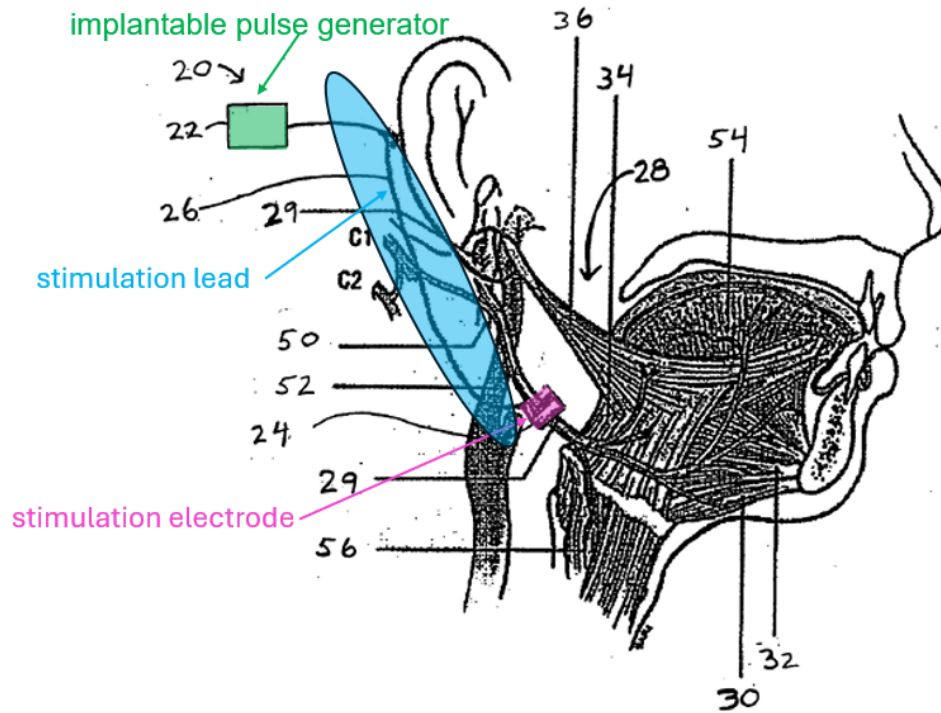


FIG. 1

EX-1006, FIG. 1; EX-1003 ¶¶122-123.

A POSITA understood that a cuff electrode, as disclosed by Durand, would be considered an “implantable electrode” given that the cuff is wrapped around the hypoglossal nerve and is thus implanted within a patient, shown in FIG. 1 of Durand. EX-1006 ¶16. A POSITA further understood that lead wire 26 connecting electrode 24 and control system 22 provided an electrical connection between the two components for the device to function electronically. EX-1003 ¶¶122-123.

Durand discloses [1.d] and claim 1 is obvious from Durand-Hoegh. EX-1003 ¶¶123-124.

b. **Claim 2**

- i. [2] *The device of claim 1, wherein the asynchronous timing of the stimulation relative to patient breathing comprises the timing being not based on actively-sensed respiration during application of the first stimulation therapy protocol.*

Durand discloses that the timing of pulse trains [*stimulation periods*] is implemented without detecting a physical process or requiring feedback from the nerve [*not based on actively-sensed respiration during application of the first stimulation therapy protocol*].

In a third embodiment of the method, *the controller can be programmed to provide stimulation at a predetermined interval without either detecting a physical process or requiring feedback from the nerve being stimulated. In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate...* In this embodiment, *the stimulation is provided at predetermined rate or pace without the added complexity of closed-loop feedback.*

EX-1006 ¶25; EX-1003 ¶¶125-126.

Durand discloses the limitations of claim 2. EX-1003 ¶127.

c. **Claim 3**

- i. [3] *The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory pattern.*

Durand discloses the reference respiratory-related parameter is a patient's observed nighttime resting respiratory rate [*a reference respiratory pattern*].

In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the *patient's normal nighttime respiration cycle*.

EX-1006 ¶25; EX-1003 ¶128.

Durand discloses the limitations of claim 3, EX-1003 ¶¶128-129, as does Hoegh. EX-1003 ¶¶130-131.

d. **Claim 4**

- i. [4.a] *The device of claim 3, wherein the reference respiratory pattern comprises a reference respiratory cycle, and*

Durand discloses the reference respiratory pattern is a patient's observed nighttime resting respiratory rate [*a reference respiratory cycle*].

In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the *patient's normal nighttime respiration cycle*.

EX-1006 ¶25; EX-1003 ¶¶132-134.

Durand discloses [4.a], either alone or in combination with Hoegh. EX-1003 ¶135.

- ii. ***[4.b] wherein a duration of each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle.***

Durand discloses providing a train of stimulation pulses for 2-3 seconds [*a duration of each respective stimulation period*].

The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle. For example, ***a train of stimulus pulses can be applied for about 2 seconds to about 3 seconds, and more particularly, for about 2½ seconds, with a wait of at least 2 seconds to about 3 seconds between the pulse trains.***

EX-1006 ¶25; EX-1003 ¶136.

Thus, Durand discloses relative durations of stimulation and non-stimulation and the overall stimulation cycle should be based on the patient's nighttime respiratory rate, but does not expressly state that each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle. Hoegh discloses stimulating the hypoglossal nerve for at least 300 ms longer than the inspiratory phase of the patient to mimic the natural physiology of the patient [*each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle*].

To mimic this natural physiology, ***stimulation may be delivered to the hypoglossal nerve during the inspiratory phase plus a brief pre-inspiratory period of about 300 ms.***

EX-1007 ¶92; EX-1003 ¶137.

Hoegh further discloses stimulation duration [*stimulation period*] may be increased when operating asynchronously (i.e., when the respiratory signal is lost) to increase the likelihood of overlapping the stimulation with the patient's inspiratory period.

The stimulation duty cycle may be fixed or adaptive. In the fixed mode, the stimulation duty cycle may be set using the programmer system 2100 to designate a fixed percentage value. ***This fixed value may be increased when the respiratory period signal is lost, increasing the likelihood of aligning with actual inspiration...*** Thus, in some instances, ***the stimulation duty cycle may run above normal (e.g., above 50% to 60%) to achieve a better likelihood of covering the inspiratory phase.***

EX-1007 ¶97; EX-1003 ¶138.

Thus, the teachings of Durand-Hoegh disclose that a duration of each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle. EX-1003 ¶139.

Durand-Hoegh discloses [4.b] and renders obvious claim 4. EX-1003 ¶140.

e. **Claim 5**

- i. **[5] *The device of claim 1, wherein the reference respiratory-related parameter is based on stable respiration.***

Durand discloses that a reference respiratory-related parameter is based on a patient's observed nighttime resting respiratory rate [*stable respiration*].

In this method, the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., ***based on the patient's observed nighttime resting respiratory rate.*** The resultant timing of the stimulation pulse trains will closely ***simulate the patient's normal nighttime respiration cycle.***

EX-1006 ¶25; EX-1003 ¶¶141-143.

A POSITA understood a patient's basal metabolism to be the patient's minimum metabolic rate to function at a basic level, which was known in the art.

EX-1003 ¶142. A POSITA understood that Durand's goal was to identify a stable respiratory rate for the patient while the patient is sleeping in order to apply stimulus at this rate to maintain the patient's natural (unobstructive) sleeping rhythm. EX-1006 ¶25; EX-1003 ¶¶142-143.

Durand discloses claim 5. EX-1003 ¶144.

f. Claim 6

- i. [6.a] The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle and*

Durand discloses [6.a] for the same reasons discussed in X.A.4.d.i ([4.a]).

EX-1003 ¶145.

- ii. [6.b] wherein a combined duration of each respective stimulation period and of each respective non-stimulation period is less than the reference respiration-related parameter, which comprises a duration of a reference breath.*

Durand discloses stimulation cycles as short as four seconds (2 seconds stimulation; 2 seconds waiting), EX-1006 ¶25, but does not expressly identify the duration of a patient's respiratory cycle/breath. EX-1003 ¶146. Hoegh discloses that a patient's respiratory cycle is about 5 seconds, EX-1007 ¶114, and a four-second stimulation cycle has a duration less than a patient's five-second respiratory rate, which a POSITA understood to be a reference breath. EX-1003 ¶¶146-147.

Durand-Hoegh discloses [6.b] and renders claim 6 obvious. EX-1007 ¶¶92, 97, 114; EX-1003 ¶¶148-150.

g. Claim 7

- i. [7.a] The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle and*

Durand discloses [7.a] for the same reasons discussed in X.A.4.d.i ([4.a]).

EX-1003 ¶151.

- ii. ***[7.b] wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is no greater than a duration of a reference respiratory cycle.***

Durand-Hoegh discloses [7.b] for the same reasons discussed in X.A.4.f.ii and renders claim 7 obvious. EX-1003 ¶¶152-153.

h. Claim 8

- i. ***[8] The device of claim 1, wherein the duration of the respective stimulation periods remain uniform.***

Durand discloses consistent trains of pulses [*duration of respective stimulation periods remain uniform*], as does Hoegh. EX-1006 ¶¶4, 25; EX-1007 ¶¶97, 114; EX-1003 ¶¶154-157.

Durand discloses the limitations of claim 8, either alone or in combination with Hoegh. EX-1003 ¶¶157-158.

i. Claim 10

- i. ***[10] The device of claim 1, wherein a respective one of the stimulation periods and a respective one of the non-stimulation periods are in a proportion of at least 1.5 to 1.***

Durand discloses providing a train of stimulation pulses [*a respective one of the stimulation periods*] for 3 seconds and a wait period [*a respective one of the non-stimulation periods*] of 2 seconds. EX-1006 ¶25; EX-1003 ¶159. A three-second train of stimulation pulses and a two-second wait period is a proportion of

1.5 to 1. EX-1003 ¶¶160-161. Hoegh's disclosure of a 69% duty cycle also discloses this limitation. EX-1007 ¶69; EX-1003 ¶¶162-163

Durand discloses the limitations of claim 10, either alone or with Hoegh. EX-1003 ¶¶164-165.

j. **Claim 11**

- i. ***[11] The device of claim 1, wherein a duration of a respective one of the stimulation periods exceeds the duration of a respective one of the non-stimulation periods by a factor of 3.***

Hoegh discloses using exemplary duty cycles ranging between 41% to 69%. EX-1007 ¶98. A 69% duty cycle provides stimulation pulses [*stimulation period*] for a duration that exceeds the wait period [*non-stimulation period*] by over a factor of 2 (i.e., $69\%/31\% = 2.23$). EX-1003 ¶166.

Hoegh disclosure of duty cycles is not limiting, as “[t]he stimulation duty cycle may vary to meet efficacy and safety requirements.” EX-1007 ¶¶96, 98. Given these express teachings, a POSITA understood that the duty cycle could be increased beyond 69%, such as to 75% to provide a duration of the stimulation period that exceeds a duration of the non-stimulation period by a factor of three ($75\%/25\% = 3$), to meet the desired efficacy, requiring only routine skill, as the prior art includes examples of duty cycles of up to 92% (e.g., an on/off period of 60/5). EX-1006 ¶22; EX-1008 ¶48; EX-1003 ¶¶167-170.

Durand-Hoegh renders obvious claim 11. EX-1003 ¶¶170-171.

k. **Claim 12**

- i. ***[12.a] The device of claim 1, wherein a combination of a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle, and***

Durand discloses intermittent electrical stimulation [*stimulation cycle*], including a stimulation period and a non-stimulation period.

More particularly, a method provided in accordance with the invention includes controlling the patency of a patient's airway by stimulating a nerve using at least one of the following techniques:... (c) ***intermittently electrically stimulating a nerve at controlled intervals, predetermined based on the patient's resting nighttime metabolism, which can be determined from the patient's observed respiratory rate***, for example.

EX-1006 ¶¶13, 25; EX-1003 ¶172.

Durand discloses [12.a]. EX-1003 ¶173.

- ii. ***[12.b] wherein a duration of the respective one of the stimulation periods comprises at least 80 percent of a duration of the stimulation cycle.***

Durand discloses providing a train of stimulation pulses for 2-3 seconds, waiting 2-3 seconds, and then again applying the stimulation. EX-1006 ¶25.

Durand thus discloses a stimulation period comprising 60% of a duration of the stimulation cycle (e.g., 3 second stimulation, 2 second wait). EX-1003 ¶174.

Hoegh discloses using exemplary duty cycles ranging between 41%-69%, the duty cycles are not limiting, and “[t]he stimulation duty cycle may vary to meet efficacy and safety requirements.” EX-1007 ¶¶96, 98; EX-1003 ¶¶175-176.

Given these express teachings, a POSITA understood that the duty cycle could be increased beyond 69%, such as to 80%, to meet the desired efficacy, as the prior art includes examples of duty cycles of up to 92% (e.g., an on/off period of 60/5). EX-1006 ¶22; EX-1008 ¶48; EX-1003 ¶¶177-179. Providing stimulation cycles in which a duration of the stimulation period is at least 80% of a duration of the stimulation cycle required nothing more than the exercise of routine skill, which a POSITA would have been motivated to provide to increase the efficacy and safety. EX-1007 ¶96; EX-1003 ¶¶178-179.

Durand-Hoegh discloses [12.b] and renders obvious claim 12. EX-1003 ¶¶179-180.

I. Claim 13

i. [13] The device of claim 1, wherein each respective stimulation period comprises continuous pulsed stimulation.

The '526 Patent describes continuous stimulation as “a train of stimulation pulses which occur in a relatively short time frame,” such as “a finite number (e.g. 5, 10, etc.) of stimulation pulses per second.” EX-1001 4:37-43. Similarly,

Durand discloses 10-30 pulses per second (i.e., 10-30 Hertz) [*continuous pulsed stimulation*].

For example, *the electrical stimulation can be provided by pulse trains of an intermittent duration or continuously, at a frequency of about 10 Hertz (Hz) to about 30 Hertz (Hz)*, with a pulse width of about 50 microseconds (μ s).

EX-1006 ¶¶ 21, 25; EX-1003 ¶¶181-182.

Durand discloses claim 13. EX-1003 ¶183.

m. Claim 14

**i. [14.a] *The device of claim 1, comprising:
a processor; and***

Durand discloses the “control system 22 also typically includes *a processor* for setting up stimulation parameters....” EX-1006 ¶¶14-15; EX-1003 ¶184.

Durand discloses [14.a]. EX-1003 ¶185.

**ii. [14.b] *a non-volatile computer readable medium
storing instructions, executable on the processor,
to implement the first stimulation therapy
protocol via the non-cardiac stimulation means
for stimulating.***

Durand discloses that the processor sets up stimulation parameters to achieve the desired outcome [*implement the first stimulation therapy protocol*]. EX-1006 ¶¶14-15. A POSITA understood that a processor functions by executing instructions that are stored in a non-volatile computer-readable medium, including as evidenced by Hoegh. EX-1007 ¶¶82, 85; EX-1003 ¶¶186-187. Based on

Durand's and Hoegh's disclosures, a POSITA understood [14.b] to be obvious from Durand-Hoegh. EX-1003 ¶188.

Durand-Hoegh discloses claim element [14.b] and renders obvious claim 14. EX-1003 ¶188.

n. Claim 15

- i. [15] The device of claim 1, wherein the first stimulation therapy protocol is to be applied during a treatment period in which the patient is to engage in sleeping behavior.*

Durand discloses that electrical stimulation is applied to the HGN [*the first stimulation therapy protocol*] to treat OSA, which a POSITA understood occurs only when a patient is sleeping. VIII.B; EX-1006 ¶¶2, 12; EX-1003 ¶189.

Durand discloses the limitations of claim 15. EX-1003 ¶190.

o. Claim 16

- i. [16.pre] A device for treating obstructive sleep apnea, comprising:*

See X.A.4.a.i. EX-1003 ¶191.

- ii. [16.a1] a non-cardiac means for stimulating an upper airway patency-related nerve,*

See X.A.4.a.ii. EX-1003 ¶192.

- iii. [16.a2] according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,**

See X.A.4.a.iii. EX-1003 ¶194.

- iv. [16.b] wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period,**

See X.A.4.a.iv. EX-1003 ¶195.

- v. [16.c] wherein each stimulation period comprises continuous pulsed stimulation, and**

See X.A.4.1. EX-1003 ¶196.

- vi. [16.d] wherein the first stimulation therapy protocol is to deliver multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle, and**

Hoegh discloses inspiration for 25-50% of a five-second respiratory cycle and adding 300 ms to the inspiration period to mimic natural physiology, EX-1007 ¶¶92, 96, 114, which corresponds to a stimulation period of 1.55 seconds ($25\% \times 5s + 0.3s = 1.55s$). EX-1003 ¶¶197-198. Hoegh discloses using duty cycles of 69% to avoid fatigue, which corresponds to a 1.55 second stimulation period followed by a wait period of 0.7 seconds for a 2.25-second stimulation cycle duration. EX-1007 ¶98; EX-1003 ¶¶199-200. Accordingly, two 2.25-stimulation cycles have a duration of 4.5 seconds, which is within the 5 second respiratory cycle disclosed by Hoegh. EX-1007 ¶114; EX-1003 ¶¶198-202.

Delivering multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle required nothing more than the exercise of routine skill, i.e., optimizing a stimulation period and stimulation cycle duration, a POSITA would have been motivated to provide to increase the efficacy while maintaining the safety. EX-1007 ¶96; EX-1003 ¶¶201-202.

Durand-Hoegh discloses [16.d]. EX-1003 ¶¶201-204.

- vii. [16.e] *wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.***

See X.A.4.a.vi. EX-1003 ¶204.

Durand-Hoegh renders claim 16 obvious. EX-1006 ¶205.

p. Claim 17

- i. [17] *The device of claim 16, wherein the duration of each respective non-stimulation period is at least less than half of the duration of each respective stimulation period.***

Hoegh discloses duty cycles of up to 69%, which equates to stimulation pulses [*respective stimulation period*] being applied by a proportion of over two relative to non-stimulation periods, i.e., $69\%/31\%=2.23$. EX-1007 ¶96; EX-1003 ¶¶206-207. Further, adjusting the duration of a stimulation cycle and/or the duty cycle of the stimulation period was routinely performed and required nothing beyond the exercise of routine skill in the art. EX-1003 ¶¶207-208.

Durand-Hoegh renders obvious claim 17. EX-1003 ¶¶208-209.

q. **Claim 18**

- i. [18] *The device of claim 16, wherein the reference respiratory cycle comprises at least one of: a historical patient-specific reference respiratory cycle; and a multiple patient reference respiratory cycle.*

Durand discloses that the stimulation is provided to simulate the patient's normal respiration cycle [*a historical patient-specific reference respiratory cycle*].

In this method, *the stimulation interval can be determined from the patient's nighttime basal metabolism, e.g., based on the patient's observed nighttime resting respiratory rate. The resultant timing of the stimulation pulse trains will closely simulate the patient's normal nighttime respiration cycle.*

EX-1006 ¶25; EX-1003 ¶210.

Thus, given the express teachings of Durand-Hoegh, a POSITA would have been motivated to base the reference respiratory cycle on a historical patient-specific average respiratory cycle for stable respiration to simulate the patient's normal nighttime respiration cycle and mimic the patient's natural physiology.

EX-1006 ¶25; EX-1007 ¶¶92-93; EX-1003 ¶¶211-212.

Durand-Hoegh renders obvious claim 18. EX-1003 ¶212.

r. **Claim 21**

- i. ***[21.a] The device of claim 16, wherein a combination of a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle, and***

Durand discloses intermittent electrical stimulation [*stimulation cycle*] that includes a stimulation period and a non-stimulation period.

More particularly, a method provided in accordance with the invention includes controlling the patency of a patient's airway by stimulating a nerve using at least one of the following techniques:...

(c) ***intermittently electrically stimulating a nerve at controlled intervals, predetermined based on the patient's resting nighttime metabolism, which can be determined from the patient's observed respiratory rate,*** for example.

EX-1006 ¶¶13, 25; EX-1003 ¶¶213-214.

Durand discloses [21.a]. EX-1003 ¶214.

- ii. ***[21.b] wherein the first stimulation therapy protocol is to deliver more than one stimulation cycle within a duration of the reference respiratory cycle.***

Durand-Hoegh discloses [21.b] for reasons similar to those discussed above in X.A.4.o.vi. EX-1006 ¶25; EX-1007 ¶¶92, 96, 114; EX-1003 ¶¶215-216.

Further, adjusting the duration of a stimulation cycle and/or the duty cycle of the

stimulation period was routinely performed and required nothing beyond the exercise of routine skill in the art. VIII.B-VIII.C; EX-1003 ¶¶217-221.

Durand-Hoegh discloses [21.b] and renders obvious claim 21. EX-1003 ¶¶220-222.

s. **Claim 22**

- i. [22.pre] *A device for treating obstructive sleep apnea, comprising:*

See X.A.4.a.i. EX-1003 ¶223.

- ii. [22.a1] *a non-cardiac means for stimulating an upper airway patency-related nerve,*

See X.A.4.a.ii. EX-1003 ¶224.

- iii. [22.a2] *according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,*

See X.A.4.a.iii. EX-1003 ¶225.

- iv. [22.b] *wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and*

See X.A.4.a.iv. EX-1003 ¶226.

- v. **[22.c] wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle,**

Hoegh discloses regular programmable intervals of stimulation [*respective one of the stimulation periods*] can be provided in durations longer than a respiratory cycle [*reference respiratory cycle*], such eight seconds.

Alternatively, *longer intervals (e.g. 8 seconds) may decrease the probability of missing two consecutive inspirations*, and increase the probability of providing the patient with stimulation during an entire respiratory cycle.

EX-1007 ¶114; EX-1003 ¶227.

Hoegh thus discloses a combined duration (i.e., eight seconds) of a respective one of the stimulation periods and non-stimulation periods that is greater than a five-second reference respiratory cycle. EX-1003 ¶228.

Durand-Hoegh renders [22.c] obvious. EX-1003 ¶228.

- vi. **[22.d] wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.**

See X.A.4.a.vi. EX-1003 ¶229.

Claim 22 is obvious from Durand-Hoegh. EX-1003 ¶230.

t. **Claim 23**

- i. [23] *The device of claim 22, wherein the duration of a respective one of the stimulation periods is greater than the duration of the reference respiratory cycle.*

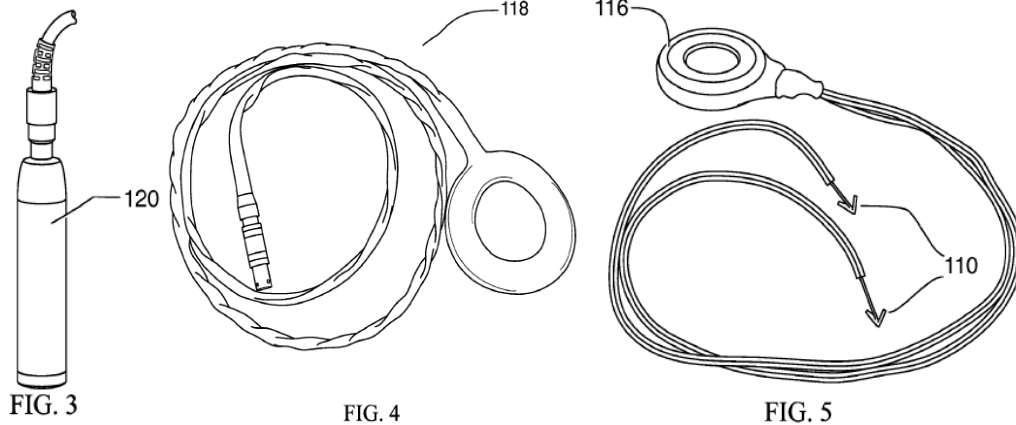
As discussed above in X.A.4.s.v, Hoegh discloses a stimulation cycle having a duration/interval of five seconds and up to eight seconds and duty cycles up to 69%. EX-1007 ¶¶ 98, 114. A 69% duty cycle of an eight-second stimulation cycles corresponds to a duration of a stimulation period of 5.52 seconds, which is greater than a five-second respiratory rate. EX-1003 ¶¶ 231-234.

Durand-Hoegh discloses claim 23. EX-1003 ¶¶ 234-235.

B. Ground 2: The Challenged Claims are Obvious from Headley-Tran

1. Headley

Headley is titled “Sleep Apnea Device and Method” and “involves the implantation of a muscle stimulation electrode directly into the muscle of the genioglossus that advances the posterior aspect of the tongue anteriorly thus relieving the obstruction of the tongue in sleep apnea.” EX-1008 Abstract. The device includes power source 120, antenna 118, receiver 116, and stimulating electrode 110. EX-1008 ¶29.



EX-1008 FIGS. 3-5; EX-1003 ¶78.

The device provides for alternating on/off “intermittent” treatment where tissue is **stimulated for a given period**, then allowed to **rest for a given period**. EX-1008 ¶48. Headley discloses on/off duty cycles ranging from 12/1 (e.g., 60 seconds on; 5 seconds off) to 1/1 (e.g., 5 seconds on; 5 seconds off), with on/off periods as short as 1 second each. EX-1008 ¶48.

2. Tran

Tran-I discloses using asynchronous electrical stimulation via an **implantable electrode** to treat OSA. EX-1009, Title, Abstract. According to Tran-I, “[n]euromuscular and hypoglossal nerve stimulation of the genioglossus” was known “to expand the oropharyngeal airway and reduce[] the severity of sleep disordered breathing.” EX-1009, Abstract. Further, “OSA occurs when the soft tissues of the upper airway collapse and occlude airflow during inspiration” and “[c]ollapse of the tongue is the most common cause of OSA.” EX-1009, p.375.

Tran-I discloses injecting a BION™, which includes an **electrode**, in or near muscles and nerves and receiving power and digital commands via RF transmission to produce stimulation pulses. EX-1009, p.375. Figure 3 of Tran-I illustrates the BION™ device implanted into the patient from under the chin along the midline, where it would stimulate the intramuscular branches of the same motor axons stimulated by the HGN:

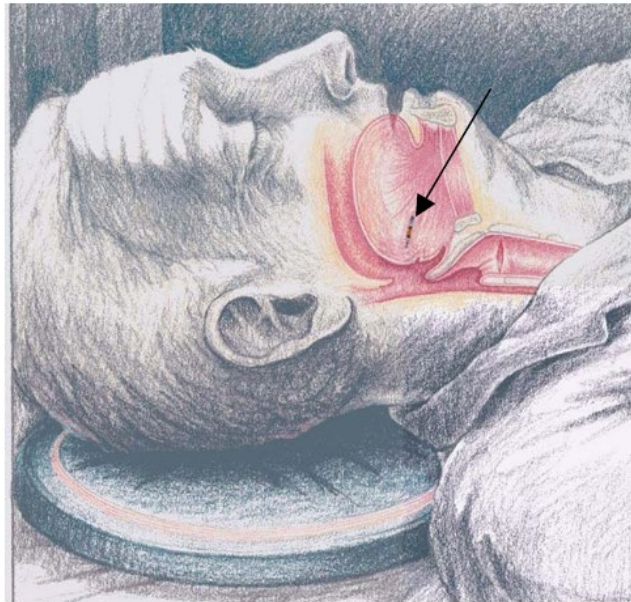


Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

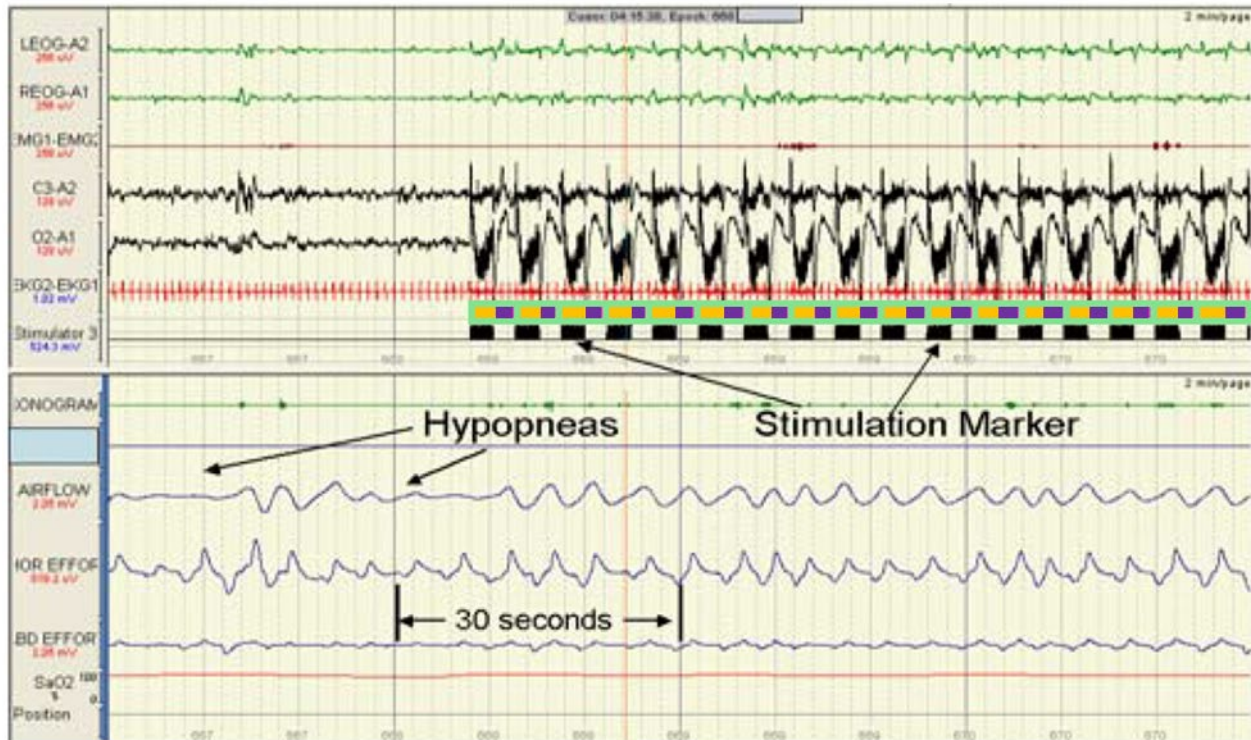
EX-1009, FIG. 3.

Tran-I further discloses “intermittent opening of airway at the same rate but not synchronized to the respiratory cycle may be effective” to treat OSA. EX-1009, p.375. Tran-I explains that “if brief **trains of stimulation pulses** were applied to the [genioglossus] at intervals close to the respiratory cycle of the patient, the patient would tend to synchronize spontaneously with the resulting intermittent

periods of patency in the airway...because an inspiratory phase that happens not to coincide with [genioglossus] stimulation will tend to be prolonged until the next train of [genioglossus] stimulation opens the airway.” EX-1009, p.377.

Tran-II is a follow-up paper to Tran-I and thus also discloses “using percutaneous electrical stimulation to simulate BION™ activation of posterior genioglossus during sleep to prevent occurrences of” OSA. EX-1010, Title, Abstract. In particular Tran-II discloses the results of ongoing clinical testing of OSA treatment using the device and techniques disclosed in Tran-I. EX-1010, p.4287; EX-1003 ¶¶85-86.

FIG. 4 of Tran-II, which is below, is a screen capture of polysomnogram of the patient being treated using the BION™ device providing asynchronous stimulation in the form of brief trains of electrical stimulus “in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant, obviating the need for a sensor to synchronize stimulation with breathing.” EX-1010, p.4287.



EX-1010, FIG. 4; EX-1003 ¶¶87-88 .

3. Motivation to Combine Headley and Tran

As detailed above, Headley discloses an implantable device that is used to treat OSA by asynchronously stimulating the GG, which is in close proximity to the HGN. Specifically, Headley discloses providing stimulation in the form of alternating on/off treatment in which the tissue is **stimulated for a given period** then allowed to **rest for a given period** before being **stimulated again**. EX-1008 ¶48.

Headley states that the intermittent treatment periods and parameters may be adjusted based on patient-specific characteristics, such as, the “patient’s physical condition” or “quality of sleep,” but does not elaborate on these characteristics and parameters. EX-1008 ¶¶10, 13. The reference concludes by incorporating by

citing and incorporating by reference several scientific papers, which would have motivated a POSITA to consider these and other papers. EX-1008 ¶¶50-62; EX-1003 ¶¶236-237.

Tran discloses a BION™ device for treating OSA that operated like the device disclosed by Headley in that the device is implanted in the tongue in close proximity to where the branches of the HGN to the GG enter the tongue. EX-1009, p.376. The device recruits the motor units stimulated by the HGN to produce symmetrical protrusion of the tongue thereby opening the airway. EX-1009, p.376. Brief trains of stimulation pulses are applied “at intervals close to the respiratory cycle of the patient” to synchronize the patient “spontaneously with the resulting intermittent periods of patency in the airway.” EX-1009, p.377; EX-1003 ¶¶238-239.

A POSITA would have been motivated to combine the teachings of Headley and Tran to provide stimulation based on the patient’s respiratory rate to have the patient spontaneously synchronize with the intermittent periods of patency in the airway. EX-1003 ¶¶239-240. Advantageously, the combination of references would provide a device that obviates the need for a sensor to synchronize stimulation with breathing while effectively improving airway patency. EX-1010, p.4288; EX-1003 ¶239.

A POSITA would have been motivated to combine Headley-Tran to provide an improved method to treat OSA and would have had a reasonable expectation of success in doing so for several reasons. *First*, both references disclose treatment methods for OSA using externally powered implantable electrodes to stimulate in close proximity to the HGN asynchronously. EX-1008 ¶¶1, 48; EX-1009, pp.375, 377; EX-1010, p.4287; EX-1039, p.3; EX-1003 ¶¶240-242.

Second, both references disclose similar implantation locations:



EX-1008, FIG. 1.

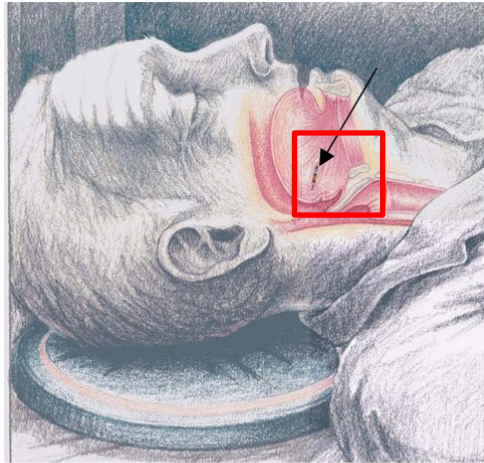


Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

EX-1009, FIG. 3; EX-1003 ¶243.

Third, the modifications to Headley based on the teachings of Tran was well within the routine skill in the art, requiring only simple software modifications and routine modifications to Headley’s stimulation periods, typically performed during the titration process. VIII.B; EX-1003 ¶¶230, 244; *KSR*, 550 U.S. at 415-16 (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”).

4. Application of Headley-Tran to the Challenged Claims

a. Claim 1

i. [1.pre] A device for treating obstructive sleep apnea, comprising:

To the extent the preamble is limiting, Headley discloses “[a] *device* and method is described *for the treatment of obstructive sleep apnea.*” EX-1008, Abstract, ¶29, FIGS. 3-5; EX-1003 ¶¶245-247.

Headley discloses [1.pre], either alone or with Tran. EX-1003 ¶¶246-248.

- i. [1.a1] a non-cardiac stimulation means for stimulating an upper airway patency-related nerve,*

Headley discloses receiver 116 and stimulating electrode 110 that are inserted into the GG to apply non-cardiac electrical stimulation [*non-cardiac means for stimulating*].

In one embodiment, there is provided a method of treating obstructive sleep apnea in a patient comprising the steps of: *applying direct intramuscular electrical stimulation to a specific set of muscle fibers in a muscle of the patient's airway*, wherein the electrical stimulation is provided by *an implanted electrode assembly, wherein the electrode assembly comprises one or more electrodes connected to an implanted receiver....*

EX-1008 ¶¶8, 28, FIG. 1; EX-1003 ¶¶249-250.

Although Headley does not expressly disclose that the receiver and electrodes stimulate “an upper airway patency-related nerve,” a POSITA understood that the GG is innervated by (i.e., supplied by) the HGN. EX-1023, p.601-603; EX-1033, p.379; EX-1003 ¶251. A POSITA understood that applying electrical stimulation by the electrode in the tongue would conduct to and be applied to the HGN. VIII; EX-1003 ¶251.

The foregoing is consistent with the '526 Patent, which discloses stimulating an upper-airway patency-related nerve by locating an electrode “in close proximity to” the HGN, which the GG is. EX-1001 11:60-12:12; EX-1003 ¶¶250-253. A POSITA understood that the intramuscular stimulation disclosed by Headley would activate motor axons whereby the activation of the motor axons would then synaptically activate muscle fibers such that the muscle fibers themselves would not be directly excited by the electrical stimulus. VIII.A-VIII.B; EX-1008 ¶¶ 8, 28, FIG. 1; EX-1033, pp.379, 382; EX-1003 ¶253.

Headley incorporates by reference several papers, including Brennick and Yoo, that expressly reference HGN stimulation in their titles and several others that describe the neuromuscular relationship between the GG and HGN. EX-1008 ¶¶50-62 (citing EX-1014, EX-1016, EX-1019, EX-1020, EX-1021, EX-1023, EX-1025, EX-1028, EX-1041, EX-1042, EX-1043, EX-1044). A POSITA understood electrodes implanted in the GG applied electrical stimulation to the HGN to achieve the desired result of maintaining upper airway patency to treat OSA. EX-1008 ¶¶8, 28-30; EX-1003 ¶254.

The foregoing is reinforced when Headley is combined with Tran, which discloses neuromuscular stimulation of the GG and HGN:

Bipolar hooked wires are inserted percutaneously into the tongue muscle, from under the chin at midline, and *used for neuromuscular stimulation*.

EX-1010, p.4287.

Bipolar wire electrodes were strategically placed *at the optimal stimulation site in the genioglossus [citing Tran-I]*.

EX-1010, p.4288.

The hypoglossal nerve branches to the [genioglossus] muscle enter the tongue inferolaterally to innervate muscle fibers that are oriented transversely, longitudinally and radially in parasagittal fans... Sanders et al using Sihler's stain have shown motor endplates near the tongue base are innervated by a separate hypoglossal nerve branch (human genioglossus illustrated in Fig. 2). This suggests that a single site of stimulation located in the midline (near these endplates as illustrated in Fig. 3) would recruit selectively these motor units that will produce symmetrical protrusion of the tongue, thereby opening the airway.

EX-1009, p.376, Figs. 2-3; EX-1039, p.3; EX-1040, p.348; EX-1003 ¶¶255-257.

Headley-Tran discloses [1.a1]. EX-1003 ¶¶257-258.

- ii. [1.a2] *according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,*

Headley discloses that receiver 116 and stimulating electrode 110 provide stimulation using “intermittent” treatment [*first stimulation therapy protocol including alternating periods of stimulation and non-stimulation*] “*wherein the*

tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period.” EX-1008 ¶¶10, 48; EX-1003 ¶259.

Although Headley discloses the use of optional sensors, such as sound-activation means and/or oxygen-sensing means, these sensors are not used for synchronizing stimulation. EX-1008 ¶14; EX-1003 ¶260. Instead, these sensors detect when a patient snores or the patient’s oxygen level falls below a threshold to initiate the therapy. EX-1008 ¶14; EX-1003 ¶261.

Headley-Tran discloses [1.a2]. EX-1003 ¶¶262-263.

iii. [1.b] wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period,

Headley discloses stimulation/on period [*stimulation period*] duration that is greater than a rest/off period [*non-stimulation period*] duration (i.e., a duty cycle (on/off period) of 12/1):

In use, the device as described herein and/or the method as described herein provides for alternating on/off “intermittent” treatment wherein *the tissue is stimulated for a given period, and then the tissue is allowed to rest for a given period...* In another preferred embodiment, *the period of stimulation is 20 seconds and the rest period is 5 seconds.* In yet another preferred embodiment, the period is 60 seconds on with 60 seconds off. On periods may range without limitations from 1 to 120 seconds, and off periods similarly. *On/off intermittent periods include* from 5/5, **20/5**, 10/10, 5/60, **60/5**, 20/20, 30/30, 40/40, 50/50, 60/60, and so forth.

EX-1008 ¶48; EX-1003 ¶¶264-265.

Headley discloses [1.b]. EX-1003 ¶¶266-268.

- iv. [1.c] wherein the duration of each respective stimulation period is based on a reference respiratory-related parameter,*

Tran discloses providing electrical stimulation based on a previously observed reference respiratory cycle [*reference respiration-related parameter*].

Two patients with documented severe OSA (>40 episodes/hr) were studied overnight. ***Baseline information such as respiratory rate and level of oxygen saturation was acquired during the first hour of sleep...*** For example, a 40% duty cycle ***in a 5 second respiration period*** means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009 p.377.

In this method, we applied a brief train of electrical pulses during an ***ON period*** followed by ***no stimulation during an OFF period***. ***This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant***, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010, p.4288, FIG. 4; EX-1003 ¶¶269-273.

A POSITA would have been motivated to base the stimulation period disclosed by Headley on the patient's natural respiratory rhythm for the reasons discussed in X.B.3. EX-1003 ¶273. Headley-Tran discloses [1.c]. EX-1003 ¶274.

- v. [1.d] *wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.*

Headley discloses stimulating electrode 110 [*implantable electrode*] emanating from [*electrically connectable to*] receiver 116 [*implantable pulse generator*].

The device itself consists of 4 parts... *Third is a receiver 116 and fourth is the stimulating electrode 110 (Fig. 5)*... This is connected to the antennae which deliver the radio frequency to the *receiver which has been implanted in the neck of the patient with the stimulating electrodes emanating from the receiver* and entering into specific muscle sites in the tongue of the patient.

EX-1008 ¶¶29-30; FIG. 5; EX-1003 ¶¶275-277.

Headley-Tran discloses [1.d] and renders obvious claim 1. EX-1003 ¶¶276-278.

b. **Claim 2**

- i. [2] *The device of claim 1, wherein the asynchronous timing of the stimulation relative to patient breathing comprises the timing being not based on actively-sensed respiration during application of the first stimulation therapy protocol.*

Headley, either alone or in combination with Tran, discloses the asynchronous timing of stimulation periods is implemented without a sensing

element for synchronization relative to patient breathing [*being not based on actively-sensed respiration during application of the first stimulation therapy protocol*] to simplify the device. EX-1008 ¶14; EX-1010, pp.4288-4289; X.B.3; X.B.4.a.ii; EX-1003 ¶¶279-281.

Headley-Tran renders claim 2 obvious. EX-1003 ¶282.

c. Claim 3

- i. [3] The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory pattern.*

Tran discloses providing stimulation based on an observed reference respiratory cycle of a patient [*reference breathing pattern*]. X.B.4.a.iii; EX-1009 p.377; EX-1010, p.4288; EX-1003 ¶283.

Headley-Tran renders obvious claim 3. EX-1003 ¶284.

d. Claim 4

- i. [4.a] The device of claim 3, wherein the reference respiratory pattern comprises a reference respiratory cycle, and*

Headley-Tran discloses [4.a] for the same reasons discussed in X.B.4.c. EX-1009, p.377; EX-1003 ¶¶285-286.

- ii. [4.b] *wherein a duration of each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle.*

Headley discloses periods of stimulation of up to 120 seconds. EX-1008

¶48. Tran discloses providing electrical stimulation based on an observed five-second reference respiratory cycle of a sleeping patient such that the stimulation period has a minimum duration equal to or greater than an inspiratory reference.

Two patients with documented severe OSA (>40 episodes/hr) were studied overnight. *Baseline information such as respiratory rate and level of oxygen saturation was acquired during the first hour of sleep.* Various duty cycles of gating of CPAP (30-50%) were studied at random during the night. For example, a 40% duty cycle *in a 5 second respiration period* means CPAP is applied for 3 sec and gated off for 2 sec.

EX-1009, p.377.

In this method, we applied a brief train of electrical pulses during an *ON period* followed by *no stimulation during an OFF period. This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping participant*, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010, p.4288; EX-1003 ¶¶287-289.

FIG. 4 of Tran-II is a screen capture of a polysomnogram of a patient, which shows a two-second inspiratory phase and the stimulation markers indicating an ON period [*stimulation period*] of approximately 2.5 seconds.

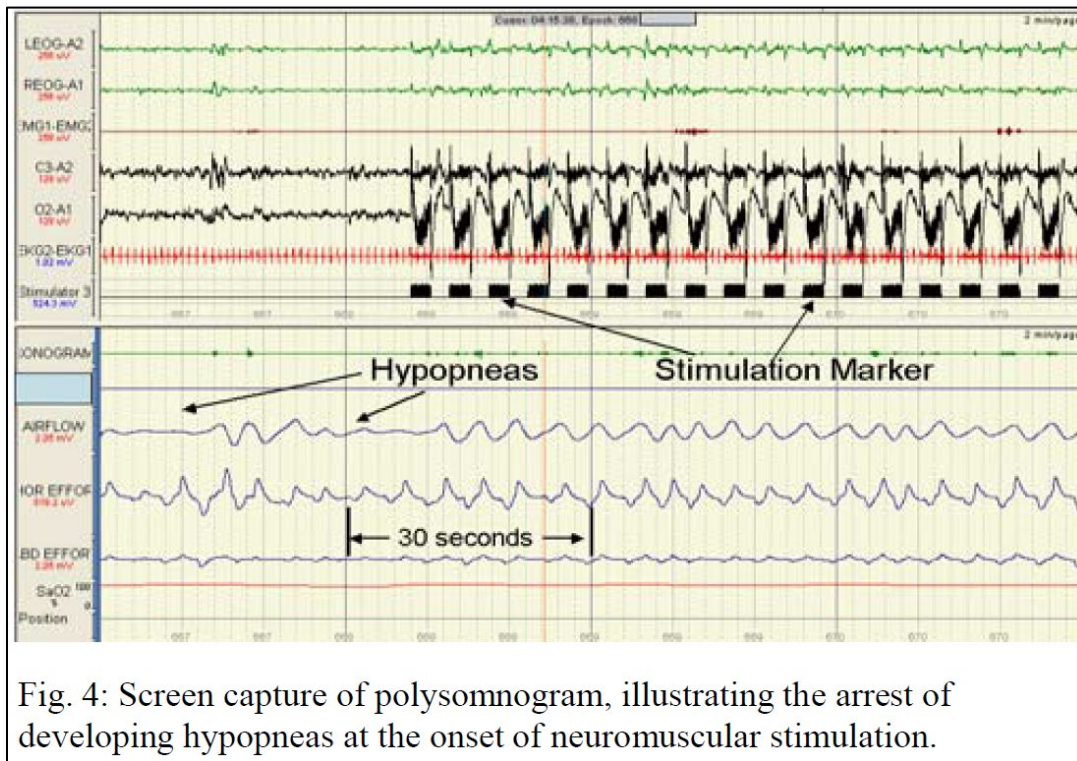


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010, FIG. 4; EX-1003 ¶288.

Thus, Tran discloses that each ON period [*each respective stimulation period*] has a duration greater than the inspiratory phase of the patient's respiratory cycle [*reference respiratory cycle*]. A POSITA understood that a period of stimulation [*stimulation period*] of 120 seconds, as disclosed by Headley, exceeded the duration of any patient's inspiratory phase, including the 2.5 second inspiratory phase disclosed by Tran. EX-1008 ¶48; EX-1010, FIG. 10; EX-1003 ¶¶288-289.

A POSITA would be motivated to modify the teachings of Headley to provide stimulation for *a duration of each respective stimulation period is greater than a duration of an inspiratory phase of the reference respiratory cycle* as taught by Tran for the reasons described in X.B.3. EX-1003 ¶¶289-290.

Headley-Tran renders obvious claim 4. EX-1003 ¶¶290-291.

e. **Claim 5**

- i. ***[5] The device of claim 1, wherein the reference respiratory-related parameter is based on stable respiration.***

Tran discloses providing electrical stimulation based on a patient's natural respiratory rhythm when sleeping, which a POSITA understood as stable respiration. X.B.4.b; EX-1010, pp.4287-4289; EX-1003 ¶¶292-293.

Headley-Tran renders obvious claim 5. EX-1003 ¶¶293-294.

f. **Claim 6**

- i. ***[6.a] The device of claim 1 wherein the reference respiratory-related parameter comprises a reference respiratory cycle and***

Headley-Tran discloses [6.a] for the same reasons discussed in X.B.4.d.i ([4.a]). EX-1003 ¶295.

- ii. [6.b] *wherein a combined duration of a respective one of the stimulation periods and a respective one of the non-stimulation periods is less than a duration of the reference respiratory cycle.***

Headley discloses stimulation cycles of two seconds (1 second on/1 second off). EX-1008 ¶48; EX-1003 ¶297. A two-second stimulation cycle is less than the duration of the five-second reference breath disclosed by Tran. EX-1009, p.377; EX-1010, p.4288; EX-1003 ¶¶296-298.

Headley-Tran discloses [6.b] and renders obvious claim 6. EX-1003 ¶¶299-300.

g. Claim 7

- i. [7.a] *The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle and***

Headley-Tran disclose [7.a] for the same reasons discussed in X.B.4.d.i ([4.a]). EX-1003 ¶301.

- ii. [7.b] *wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is no greater than a duration of a reference respiratory cycle.***

Headley-Tran disclose [7.b] for the same reasons discussed in X.B.4.f.ii ([6.b]) and render obvious claim 7. EX-1003 ¶¶302-303.

h. Claim 8

- i. [8] The device of claim 1, wherein the duration of the respective stimulation periods remain uniform.*

Headley discloses intermittent periods for stimulation each having a uniform stimulation period, and Tran illustrates uniform stimulation periods in FIG. 4. EX-1008 ¶48; EX-1010 p.4288, FIG. 4; EX-1003 ¶¶304-305.

Headley-Tran renders obvious claim 8. EX-1003 ¶306.

i. Claim 9

- i. [9.a] The device of claim 1, wherein the reference respiratory-related parameter comprises a reference respiratory cycle, and*

Headley-Tran disclose [9.a] for the same reasons discussed in X.B.4.d.i ([4.a]). EX-1003 ¶307.

- ii. [9.b] wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is less than 30 percent of duration of a reference breathing pattern.*

Headley discloses stimulation for periods [*respective one of the stimulation periods*] and off periods [*respective one of the non-stimulation periods*] as short as one second, EX-1008 ¶48, and Tran discloses a five-second natural respiratory rhythm [*duration of the reference respiratory cycle*]. EX-1009, p.377; EX-1010, p.4288; EX-1003 ¶¶308-309. A combined duration of a one-second ON period [*respective stimulation period*] and a one-second OFF period [*respective non-*

stimulation period] corresponds to 40% of a five-second respiratory period. EX-1003 ¶¶309-310.

A POSITA understood that patients may have different respiratory rates based on their level of activity and/or position. EX-1010, p.4288. As such, a POSITA understood that a respiratory rate may increase in duration and a two-second stimulation cycle may correspond to less than 30% of a patient's respiratory cycle [*reference breathing pattern*]. Further, adjusting the duration of a stimulation cycle and/or the duty cycle of the stimulation period was routinely performed and required nothing beyond the exercise of routine skill in the art. VIII.B; EX-1003 ¶¶310-311.

Headley-Tran discloses [9.b] and render obvious claim 9. EX-1003 ¶¶311-312.

j. **Claim 10**

- i. ***[10] The device of claim 1, wherein a respective one of the stimulation periods and a respective one of the non-stimulation periods are in a proportion of at least 1.5 to 1.***

Headley discloses duty cycles in which the stimulation/on period [*respective one of the stimulation periods*] and the rest/off period [*respective one of the non-stimulation periods*] are in a proportion of at least 1.5:1 (e.g., 60 on/5 off). EX-1008 ¶48; EX-1003 ¶313.

Headley-Tran renders obvious claim 10. EX-1003 ¶¶314-315.

k. Claim 11

- i. [11] The device of claim 10, wherein a duration of a respective one of the stimulation periods exceeds the duration of a respective one of the non-stimulation periods by a factor of 3.*

Headley discloses duty cycles in which the stimulation/on period [*duration of a respective one of the stimulation periods*] is 12 times greater than the rest/off period [*duration of a respective one of the non-stimulation periods*] (e.g., 60 on/5 off), which is greater than 3. EX-1008 ¶48; EX-1003 ¶317.

Headley-Tran discloses claim 11. EX-1003 ¶¶317-318.

l. Claim 12

- i. [12a] The device of claim 1, wherein a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle, and*

Headley discloses an on/off intermittent stimulation period [*a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle*]. EX-1008 ¶48; EX-1003 ¶319.

Headley discloses [12.a], either alone or with Tran. EX-1010, p.4288; EX-1003 ¶¶319-320.

- ii. [12.b] wherein a duration of the respective one of the stimulation periods comprises at least 80 percent of a duration of the stimulation cycle.**

Headley discloses a 60-second stimulation period, which is 92% (i.e., at least 80 percent) of a 65 second stimulation cycle (60 ON/5 OFF). EX-1008 ¶48; EX-1003 ¶¶321-322.

Headley discloses [12.b] and renders obvious claim 12. EX-1003 ¶323.

m. Claim 13

- i. [13] The device of claim 1, wherein each respective stimulation period comprises continuous pulsed stimulation.**

The '526 Patent describes continuous pulsed stimulation as “a train of stimulation pulses which occur in a relatively short time frame,” such as “a finite number (e.g. 5, 10, etc.) of stimulation pulses per second.” EX-1001 4:43-55; EX-1003 ¶324. Headley discloses that the pulse generator varies the properties of the electrical pulses, and Tran discloses pulses of 20 pulses-per-second (PPS).

The receiver includes an electrical pulse source, or pulse generator. ***The electrodes impart electrical pulses, generated by the pulse generator***, directly by wire to the genioglossus muscle to stimulate the specific muscle fibers to a point where the patient’s tongue is moved anteriorly to maintain upper airway patency. ***The pulse generator has an output that provides pulses having selectable properties of*** mode, polarity, amplitude, current, pulse width, and ***frequency***.

EX-1008 ¶30; EX-1010, p.4289; EX-1003 ¶¶325-327.

Headley discloses claim 13, either alone or with Tran. EX-1003 ¶¶327-328.

n. Claim 14

i. [14.a] *The device of claim 1, comprising a processor;*

Headley discloses that the pulse generator of the receiver includes a microprocessor [*processor*].

Commercially available *pulse generators provide pulses having many of the previously mentioned variables and may include microprocessors* and electronics for signal processing and cooperation with apnea detection device.

EX-1008 ¶30; EX-1003 ¶329.

Headley discloses [14.a]. EX-1003 ¶330.

ii. [14.b] *and a non-volatile computer readable medium storing instructions, executable on the processor, to implement the first stimulation therapy protocol via the non-cardiac stimulation means for stimulating.*

A POSITA understood that a commercially available pulse generator included a non-volatile computer readable medium storing instructions, executable by the microprocessor [*processor*], to perform the alternating on/off “intermittent” treatment [*first stimulation therapy protocol*] via the electrode [*non-cardiac stimulation means*]. EX-1008 ¶29; VIII.A; EX-1003 ¶331.

Headley-Tran discloses [14.b] and renders obvious claim 14. EX-1003 ¶332.

o. Claim 15

- i. [15] *The device of claim 1, wherein the first stimulation therapy protocol is to be applied during a treatment period in which the patient is to engage in sleeping behavior.***

Headley discloses that the intermittent on/off treatment [*the first stimulation therapy protocol*] is for treating OSA, which occurs when a patient is sleeping.

EX-1008 ¶ 30; EX-1003 ¶333.

Headley-Tran renders obvious claim 15. EX-1003 ¶334.

p. Claim 16

- i. [16.pre] *A device for treating obstructive sleep apnea, comprising:***

See X.B.4.a.i. EX-1003 ¶335.

- ii. [16.a1] *a non-cardiac means for stimulating an upper airway patency-related nerve,***

See X.B.4.a.ii. EX-1003 ¶¶336-337.

- iii. [16.a2] *according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,***

See X.B.4.a.iii. EX-1003 ¶338.

- iv. [16.b] *wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period,***

See X.B.4.a.iv. EX-1003 ¶339.

- v. ***[16.c] wherein each stimulation period comprises continuous pulsed stimulation, and***

See X.B.4.m. EX-1003 ¶340.

- vi. ***[16.d] wherein the first stimulation therapy protocol is to deliver multiple stimulation periods within a duration of a reference breath of a reference respiratory cycle, and***

Headley discloses that the duration of an applied stimulation may be provided for periods of 1 to 120 seconds. EX-1008 ¶48. One-second on and one-second off periods results in a two-second stimulation cycle such that multiple stimulation periods are provided within the five-second reference breathing pattern of Tran. EX-1009, p.377; EX-1010, FIG. 4; EX-1003 ¶¶341-343.

Headley-Tran discloses [16.d]. EX-1003 ¶¶343-345.

- vii. ***[16.e] wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.***

See X.B.4.a.vi. EX-1003 ¶346.

Headley-Tran renders obvious claim 16. EX-1003 ¶347.

q. **Claim 17**

- i. ***[17] The device of claim 16, wherein the duration of each respective non-stimulation period is at least less than half of the duration of each respective stimulation period.***

Headley discloses the limitations of claim 17 for the same reasons discussed in X.B.4.j. EX-1008 ¶48; EX-1003 ¶¶348-350.

Headley discloses claim 17. EX-1003 ¶¶350-351.

r. **Claim 18**

- i. ***[18] The device of claim 16, wherein the reference respiratory cycle comprises at least one of: a historical patient-specific reference respiratory cycle; and a multiple patient reference respiratory cycle.***

Tran discloses observing a sleeping patient to determine the patient's respiratory rate [*historical patient-specific average respiratory cycle*] and using the respiratory rate to provide the electrical stimulation.

Two patients with documented severe OSA (>40 episodes/hr) were studied overnight. Baseline information such as respiratory rate and level of oxygen saturation was acquired during the first hour of sleep.

EX-1009 p.377.

In this method, we applied a brief train of electrical pulses during an ON period followed by no stimulation during an OFF period. ***This method of stimulation is repeated in continuous cycles at approximately the natural respiratory rhythm of the sleeping***

participant, obviating the need for a sensor to synchronize stimulation with breathing.

EX-1010, p.4288; EX-1003 ¶352.

A POSITA would be motivated to modify the teachings of Headley to provide the reference respiratory cycle using *a historical patient-specific average respiratory cycle for stable respiration stimulation* as taught by Tran for the reasons described in X.B.3. EX-1003 ¶353.

Headley-Tran renders claim 18 obvious. EX-1003 ¶¶353-354.

s. **Claim 19**

- i. [19] *The device of claim 16, wherein the first stimulation therapy protocol is to deliver at least some of the multiple stimulation periods within a duration of an inspiratory phase of the reference respiratory cycle.*

Headley discloses that the duration of an applied stimulation may be provided for periods of 1 to 120 seconds. EX-1008 ¶48. At least one [*at least some*] of the one-second ON periods [*multiple stimulation periods*] could be provided within the 2-2.5 second *inspiratory phase of the reference respiratory cycle* of Tran. EX-1010, FIG. 4; EX-1003 ¶¶355-356.

Headley discloses claim 19. EX-1003 ¶357.

t. **Claim 20**

- i. ***[20] The device of claim 16, wherein the duration of each respective stimulation period is at least less than 30 percent of a duration of the reference respiratory cycle.***

Headley discloses a one-second stimulation period and Tran discloses a five-second reference respiratory cycle. EX-1008 ¶48; EX-1009, p.377; EX-1010, pp.4288-4289; EX-1003 ¶¶358-359. A one-second stimulation period is 20% of the five-second reference respiratory cycle disclosed by Tran. EX-1003 ¶359.

Headley-Tran renders obvious claim 20. EX-1003 ¶¶360-361.

u. **Claim 21**

- i. ***[21.a] The device of claim 16, wherein a combination of a respective one of the stimulation periods and a respective one of the non-stimulation periods comprises a stimulation cycle, and***

Headley-Tran discloses [21.a] for the reasons discussed in X.B.4.d.i ([4.a]). EX-1003 ¶362.

- ii. ***[21.b] wherein the first stimulation therapy protocol is to deliver more than one stimulation cycle within a duration of the reference respiratory cycle.***

Headley discloses a two-second stimulation cycle (e.g., one second on, one second off), which could be delivered 2.5 times within the five-second reference respiratory cycle disclosed by Tran. EX-1008 ¶48; EX-1009, p.377; EX-1010, pp.4288-4289; EX-1003 ¶¶363-365.

Headley-Tran renders obvious claim 21. EX-1003 ¶¶365-366.

v. **Claim 22**

- i. ***[22.pre] A device for treating obstructive sleep apnea, comprising:***

See X.B.4.a.i. EX-1003 ¶367.

- ii. ***[22.a1] a non-cardiac means for stimulating an upper airway patency-related nerve,***

See X.B.4.a.ii. EX-1003 ¶¶368-369.

- iii. ***[22.a2] according to a first stimulation therapy protocol including alternating stimulation periods and non-stimulation periods in which a timing of the stimulation periods is asynchronous relative to patient breathing,***

See X.B.4.a.iii. EX-1003 ¶370.

- iv. ***[22.b] wherein a duration of each respective stimulation period is greater than a duration of each respective non-stimulation period, and***

See X.B.4.a.iv. EX-1003 ¶371.

- v. ***[22.c] wherein the combined duration of a respective one of the stimulation periods and of a respective one of the non-stimulation periods is greater than a duration of a reference respiratory cycle,***

Headley discloses an on-period [*respective one of the stimulation periods*] and an off-period [*respective one of the non-stimulation periods*] may each be 120 seconds. EX-1008 ¶48. A 240 second stimulation cycle is greater than the five-

second reference respiratory cycle disclosed by Tran. EX-1009, p.377; EX-1010, pp.4288-4289; EX-1003 ¶¶372-374.

Headley-Tran discloses [22.c]. EX-1003 ¶¶375-376.

- vi. ***[22.d] wherein, the non-cardiac stimulation means for stimulating comprises an implantable electrode and/or an implantable pulse generator electrically connectable to the implantable electrode.***

See X.B.4.a.vi. EX-1003 ¶¶377-378.

Accordingly, claim 22 is obvious from Headley-Tran. EX-1003 ¶378.

w. **Claim 23**

- i. ***[23] The device of claim 22, wherein the duration of a respective one of the stimulation periods is greater than the duration of the reference respiratory cycle.***

Headley discloses an on-period [*respective one of the stimulation periods*] as long as 120 seconds. EX-1008 ¶48. A 120-second stimulation period is greater than the five-second reference respiratory cycle of Tran. EX-1009, p.377; EX-1010, pp.4288-4289; EX-1003 ¶¶379-381.

Headley-Tran render obvious claim 23. EX-1003 ¶¶382-383.

XI. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest in this Petition is Nyxoah, Inc. and Nyxoah SA.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters

As of the filing date of this Petition, the following pending judicial cases concern the '526 Patent:

- *Inspire Medical Systems, Inc. v. Nyxoah, Inc. et al.*, Case No. 1:25-cv-00667-RGA (D. Del. 2025)

2. Administrative Matters

As of the filing date of this Petition, Petitioners are not aware of any pending administrative matters that could affect, or could be affected by, a decision in this proceeding. Petitioners are aware of pending U.S. Patent Application Nos. 18/394,423 and 19/413,508.

3. Related Patents

As of the filing date of his Petition, Petitioners are aware of the following U.S. Patents: U.S. Patent Nos. 10,898,709 and 11,850,424.

C. Lead/Back-up Counsel (37 C.F.R. § 42.8(b)(3)):

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D. Notice of Service Information (37 C.F.R. § 42.8(b)(4)):

Please direct all correspondence to lead and back-up counsel at the above addresses. Petitioners consent to electronic service at the email addresses above.

XII. CONCLUSION

For the reasons set forth above, Petitioners have established a reasonable likelihood of prevailing with respect to the Challenged Claims and request the

Petition for *Inter Partes* Review of U.S. Patent No. 11,806,526

Board institute *inter partes* review and then cancel the Challenged Claim as unpatentable.

Respectfully submitted,

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ATTORNEY FOR PETITIONERS

Dated: December 18, 2025

CERTIFICATION OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on December 18, 2025, a complete and entire copy of this Petition for *Inter Partes* Review of U.S. Patent No. 11,850,526 and all supporting exhibits were served via Federal Express, postage prepaid, to the Patent Owner by serving the correspondence address of record for the '526 Patent:

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 *et seq.*, the undersigned certifies that this document complies with the type-volume limitations. This document contains 13,604 words as calculated by the “Word Count” feature of Microsoft Word 2010, the word processing program used to create it.

Dated: December 18, 2025

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