

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. 10,898,709

Issue Date: January 26, 2021

Title: STIMULATION FOR TREATING SLEEP DISORDERED BREATHING

Inter Partes Review No.: IPR2026-00090

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 10,898,709
UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.107**

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Petitioners' Exhibit List

<i>Exhibit #</i>	<i>Description</i>
1001	U.S. Patent No. 10,898,709 (the "'709 Patent")
1002	Select portions of the prosecution history of the '709 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 ("Wagner")
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")

<i>Exhibit #</i>	<i>Description</i>
1015	Glenn, et al., “Electrical Stimulation of Excitable Tissue by Radio-Frequency Transmission,” <i>Annals of Surgery</i> 160:3, 338-350 (1964) (“Glenn”)
1016	Judson, et al., “Radio-Frequency Electrophrenic Respiration – Long-Term Application to a Patient with Primary Hypoventilation,” <i>JAMA</i> 203:12, 1033-1037 (March 18, 1968) (“Judson”)
1017	Singh, et al., “Recruitment Properties of Intramuscular and Nerve-Trunk Stimulating Electrodes,” <i>IEEE Transactions on Rehabilitation Engineering</i> , 8:3, 276-285 (September 2000) (“Singh”)
1018	Richmond, et al., “Tactical Application of Sensorimotor Prosthetic Technology,” <i>Proceedings of the 25th Annual International Conference of the IEEE EMBS, Cancun, Mexico</i> (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,” <i>Am Rev Respir Dis</i> , 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,” <i>Am Rev Respir Dis</i> 140:1285-1289 (1989) (“Miki”)
1021	Decker, et al., “Functional Electrical Stimulation and Respiration During Sleep,” <i>Journal of Applied Physiology</i> , 75(3): 1053-1061 (1993) (“Decker”)
1022	Eisele, et al., “Direct Hypoglossal Nerve Stimulation,” <i>Arch. Otolaryngol Head Neck Surg.</i> , 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,” <i>Journal of Physiology</i> 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,” <i>J Appl Physiol.</i> (81(2):643-652 (1996) (“Schwartz1996”)

<i>Exhibit #</i>	<i>Description</i>
1026	Goding, et al., “Relief of Upper Airway Obstruction With Hypoglossal Nerve Stimulation in the Canine,” <i>Laryngoscope</i> , 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,” <i>Proceedings of the Second Joint EMBS/BMES Conference</i> , 2049-2050 (October 23-26, 2002) (“Yoo”)
1029	Fairbanks et al., “Neurostimulation for Obstructive Sleep Apnea: Investigations,” <i>ENT Journal</i> (January 1993) (“Fairbanks”)
1030	Schwartz, et al., “Therapeutic Electrical Stimulation of the Hypoglossal Nerve in Obstructive Sleep Apnea,” <i>Arch Otolaryngol Head Neck Surg.</i> , Vol. 127 (Oct. 2001) (“Schwartz2001”)
1031	Oliven, “Treating Obstructive Sleep Apnea with Hypoglossal Nerve Stimulation,” <i>Current Opinion in Pulmonary Medicine</i> 17:419-424 (2011) (“Oliven”)
1032	Mwenge, et al., “Targeted Hypoglossal Neurostimulation for Obstructive Sleep Apnoea: a 1-Year Pilot Study,” <i>Eur Respir J.</i> 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,” <i>Neuromodulation</i> ; 16:376-386 (2012) (“Zaidi”)
1034	Steier, et al., “Continuous Transcutaneous Submental Electrical Stimulation in Obstructive Sleep Apnea,” <i>Chest</i> 140:998-1007 (2011) (“Steier”)
1035	Agnew, et al., “Considerations for Safety with Chronically Implanted Nerve Electrodes,” <i>Epilepsia</i> , 31 (Suppl. 2): S27-32 (1990) (“Agnew”)
1036	U.S. Patent No. 7,277,749 (“Gordon”)
1037	Meadows, et al., “Effects of Targeted Activation of Tongue Muscles on Oropharyngeal Patency in the Rat,” <i>Journal of the Neurological Sciences</i> , 346:178-193 (August 2014) (“Meadows”)

<i>Exhibit #</i>	<i>Description</i>
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”)
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”)

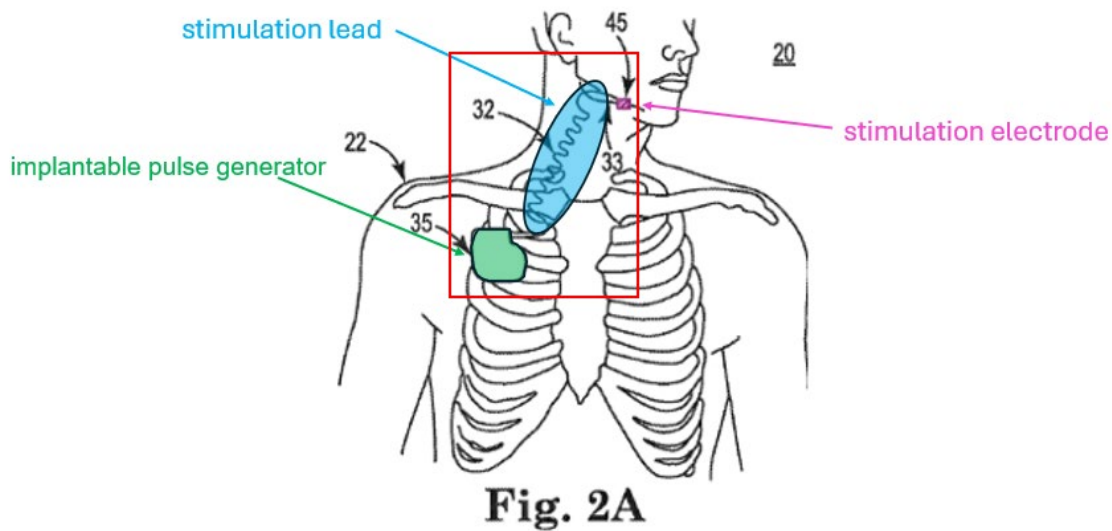
I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311 *et seq.* and 37 C.F.R. §§ 42.1 *et seq.*, Nyxoah, Inc. and Nyxoah SA (collectively, “Petitioners”) hereby petition for *inter partes* review of U.S. Patent 10,898,709 (the “’709 Patent”). Petitioners respectfully submit that Claims 1-15 (the “Challenged Claims”) of the ’709 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 ’709 Patent pursuant to 37 C.F.R. § 42.108 is respectfully requested.

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 element to engage and to stimulate an upper-airway-patency-related nerve using a series of repeating stimulation cycles, where each cycle is based on reference respiratory cycle information (e.g., collected during normal breathing) rather than actively-sensed respiratory information from the patient being treated.

Annotated FIG. 2A of the '709 Patent shows a **device** having **electrode portion** 45, electrically coupled to **implantable pulse generator** 35 via **stimulation lead** 32, which engages and stimulates upper-airway-patency-related nerve 33, e.g., the hypoglossal nerve ("HGN").

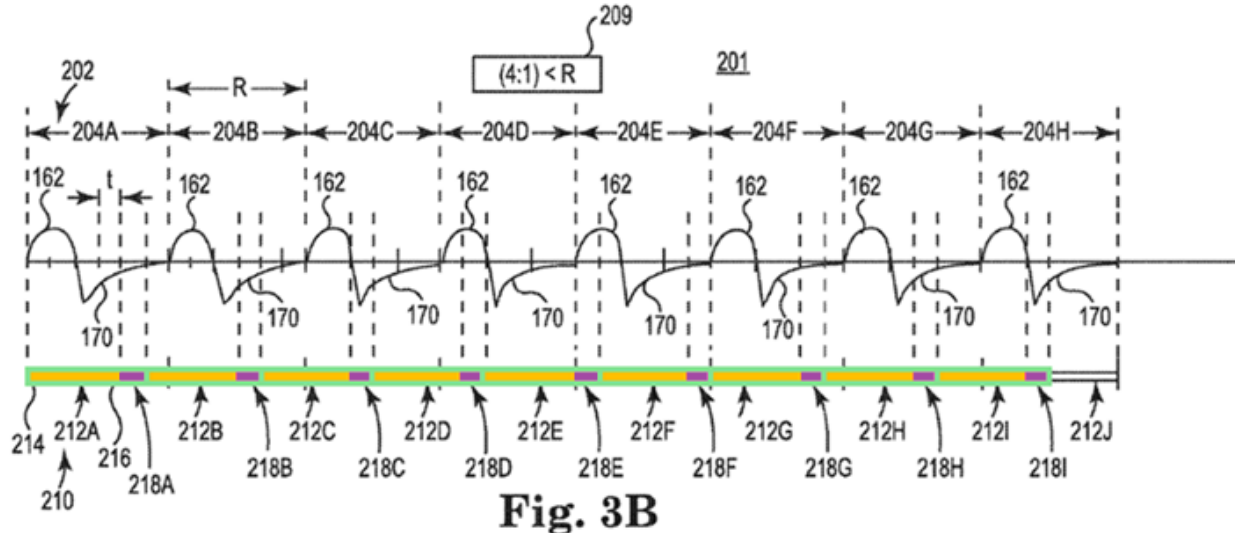


EX-1001 FIG. 2, 9:51-61, 11:55-59.¹

The '709 Patent acknowledges neurostimulation devices for treating OSA, which included non-cardiac stimulation elements to engage and stimulate the HGN, were well-known and widely implemented prior to March 2015. EX-1001 8:63-10:3.

¹ All annotations added unless otherwise stated.

The purported novelty of the '709 Patent is treating OSA using asynchronous stimulation (i.e., stimulation applied based on a stimulation cycle not synchronized to actively-sensed respiration). Specifically, the Challenged Claims require each repeating stimulation cycle to include a stimulation period that is longer in duration than both a non-stimulation (rest) period and a reference inspiratory (breathing-in) phase of the reference respiratory cycle, which is determined using either a historical patient-specific or multi-patient average.



EX-1001 FIG. 3B, 12:57-13:7, 13:21-28.

Treatment of OSA using asynchronous stimulation was not new, having been disclosed over a decade before the priority date of the '709 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 respiration for timing).

Ground 1 demonstrates Challenged Claims 1-12 and 14-15 are obvious from the combination of Durand and Hoegh. Durand discloses identical architecture as the '709 Patent for treating OSA:

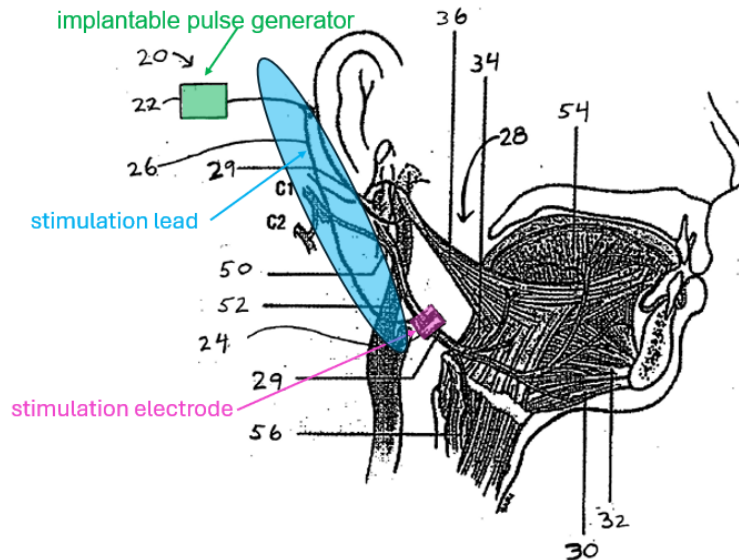


FIG. 1

EX-1006 FIG. 1.

Durand discloses an apparatus 20 including an **implantable pulse generator** 22 for generating the desired electrical stimulus via a **stimulus lead** 26 connected to a **stimulation electrode** 24 wrapped around the nerve. EX-1006 ¶14. Durand further discloses intermittent electrical stimulation at controlled intervals (predetermined based on the patient's resting nighttime metabolism and determined 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 stimulation. While Durand does not expressly disclose the duration of the stimulation period relative to the patient’s inspiratory phase, 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 that “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 and the patient’s inspiratory phase (e.g., duty cycles of >50%). EX-1007 ¶¶98, 114.

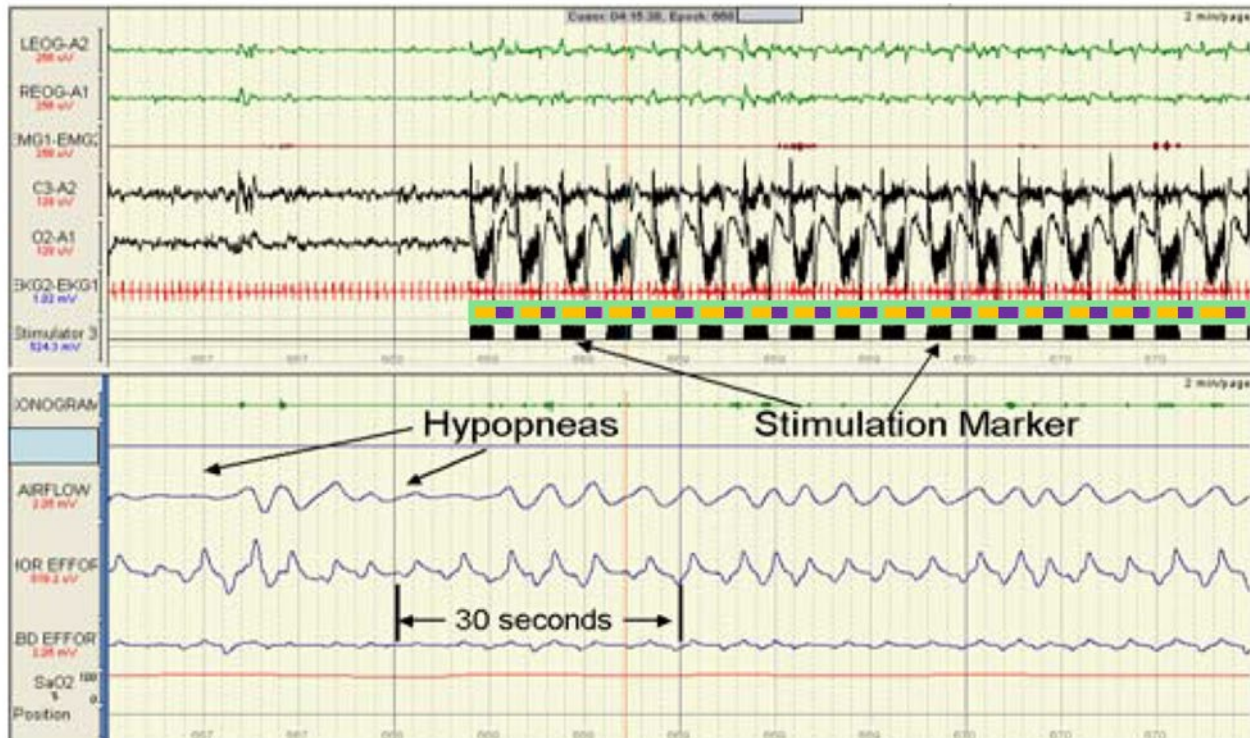
A POSITA understood that the teachings of Durand and Hoegh could be combined given that the two references disclose the same type of devices for treating OSA and use the same technique, i.e., asynchronously stimulating the HGN, and would have been motivated to combine the teachings of Durand and Hoegh 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 ¶¶93-102, 109, 112, 117-118, 122, 126-129. As demonstrated below, Challenged Claims 1-12 and 14-15 are obvious from the combination of Durand and Hoegh.

With respect to Ground 2, Headley discloses an implantable device for treating OSA, which 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 discloses a stimulation period duration greater than a non-stimulation period duration (*id.*), Headley does not expressly disclose using a reference respiratory cycle.

However, 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 genioglossus. EX-1009 p.376; EX-1003 ¶86. 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 approximately 3 seconds and a **non-stimulation period** (OFF period) of approximately 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 ¶¶194-195.

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 ¶194.

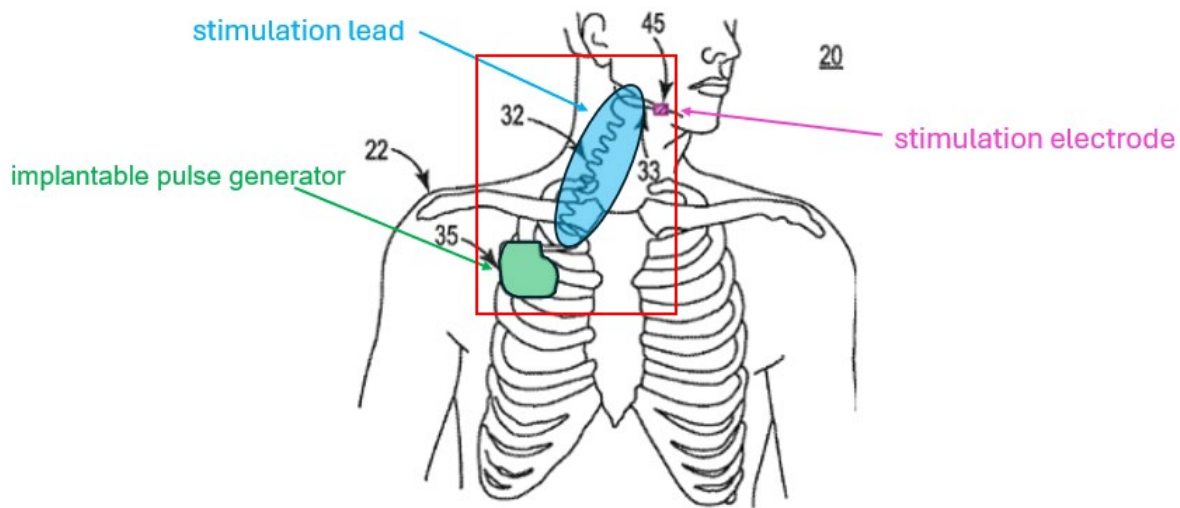
Thus, the references used in the Grounds below demonstrate that the purported invention of the Challenged Claims was well-known at the time of the '709 Patent and unpatentable.

III. GROUNDS FOR STANDING (37 C.F.R. §42.104(A))

Petitioners certify that the '709 Patent is available for *inter partes* review and that Petitioners are not barred or estopped from requesting *inter partes* review of the Challenged Claims. 37 C.F.R. §42.104(a). This Petition is filed pursuant to 37 C.F.R. §42.106(a).

IV. '709 PATENT SUMMARY

The '709 Patent discloses a device for treating OSA through stimulation of an upper-airway-patency-related nerve. EX-1001 Abstract. FIG. 2A illustrates system 20 including implantable pulse generator (IPG) 35 and stimulation lead 32 electrically coupled thereto. Lead 32 includes stimulation electrode portion 45 that may be positioned in contact with, and enables stimulation of, the upper-airway-patency-related nerve. EX-1001 9:51-10:24.



EX-1001 FIG. 2A.

In another embodiment, system 80 includes nerve-coupling **electrode portion** 82 and **pulse generator** 84, which may include internal components 90 and external components 92. **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. 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.

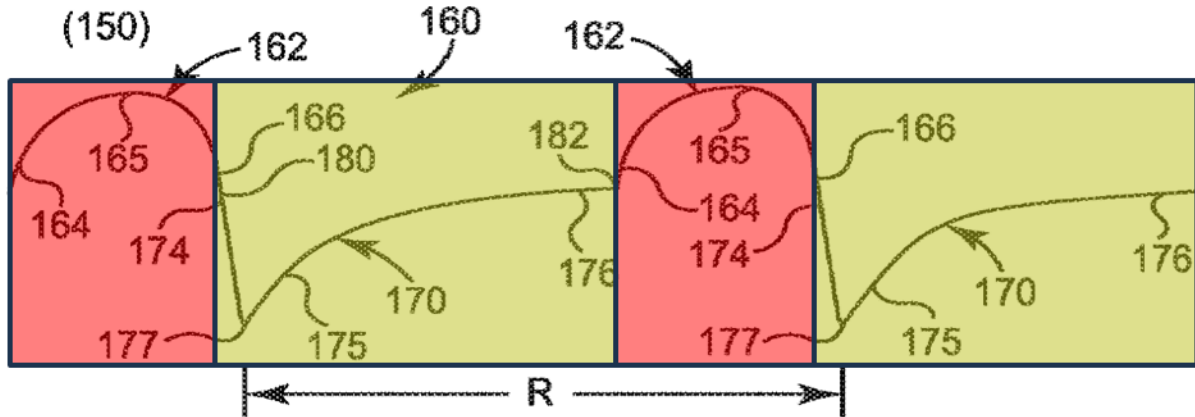


Fig. 3A

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.

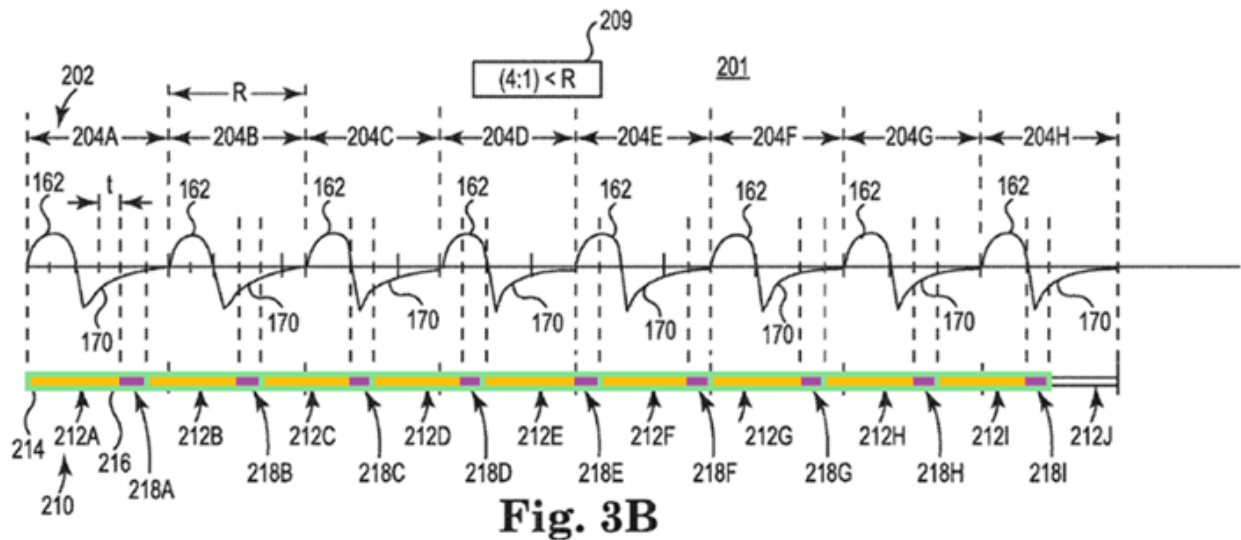


Fig. 3B

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 (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 '709 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 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, 18:8-16.

The '709 Patent also discloses that the stimulation system may operate in cooperation with a sensing function. Sensing element 330 of FIG. 7A may be incorporated into **IPG** 50 of FIG. 2B. Sensing element 330 receives and tracks signals from at least one physiologic sensor to gather information regarding sleep

disordered breathing, such as a respiratory state, whether the patient is sleeping, or other respiratory-associated indicators. EX-1001 24:4-25:3.

V. PROSECUTION HISTORY

A. Filing Date and Priority

The application that issued as the '709 Patent was 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 '709 Patent’s earliest-claimed priority date—March 19, 2015—is the priority date.

B. Prosecution

The '714 Application entered the U.S. national phase with 128 claims. EX-1002 0001-135. A preliminary amendment was filed canceling claims 1-128 and adding claims 129-148. EX-1002 0192-199.

During prosecution, all pending claims were finally rejected over Bolea (EX-1012) in combination with one or more references. EX-1002 0313-323. In response, Applicant amended the claims to clarify that the first stimulation protocol was a “first stimulation therapy protocol.” EX-1002 0338-364. Applicant argued Bolea only discloses using an asynchronous (fixed) mode during daytime familiarization and not as a therapy for sleep apnea. *Id.*

The Examiner, having been incorrectly persuaded by Applicant's arguments and apparently misapprehending or overlooking certain disclosures in Bolea, issued another non-final rejection objecting to claims 134, 137-140, and 149 and rejecting the remainder of the claims based on Christopherson, alone or in combination with other references, including Bolea. EX-1002 0365-375; EX-1003 ¶¶61-67.

In response, Applicant amended the independent claims to include subject matter previously identified as being allowable. Specifically, Applicant amended the independent claims to require: (1) each stimulation period of a stimulation cycle includes continuous stimulation having a duration equal to or greater than an inspiratory reference of a reference respiratory cycle that comprises at least one of a patient-specific or multi-patient average respiratory cycle and (2) each stimulation period of a stimulation cycle has a duration greater than a duration of the inspiratory reference and the non-stimulation period. EX-1002 0409-417.

Claim 1 as allowed recites:

1.pre	<i>A device for treating obstructive sleep apnea, comprising:</i>
1.a1	<i>a non-cardiac stimulation element to engage and to stimulate an upper-airway-patency-related nerve,</i>
1.a2	<i>according to a first stimulation therapy protocol not synchronized relative to actively-sensed respiratory information,</i>

1.b	<i>wherein the first stimulation therapy protocol comprises a series of repeating stimulation cycles in which each stimulation cycle includes a stimulation period and a non-stimulation period,</i>
1.c	<i>wherein each stimulation period includes continuous stimulation and has a minimum duration equal to or greater than an inspiratory reference of a reference respiratory cycle, wherein the inspiratory reference corresponds to a duration of an inspiratory phase of the reference respiratory cycle, and</i>
1.d	<i>wherein the reference respiratory cycle comprises at least one of: a historical patient-specific average respiratory cycle for stable respiration; and a multi-patient average respiratory cycle for stable respiration, and</i>
1.e	<i>wherein each stimulation period of each respective stimulation cycle has a duration greater than a duration of the inspiratory reference of the reference respiratory cycle and the stimulation period is followed by the non-stimulation period of the respective stimulation cycle comprising a duration less than the duration of the stimulation period.</i>

VI. CLAIM CONSTRUCTION

Each claim term in the Challenged Claims should be given its plain and ordinary meaning in this proceeding. 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 ’709 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 ¶¶22-25.

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 cuff electrodes wrapped around peripheral nerve trunks or branches, patch electrodes sutured onto the connective tissue of a nerve, muscle, or fascia, and intramuscular 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 16:13-35; EX-1003 ¶33.

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 ¶¶34-36.

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 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 ¶37.

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 ¶38.

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 ¶39.

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 sleeping respiratory rate. EX-1012 ¶266; EX-1026, p.163; EX-1030, p.1217; EX-1033, p.384; EX-1003 ¶¶40-41.

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 ¶42.

IX. IDENTIFICATION OF CHALLENGES

A. Challenged Claims

Claims 1-15 of the '709 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	Reference(s)
1	1-12, 14-15	§103	Durand in view of Hoegh
2	1-2, 4-10, 12-13, 15	§103	Headley in view of Tran

Ground 1: Claims 1-12 and 14-15 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 300 references cited in an IDS filed on January 23, 2018 (EX-1003 ¶70), 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.

² Referred to herein as “Durand-Hoegh.”

Ground 2: Claims 1-2, 4-10, 12-13, and 15 are obvious over International Patent Application Publication WO2010/006218 (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™ 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.

³ Referred to herein as “Headley-Tran.”

X. IDENTIFICATION OF HOW THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground 1: Claims 1-12, 14-15 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 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 ¶71.

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

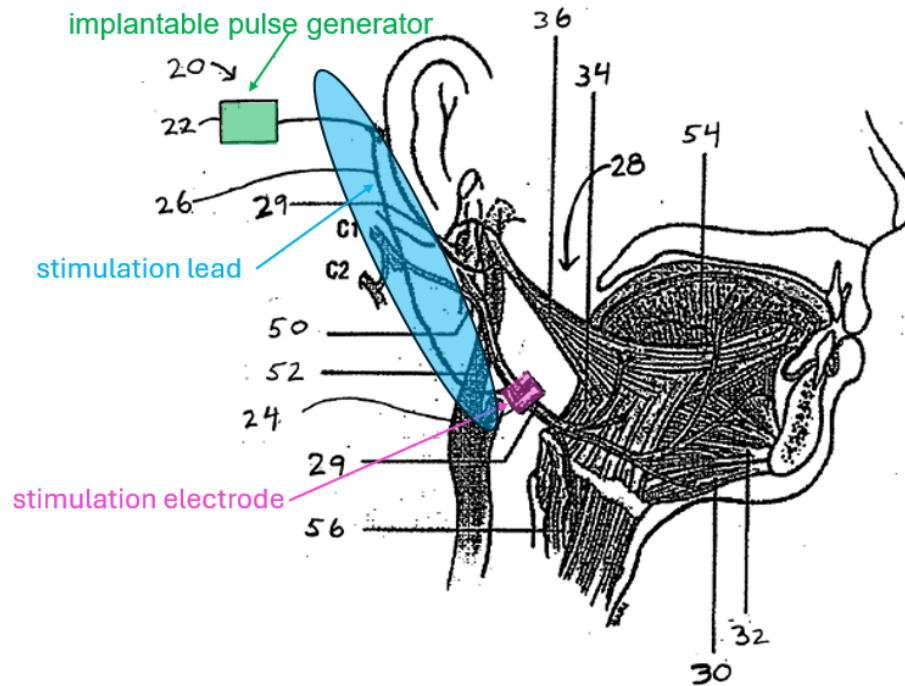


FIG. 1

EX-1006, FIG. 1; EX-1003 ¶72.

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 ¶¶72-73.

Durand discloses both synchronous and asynchronous techniques for treating OSA. In Durand's asynchronous technique, the method 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 seconds to about 3 seconds and a wait of at least 2 seconds to about 3 seconds between the pulse trains. EX-1006 ¶25; EX-1003 ¶¶74-75.

2. Hoegh

Hoegh, titled "Obstructive sleep apnea treatment screening methods," relates to methods for treating OSA. EX-1007 Title, Abstract, ¶2. Hoegh discloses "an implanted hypoglossal nerve stimulation (HGNS) device." EX-1007 Abstract; EX-1003 ¶77.

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 ¶¶78-79.

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 that uses **trains of stimulus pulses** at stimulation intervals that are “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. This is not surprising because, as discussed above 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 ¶¶93-94.

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 ¶¶95-96.

Hoegh 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 duty cycle 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. 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. Hoegh’s disclosure is consistent with Durand’s disclosure. EX-1003 ¶97.

A POSITA would have been 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 ¶¶97-98, 118, 122, 127-129. 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 ¶98; *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) (“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 ¶¶14-16; EX-1007 ¶¶50-51; EX-1003 ¶99.

Second, both references disclose similar implantation locations. *Compare* EX-1006, FIG. 1 *with* EX-1007, FIG. 1; EX-1003 ¶100.

Third, both references disclose a duty cycle that is determined 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 ¶101.

A POSITA recognized that such modification was well within the routine skill in the art as demonstrated by the State of the Art section, 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 ¶102; *KSR*, 550 U.S. at 415-16.

4. Application of Durand-Hoegh to Claims 1-12, 14-15

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, FIG. 1; EX-1003 ¶103.

Durand discloses [1.pre]. EX-1003 ¶104.

ii. [1.a1] *a non-cardiac stimulation element to engage and to stimulate an upper-airway-patency-related nerve;*

Durand discloses the apparatus includes control system 22 and cuff electrode 24 [*non-cardiac stimulation element*] that is connected to [*engages*] 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 ¶105.

Durand discloses [1.a1]. EX-1003 ¶106.

iii. [1.a2] *according to a first stimulation therapy protocol not synchronized to actively-sensed respiratory information,*

Durand discloses that control system 22 generates intermittent electrical stimulation at controlled intervals based on the patient's previously observed respiratory rate [*first stimulation therapy protocol*].

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 ¶107.

Durand further discloses that control system 22 does not detect a physical process or require feedback from the nerve being stimulated because the rate is predetermined [*not synchronized to actively-sensed respiratory information*].

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 ¶¶108-109.

Durand discloses [1.a2]. EX-1003 ¶110.

- iv. [1.b] *wherein the first stimulation therapy protocol comprises a series of repeating stimulation cycles in which each stimulation cycle includes a stimulation period and a non-stimulation period,*

Durand discloses intermittent electrical stimulation [*first stimulation therapy protocol*] in which stimulation pulse trains are applied for a period [*stimulation period*] and then applied again [*repeating stimulation cycle*] after a wait period [*non-stimulation period*].

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...* 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 ¶¶111-112.

Durand discloses [1.b]. EX-1003 ¶113.

- v. [1.c] *wherein each stimulation period includes continuous stimulation and has a minimum duration equal to or greater than an inspiratory reference of a reference respiratory cycle, wherein the inspiratory reference corresponds to a duration of an inspiratory phase of the reference respiratory cycle, and*

The '709 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; EX-1003 ¶114.

Durand discloses stimulation pulse trains having a frequency of about 10-30 Hertz (i.e., 10-30 pulses per second) [*continuous stimulation*], applied for about 2-3 seconds [*stimulation period*] so that the stimulation pulse trains closely simulate the patient's normal nighttime respiration cycle [*reference respiratory cycle*].

Other suitable combinations of stimulation amplitude and frequency can be provided on a patient-dependent basis. 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.

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... ***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...*** 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 ¶115.

A POSITA understood that by simulating the patient's observed nighttime resting respiratory rate [*reference respiratory cycle*], the train of stimulation pulses would be applied [*stimulation period*] for a period at least as long as the patient's inspiratory phase to ensure that the tongue is protruding during inspiration to maintain airway patency. EX-1006 ¶20. Thus, Durand discloses [1.c]. EX-1003 ¶116.

To the extent PO argues that Durand does not expressly disclose a *minimum duration...corresponds to a duration of an inspiratory phase of the reference respiratory cycle*, Hoegh does, and a POSITA would have modified Durand's teachings to include Hoegh's teaching as discussed above. X.A.3; EX-1003 ¶117. Specifically, Hoegh discloses delivering stimulation to the HGN [*upper-airway-patency-related nerve*] for 300 ms longer than the inspiratory phase of a patient's respiratory cycle to mimic the patient's natural physiology:

In people without OSA, *inspiration is typically 25-50% of the respiratory cycle*, with variations in respiration rate being common. Variations may cause actual inspiration to differ from predicted inspiration. *The hypoglossal nerve usually activates approximately 300 ms before inspiration and remains active for the entire inspiratory phase. 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 ¶118.

Durand-Hoegh discloses [1.c]. EX-1003 ¶119.

- vi. [1.d] *wherein the reference respiratory cycle comprises at least one of:
a historical patient-specific average respiratory cycle for stable respiration; and
a multi-patient average respiratory cycle for stable respiration, and*

Durand expressly discloses stimulation provided to closely simulate the patient's normal nighttime respiration cycle [*historical patient-specific average respiratory cycle for 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 ¶120.

To the extent that PO argues that Durand does not expressly disclose [1.d], a POSITA would have modified Durand's teachings to include Hoegh's teaching that fixed mode stimulation may be applied asynchronously, i.e., without being synchronized to the patient's breathing based on actively-sensed respiratory information, during OSA therapy, at a rate based on the patient's respiratory cycle [*a historical patient-specific average respiratory cycle for stable respiration*]:

Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals (e.g., 2.5 seconds of stimulation),

followed by 2.5 seconds off). *The intervals may be set to a rate similar to a respiratory cycle (e.g., 5 seconds)...Asynchronous stimulation may be initiated by* programming the device to fixed mode and *starting a therapy session.*

EX-1007 ¶¶114, 127; EX-1003 ¶121.

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, 94; EX-1003 ¶122.

Durand-Hoegh discloses [1.d]. EX-1003 ¶123.

- vii. [1.e] *wherein each stimulation period of each respective stimulation cycle has a duration greater than a duration of the inspiratory reference of the reference respiratory cycle and the stimulation period is followed by the non-stimulation period of the respective stimulation cycle comprising a duration less than the duration of the stimulation period.*

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

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 ¶124.

Durand discloses a two-second wait period [*non-stimulation period*], which has a duration that is less than a 2½ second train of stimulation pulses [*stimulation period*] that closely simulates the patient's normal nighttime respiratory cycle.

EX-1006 ¶25; EX-1003 ¶125.

To the extent that PO argues that Durand does not expressly disclose [1.e], 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 [*each stimulation period of each respective stimulation cycle has a duration greater than a duration of the inspiratory reference of the reference respiratory cycle*] to mimic the natural physiology of the patient:

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 ¶¶126-127.

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.

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 ¶128.

Thus, Durand-Hoegh discloses that each stimulation period of each respective stimulation cycle has a duration greater than a duration of the inspiratory reference of the reference respiratory cycle. EX-1003 ¶129. Hoegh further provides an express teaching and motivation for increasing the duration of the stimulation period relative to the non-stimulation period. EX-1007 ¶¶92, 98; VIII.C; EX-1003 ¶129.

Durand-Hoegh discloses [1.e] and renders claim 1 obvious. EX-1003 ¶130.

b. Claim 2

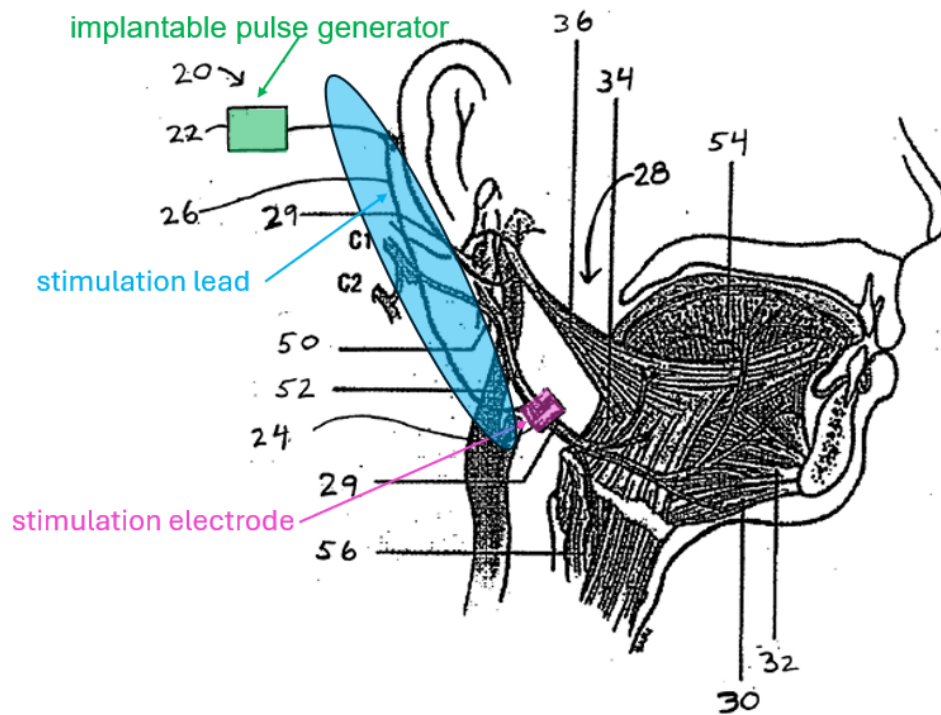
- i. [2] The device of claim 1, wherein the non-cardiac stimulation element comprises an implantable electrode and a pulse generator electrically connected to the implantable electrode.*

Durand discloses cuff electrode 24 providing intimate connection to the HGN [*implantable electrode*] and that control system 22 for generating the desired

electrical stimulus can be an IPG [*pulse generator*] that is connected to cuff electrode 24 by lead wire 26 [*electrically connected*].

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... A lead wire 26 connects the electrode 24 to the control system 22 in the illustrated embodiment.*

EX-1006 ¶14.



EX-1006, FIG. 1; EX-1031.

The IPG can be implanted in the body of the patient. EX-1006 ¶14; EX-1003 ¶¶131-132.

Durand discloses claim 2. EX-1003 ¶133.

c. **Claim 3**

- i. [3] *The device of claim 2, wherein the implantable electrode comprises a cuff electrode including at least one operative contact group through which the stimulation is deliverable non-selectively to the upper-airway-patency-related nerve.*

Durand discloses “[t]he electrode 24 preferably is a cuff electrode that provides an intimate connection to the [upper-airway patency-related] nerve” and for non-selectively delivering stimulation. EX-1006 ¶14; EX-1003 ¶134.

To the extent PO argues that Durand does not expressly disclose certain limitations of this claim element, Hoegh discloses a cuff electrode having a contact group for non-selectively delivering stimulation to the upper-airway-patency-related nerve as disclosed by the ’709 Patent. EX-1001 10:9-24; EX-1007, FIG. 3A, ¶98; EX-1003 ¶¶135-137.

Durand discloses claim 3, either alone or in combination with Hoegh. EX-1003 ¶¶135-138.

d. **Claim 4**

- i. ***[4] The device of claim 1, wherein a total duration of stimulation via the first stimulation protocol during a treatment period is greater than 30 percent of the total duration of the treatment period.***

Durand discloses providing a stimulation pulse train for 2-3 seconds followed by waiting 2-3 seconds, which results in a total duration of stimulation during a treatment period from 40% (2 seconds on; 3 seconds off) to 60% (3 seconds on; 2 seconds off), i.e., greater than 30%. EX-1006 ¶25; EX-1003 ¶¶139-140.

Durand discloses claim 4. EX-1003 ¶141.

e. **Claim 5**

- i. ***[5] The device of claim 1, wherein the duration of the stimulation period comprises at least 50 percent of a duration of the stimulation cycle.***

Durand discloses this limitation for the same reasons as discussed with respect to claim 4. EX-1006 ¶25; EX-1003 ¶¶142-144.

f. **Claim 6**

- i. ***[6] The device of claim 1, wherein the duration of the stimulation period comprises at least 50 percent of a duration of the reference respiratory cycle.***

Durand discloses that the stimulation protocol can be based on the patient's respiratory rate [*reference respiratory period*] and stimulation pulses can be

provided for about 2-3 seconds [*stimulation period*] followed by a wait period of 2-3 seconds. EX-1006 ¶25; EX-1003 ¶145.

Hoegh discloses that a patient's respiratory cycle is about five seconds [*duration of the reference respiratory cycle*] and stimulation may be delivered for 2.5 seconds [*duration of the stimulation period*], which is at least 50 percent of the reference respiratory cycle. EX-1007 ¶114; EX-1003 ¶146.

A POSITA understood providing pulse trains for 2½-3 seconds [*stimulation period*] of a patient's five second respiratory cycle [*reference respiratory cycle*] corresponds to a duration of the stimulation period comprising at least 50% of a duration of the reference respiratory cycle. EX-1003 ¶¶147-148.

Durand-Hoegh renders claim 6 obvious. EX-1003 ¶¶148-149.

g. Claim 7

- i. [7] The device of claim 1, wherein the duration of each respective stimulation cycle is less than the duration of the reference respiratory cycle, and a duration of the stimulation period exceeds the duration of the non-stimulation period by a factor of at least 3.*

Durand discloses four-second stimulation cycles (2 seconds stimulation; 2 seconds waiting), EX-1006 ¶25, and Hoegh discloses that a patient's respiratory cycle is about 5 seconds and duty cycles ranging between 41% to 69%. EX-1007 ¶¶98, 114; EX-1003 ¶150.

A POSITA understood a four-second stimulation cycle has a duration less than a patient's five-second respiratory cycle and a 69% duty cycle would provide stimulation pulses [*stimulation period*] for a duration that exceeds the wait period [*non-stimulation period*] by over a factor of two (i.e., $69\%/31\% = 2.23$). EX-1003 ¶151. Hoegh additionally discloses that the disclosed duty cycles are not limiting and that "[t]he stimulation duty cycle may vary to meet efficacy and safety requirements." EX-1007 ¶96; EX-1003 ¶151.

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 desired efficacy. EX-1006 ¶22; 1003 ¶152. Indeed, the prior art includes duty cycles of up to 92%. EX-1008 ¶48 (disclosing an on/off period of 60/5, i.e., a factor of 12); EX-1003 ¶¶152-153.

Providing stimulation cycles in which a duration of the stimulation period exceeds the duration of the non-stimulation period by a factor of at least three required nothing more than the exercise of routine skill, i.e., optimizing a duty cycle, which a POSITA would have been motivated to provide to increase the efficacy while maintaining the safety. EX-1007 ¶96; EX-1003 ¶154.

Durand-Hoegh renders claim 7 obvious. EX-1003 ¶¶153-155.

h. Claim 8

- i. [8] *The device of claim 1, wherein the duration of each respective stimulation cycle is greater than the duration of the reference respiratory cycle.***

Hoegh discloses a five-second patient respiratory cycle and an eight-second stimulation interval [*stimulation cycle*] may be used to increase the probability of providing the patient with stimulation during an entire respiratory cycle:

Asynchronous mode (fixed mode) is when stimulation is delivered at regular programmable intervals (e.g., 2.5 seconds of stimulation, followed by 2.5 seconds off). *The intervals may be set to a rate similar to a respiratory cycle, (e.g. 5 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 ¶156.

Thus, Hoegh discloses a duration of a stimulation cycle that is greater than the duration of a patient's respiratory cycle [*reference respiratory cycle*]. EX-1003 ¶¶157-158.

Durand-Hoegh renders obvious claim 8. EX-1003 ¶¶158-159.

i. **Claim 9**

- i. [9] *The device of claim 8, wherein the stimulation period and the non-stimulation period are in a proportion of at least 1.5 to 1.*

Hoegh discloses duty cycles of up to 69%, which equates to the stimulation pulses [*stimulation period*] being applied by over a factor of 2. X.A.4.g; EX-1007 ¶96. Thus, Hoegh discloses that the stimulation pulses [*stimulation period*] and the wait period [*non-stimulation period*] are in a proportion of over 2:1, which is at least 1.5:1. EX-1003 ¶¶160-162.

Durand-Hoegh renders obvious claim 9. EX-1003 ¶¶162-163.

j. **Claim 10**

- i. [10] *The device of claim 8, wherein the duration of the stimulation cycle is less than a duration of two consecutive reference respiratory cycles.*

Hoegh discloses applying stimulation pulses and wait periods [*stimulation cycles*] based on the patient's five-second resting respiratory rate [*reference respiratory cycles*]. EX-1006 ¶25; EX-1007 ¶114; EX-1003 ¶164. A POSITA understood both references as disclosing that the duration of a stimulation cycle (i.e., a period including both simulation and waiting) to be about five seconds, which is less than a duration of two consecutive reference respiratory periods (i.e., ten seconds). EX-1006 ¶25; EX-1007 ¶114; EX-1003 ¶¶165-166.

Durand-Hoegh renders obvious claim 10. EX-1003 ¶¶166-167.

k. **Claim 11**

- i. [11] *The device of claim 1, wherein the duration of each respective stimulation cycle is equal to the duration of the reference respiratory cycle, and wherein the duration of the reference respiratory cycle differs from a duration of a real time respiratory cycle from actively-sensed respiration information by an amount exceeding a duration variability criteria.*

Durand-Hoegh discloses embodiments that use actively sensed respiration information, EX-1006 ¶¶22-23; EX-1007 ¶85, and the period of stimulation pulses and wait period [*stimulation cycle*] is based on/equal to the patient's respiratory cycle [*reference respiratory cycle*]. X.A.4.a.iv-X.A.4.a.vi; EX-1006 ¶25; EX-1007 ¶114; EX-1003 ¶168. Hoegh further discloses a patient's respiratory rate may change over time and the INS records the patient's respiratory rate and uses such data to change stimulation levels. EX-1007 ¶¶91-92 ("In people without OSA, inspiration is typically 25-50% of the respiratory cycle, ***with variations in respiratory rate being common.***"); EX-1003 ¶168.

Hoegh further discloses the adaptive mode may be used when predicted inspiration is less accurate due to higher variability in respiratory rate [*duration variability criteria*] in which case the duty cycle is increased [*the duration of the reference respiratory cycle differs from a duration of a real time respiratory cycle from actively-sensed respiration information*]:

In adaptive mode, the duty cycle may be allowed to vary as a function of a characteristic of respiration. *For example, the adaptive duty cycle may increase when prediction is less accurate (higher variability in respiration rate) or when respiratory signal is lost.*

EX-1007 ¶97.

As mentioned above, *the adaptive mode allows the duty cycle to decrease when respiratory period is stable and increase with respiratory period variability....*

EX-1007 ¶98; EX-1003 ¶169.

A POSITA understood from the foregoing disclosures in Hoegh that a patient's respiratory rate may vary, but that the overall duration of the reference respiratory cycle would not change—only the duty cycle would be increased. EX-1003 ¶¶170-171.

Durand-Hoegh renders claim 11 obvious. EX-1003 ¶¶171-172.

I. Claim 12

**i. [12.a] *The device of claim 1, comprising:
a processor; and***

Durand discloses that the control system includes a processor for setting up stimulation parameter and controlling the stimulation [*first stimulation therapy protocol*]. EX-1006 ¶15; EX-1003 ¶173.

Durand discloses [12.a]. EX-1003 ¶174.

- ii. **[12.b] *a non-volatile computer readable medium storing instructions, executable on the processor, to implement the non-cardiac stimulation element and to perform the first stimulation therapy protocol.***

Durand discloses that the control system includes a processor (X.A.4.1.i), and a POSITA understood a processor functions by executing instructions stored in a non-volatile computer-readable medium. VIII.A; EX-1003 ¶¶29-33, 175. To the extent PO argues that Durand does not disclose this claim element, Hoegh does. EX-1007 ¶¶82, 85, 100; EX-1003 ¶¶175-177.

Durand-Hoegh renders obvious claim 12. EX-1003 ¶¶176-178.

m. **Claim 14**

- i. **[14.a] *The device of claim 1, comprising: a sensing element to obtain the actively-sensed respiratory information; and***

Durand discloses providing sensor(s) [*sensing element*] to detect a physical process, such as inspiratory efforts [*actively-sensed respiratory information*].

Thus the system can include one or more sensors for detecting a physical process, such as inspiratory efforts (i.e. the beginning of an attempt to breathe), for example, other than through the signals present in the hypoglossal nerve itself for activating the muscles.

EX-1006 ¶23; EX-1003 ¶¶179-180.

To the extent PO argues Durand fails to disclose [14.a], Hoegh discloses an RSL that measures bio-impedance [*actively-sensed respiratory information*]. EX-1007 ¶50; EX-1003 ¶181.

Durand-Hoegh discloses [14.a]. EX-1003 ¶182.

- ii. [14.b] a control portion including:
a processor; and
a non-volatile memory storing instructions,
executable via the processor to:**

Durand discloses this claim element as demonstrated above with respect to claim 12. X.A.4.1; EX-1003 ¶183.

- iii. [14.c] provide convertible operation via a therapy manager between:
a first stimulation mode implementing the first stimulation therapy protocol; and**

Hoegh discloses that INS circuit 1130 [*control portion*], which includes a microprocessor [*processor*], delivers stimulation in two modes [*provide convertible operation via a therapy manager*], including an asynchronous mode [*first stimulation mode implementing the first stimulation therapy protocol*].

The INS circuit 1130 may utilize a microprocessor to control telemetry communications with the programmer system 2100, operating the sensing circuits to monitor respiration via the RSL 1200, controlling the delivery of output stimuli via the STL 1300, monitoring the accelerometer, magnetically sensitive reed switch and the real-time clock.

EX-1007 ¶82.

Stimulation may also be delivered in two modes which are not inspiratory synchronous: manual stimulation and asynchronous (fixed) stimulation.

EX-1007 ¶113, 97; X.A.4.1; EX-1003 ¶184.

Thus, Hoegh discloses that the INS includes a microprocessor that controls the stimulation applied to the HGN and may automatically provide fixed/asynchronous stimulation if the respiratory signal from the RSL is lost during a therapy session. EX-1007 ¶¶82, 97, 113; EX-1003 ¶185.

Durand-Hoegh discloses [14.c]. EX-1003 ¶¶185-186.

iv. [14.d] a second stimulation mode of stimulating the upper-airway-patency-related nerve synchronous with a characteristic of the actively-sensed respiratory information.

Hoegh discloses monitoring bio-impedance via the RSL [*characteristic of the actively-sensed respiratory information*] and stimulating the HGN [*upper-airway-patency-related nerve*] via the stimulation lead synchronously with the patient's inspiration.

The HGNS system 100 may treat obstructive sleep apnea (OSA) by increasing neuromuscular activity to the genioglossus muscle via *stimulation of the hypoglossal nerve (HGN), such as synchronous with inspiration, to mitigate upper airway collapse during sleep.* Stimulation may be generated by an implantable neurostimulator (INS) 1100, for example *synchronized with inspiration as measured by the*

respiration sensing lead (RSL) 1200 using bio-impedance, and delivered to the hypoglossal nerve by a stimulation lead (STL) 1300.

EX-1007 ¶50; EX-1003 ¶187.

Hoegh discloses [14.d], and Durand-Hoegh renders obvious claim 14. EX-1003 ¶¶187-188.

n. Claim 15

- i. [15] The device of claim 1, wherein the stimulation period and the non-stimulation period are in a proportion of at least 1.5 to 1.*

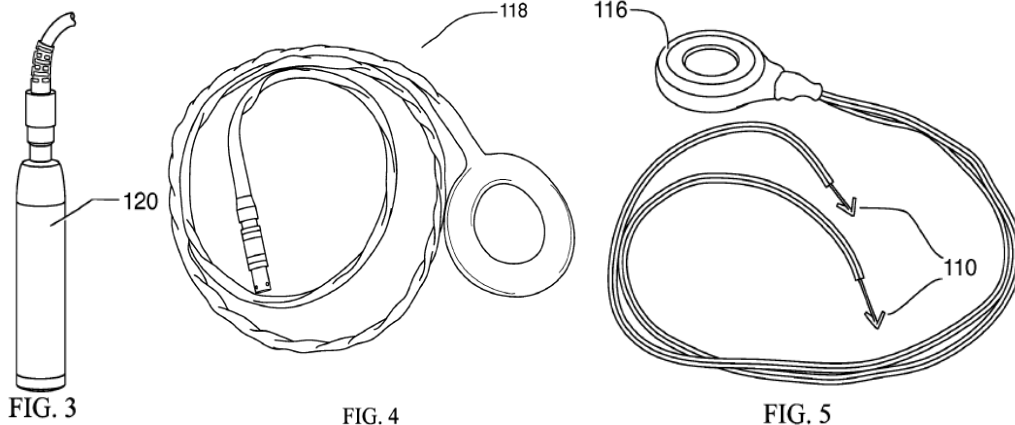
Durand-Hoegh discloses the limitations of claim 15 for the same reasons discussed in X.A.4.i. EX-1003 ¶189.

Durand-Hoegh renders obvious claim 15. EX-1003 ¶¶189-190.

B. Ground 2: Challenged Claims 1-2, 4-10, 12-13, 15 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 ¶81.

In use, 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; EX-1003 ¶82.

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; EX-1003 ¶85.

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:

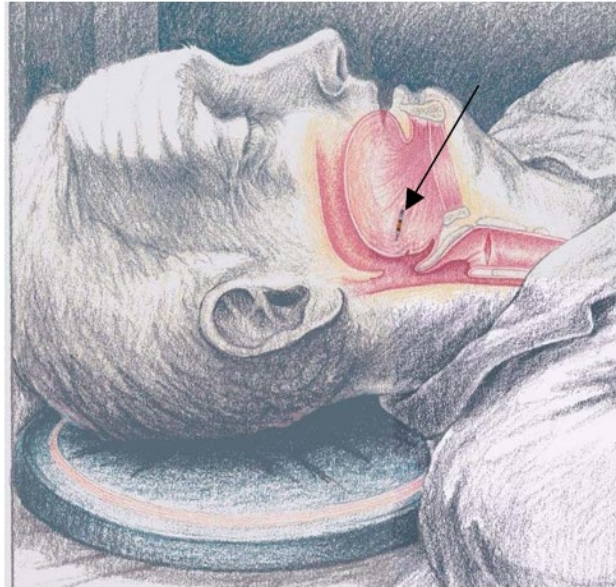


Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

EX-1009, FIG. 3; EX-1003 ¶86.

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; EX-1003 ¶87.

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 ¶¶88-90.

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 ¶¶90-91.

3. Motivation to Combine Headley and Tran

As detailed above, Headley discloses an implantable device that is used to stimulate the GG, which is in close proximity to the HGN, asynchronously to treat OSA. 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 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 ¶¶191-192.

Tran discloses a BION™ device for treating OSA that operated like the device disclosed by Headley in that the device could be 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 ¶193.

While Headley provides high level disclosure of the stimulation parameters, Tran uses clinical results to provide detailed stimulation parameters for a stimulation device like the one described in Headley. For example, Tran discloses the duration of stimulation relative to the patient’s respiratory rate, including the duration of the stimulation relative to the duration of the inspiratory phase. EX-1009, p.377; EX-1010, p.4288. Tran also teaches the duration of stimulation relative to the total duration of the treatment period. EX-1010 p. 4289. Further, Tran teaches the use of historical patient specific averages to estimate the patient’s respiratory rate. EX-1009, p.377; EX-1003 ¶194.

A POSITA would have been motivated to combine the teachings of Headley to provide a stimulation device that could be programmed with the stimulation parameters taught by Tran for treating OSA that provides 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 ¶194. Advantageously, the combination of Headley-Tran would provide a stimulation device that obviates the need for a sensor to synchronize stimulation with breathing while effectively improving airway patency. EX-1009, p.375; EX-1010, p.4288; EX-1003 ¶194.

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. EX-1003 ¶195. *First*, both references disclose treatment methods for OSA using **implantable electrodes** that are externally powered to stimulate the tongue in close proximity to the HGN asynchronously. EX-1008 ¶29; EX-1009, pp.375, 377; EX-1010, p.4287. Indeed, Tran taught the use of a low-risk, reliable, and cost-effective method using a **stimulation electrode** in close proximity to various nerves, including the HGN. EX-1009, p.375; EX-1039, p.3; EX-1003 ¶¶194, 196-197.

Second, both references disclose similar implantation locations:



EX-1008, FIG. 1.

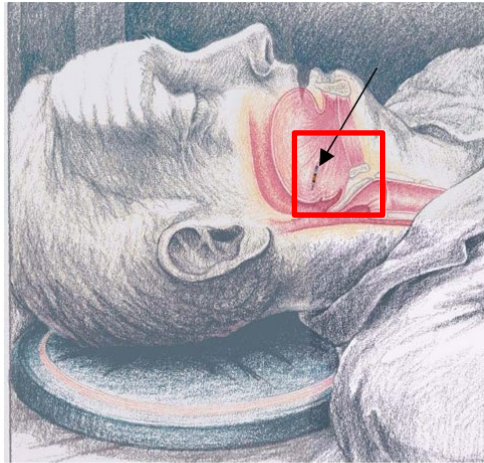


Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

EX-1009, FIG. 3; EX-1003 ¶198.

Third, the modifications to Headley based on the teachings of Tran were well within the routine skill in the art. Specifically, because both references disclose using implantable electrodes to stimulate the tongue asynchronously in substantially the same way, a POSITA would have recognized that modifying Headley's asynchronous stimulation cycle to approximate the patient's respiratory cycle, as taught by Tran, would require only simple software modifications and routine modifications to Headley's intermittent stimulation periods, which was typically performed during the titration process after device implantation. VIII.B. The stimulation parameters as taught by Tran would thus be programmed into the pulse generator of Headley. EX-1008 ¶29; EX-1003 ¶199. Thus, a POSITA would have had a reasonable expectation of success in combining Headley's and Tran's teachings because both references disclose applying methods (asynchronous

stimulation) using devices (implantable electrodes) to achieve results (treating OSA) that were known in the art before the priority date of the '709 Patent, such that their teachings would have been readily applied to the other using only routine skill. VIII.B; EX-1003 ¶199; *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 Claims 1-2, 4-10, 12-13, 15

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 for treating OSA. Headley discloses “[*a*] **device** and method is described **for the treatment of obstructive sleep apnea.**” EX-1008 Abstract, ¶29, FIGS. 3-5; EX-1003 ¶¶200-202.

Headley discloses the preamble. EX-1003 ¶¶201-203.

ii. [1.a1] *a non-cardiac stimulation element to engage and to stimulate an upper-airway-patency-related nerve;*

Headley discloses receiver 116 and stimulating electrode 110 are inserted into the genioglossal muscle of the tongue to apply electrical stimulation [*non-cardiac stimulation element*] to stimulate the genioglossus muscle:

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 ¶204.

A POSITA understood that by inserting electrodes into the genioglossus, the electrodes would not be providing cardiac stimulation because the applied stimulation to the tongue would not stimulate the heart and thus would provide non-cardiac stimulation. EX-1014; EX-1015; EX-1016; EX-1003 ¶205.

Further, a POSITA understood that insertion of the electrodes into the tongue/genioglossus places the electrodes in close proximity to the HGN, which terminates in the genioglossus. VIII.A-VIII.B; EX-1023, pp.601-603; EX-1033, p.379; EX-1003 ¶206. Specifically, a POSITA understood that the genioglossus is innervated by (i.e., supplied by) the HGN thus forming a neuromuscular system. EX-1023, pp.601-603; EX-1033, p.379; EX-1003 ¶206. A POSITA thus understood that implanting an electrode into the genioglossus engages the neuromuscular system, including the HGN. EX-1023, pp.601-603; EX-1033, p.379; EX-1003 ¶206. A POSITA further understood that electrical stimulation applied by the electrode would conduct to and be applied to the HGN consistent

with the disclosure of the '709 Patent. EX-1003 ¶¶206-208; EX-1001 11:60-12:12 (“In some examples, the nerve-coupling electrode portion is not mechanically coupled to the nerve 72, but is mechanically coupled or secured in a location in close proximity to the nerve 72 and that enables electrically coupling of the electrode portion 82 relative to the nerve 72”); *see also* VIII.

Moreover, Headley incorporates by reference several scientific papers, including papers by Brennick and Yoo that describe the neuromuscular relationship between the genioglossus muscle 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 that implanting electrodes into the genioglossus includes engaging the HGN and applying electrical stimulation at the site identified in FIG. 1 of Headley stimulates the HGN [*upper-airway-patency-related nerve*] to achieve the desired result of maintaining upper airway patency to treat OSA. EX-1008 ¶¶8, 28-30; EX-1003 ¶209.

To the extent PO asserts that Headley does not expressly state placing the electrodes in proximity to the HGN, Tran expressly discloses neuromuscular stimulation and placing the electrodes of the BION™ in close proximity to the 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.

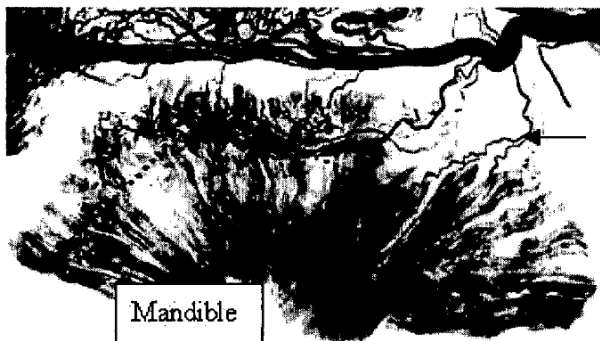


Fig. 2. The human genioglossus (GG), as shown in sagittal view. The single motor endplate band (red dotted line). A separate nerve branch innervates the motor endplates near the tongue base (arrow). Photo courtesy of Dr. Ira Sanders.



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, FIGS. 2-3; EX-1003 ¶210.

A POSITA understood that the BION™ disclosed by Tran could be implanted in a patient at a variety of locations, including adjacent to or attached to the HGN, as had been done prior to March 19, 2015. EX-1039, p.3; EX-1040, p.348; EX-1003 ¶211. A POSITA would be motivated to modify the teachings of Headley to place the electrodes in close proximity to the HGN as taught by Tran for the reasons discussed in X.B.3; EX-1003 ¶¶191-199, 212.

Thus, to the extent Headley does not expressly disclose engaging and stimulating an upper-airway-patency-related nerve, such as the HGN, Headley in view of Tran does, and Headley-Tran discloses [1.a1]. EX-1003 ¶¶212-213.

iii. [1.a2] according to a first stimulation therapy protocol not synchronized to actively-sensed respiratory information,

Headley discloses that receiver 116 and stimulating electrode 110 provide stimulation using intermittent treatment [*first stimulation therapy protocol*]:

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.***

EX-1008 ¶10; EX-1003 ¶214.

Although Headley discloses the use of optional sensors, such as sound-activation means and/or oxygen-sensing means, these sensors are not actively

sensing respiration. EX-1008 ¶14. Instead, these sensors detect when a patient snores or the patient's oxygen level falls below a threshold to initiate the stimulation, and thus Headley discloses the limitations of [1.a2]. EX-1003 ¶¶215-217. To the extent PO argues that Headley uses actively-sensed respiratory information, Tran expressly does not to avoid the need for a sensor. EX-1010, pp.4288-4289; EX-1003 ¶218.

Headley discloses [1.a2]. EX-1003 ¶¶217-218.

- iv. **[1.b] wherein the first stimulation therapy protocol comprises a series of repeating stimulation cycles in which each stimulation cycle includes a stimulation period and a non-stimulation period,**

Headley discloses the intermittent treatment [*first stimulation therapy protocol*] includes a period of stimulation [*stimulation period*] and a rest period in which the stimulation is turned off [*non-stimulation period*]:

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.***

EX-1008 ¶48; EX-1003 ¶219-220.

Thus, Headley discloses [1.b], as does Tran. EX-1010, p.4288; EX-1003 ¶¶219-221.

- v. ***[1.c] wherein each stimulation period includes continuous stimulation and has a minimum duration equal to or greater than an inspiratory reference of a reference respiratory cycle, wherein the inspiratory reference corresponds to a duration of an inspiratory phase of the reference respiratory cycle, and***

The '709 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; EX-1003 ¶222.

Headley discloses that the pulse generator is configured to vary the properties of the electrical pulses applied during the therapy.

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-1003 ¶223.

Headley does not expressly describe a minimum duration equal to or greater than an inspiratory reference of a reference respiratory cycle, but Tran does. Tran discloses that the electrical stimulation may be applied at 20 pulses per second. EX-1010, p.4289; EX-1003 ¶224. Tran further 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 ¶¶225-226.

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.

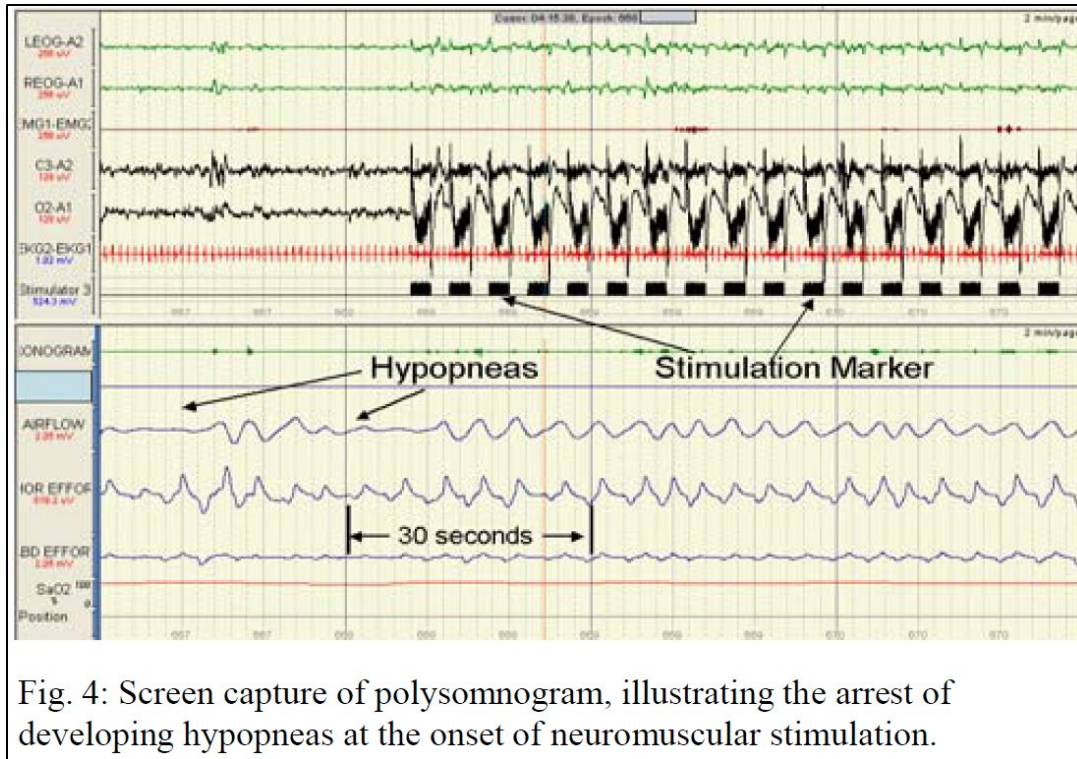


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010, FIG. 4; EX-1003 ¶227.

Thus, Tran discloses that the ON period [*stimulation period*] has a minimum duration equal to or greater than the inspiratory phase of the patient's respiratory cycle [*reference respiratory cycle*]. Moreover, Headley expressly discloses periods of stimulation of up to 120 seconds. EX-1008 ¶48. A POSITA understood that a period of stimulation [*stimulation period*] of 120 seconds exceeded the duration of any patient's inspiratory phase – especially given Tran's five-second respiratory cycle duration. EX-1009, p.377; EX-1003 ¶228. A POSITA would be motivated to modify the teachings of Headley to provide stimulation for *a minimum duration equal to or greater than an inspiratory reference of a reference*

respiratory cycle, wherein the inspiratory reference corresponds to 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 ¶¶191-199, 228.

Headley-Tran discloses [1.c]. EX-1003 ¶229.

- vi. ***[1.d] wherein the reference respiratory cycle comprises at least one of:
a historical patient-specific average respiratory cycle for stable respiration; and
a multi-patient average respiratory cycle for stable respiration, and***

Tran discloses observing a sleeping patient to determine the patient's respiratory rate [*historical patient-specific average respiratory cycle for stable respiration*] 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 ¶230.

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 ¶¶191-199, 231.

Headley-Tran discloses [1.d]. EX-1003 ¶232.

- vii. [1.e] *wherein each stimulation period of each respective stimulation cycle has a duration greater than a duration of the inspiratory reference of the reference respiratory cycle and the stimulation period is followed by the non-stimulation period of the respective stimulation cycle comprising a duration less than the duration of the stimulation period.***

As detailed above, Headley in view of Tran discloses that the ON period [*stimulation period*] has a minimum duration that is greater than the inspiratory phase [*inspiratory reference*] of the patient's respiratory cycle [*reference respiratory cycle*]. X.B.4.a.v; EX-1003 ¶233.

Headley-Tran also discloses that the stimulation period is followed by the non-stimulation period. X.B.4.a.iv; EX-1003 ¶234. Headley discloses that a duration of the rest/off period [*non-stimulation period*] is less than a duration of the of the stimulation/on period [*stimulation period*], as Headley discloses duty cycles (on/off periods) ranging from 12:1 (60/5) to 1:12 (5/60):

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...* 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 ¶234.

Headley-Tran discloses [1.e] and renders obvious claim 1. EX-1003 ¶235.

b. Claim 2

- i. [2] The device of claim 1, wherein the non-cardiac stimulation element comprises an implantable electrode and a pulse generator electrically connected to the implantable electrode.*

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

The device itself consists of 4 parts. First is a power source 120 (Fig. 3). Second is an antenna 118 (Fig. 4). *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.

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 simulate 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 electrical pulses* having selectable properties of mode, polarity, amplitude, current, pulse width, and frequency.

EX-1008 ¶30, FIG. 5; EX-1003 ¶¶236-237.

Tran also discloses the limitations of claim 2 and the teachings of Tran are consistent with those of Headley. EX-1009, p.375; EX-1003 ¶238.

Headley-Tran renders obvious claim 2. EX-1003 ¶237.

c. Claim 4

- i. [4] The device of claim 1, wherein a total duration of stimulation via the first stimulation protocol during a treatment period is greater than 30 percent of the total duration of the treatment period.*

Headley discloses a treatment protocol in which a duration of the period of stimulation/on [*stimulation period*] may be equal to or greater than a duration of the rest/off period [*non-stimulation period*]:

In one preferred embodiment, the device or method *applies stimulation for 5 seconds, and then stimulation is turned off for 5 seconds...*In another preferred embodiment, *the period of stimulation is 20 seconds and the rest period is 5 seconds...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 ¶239.

Given Headley's express disclosure that the treatment includes alternating on/off periods, a POSITA understood the total duration of stimulation applied during the treatment would correspond to the duty cycle (on/off periods). EX-1008 ¶48; EX-1003 ¶240. Thus, Headley discloses that the total period of stimulation/on period [*total duration of stimulation*] may range from about 8% (e.g., on/off period of 5/60) to about 92% (e.g., on/off period of 60/5). EX-1003 ¶240.

To the extent that PO asserts that Headley does not expressly state 30%, Tran discloses that duty cycles of 30% or greater were well-tolerated and effective and a duty cycle of approximately 50% is shown in FIG. 4.

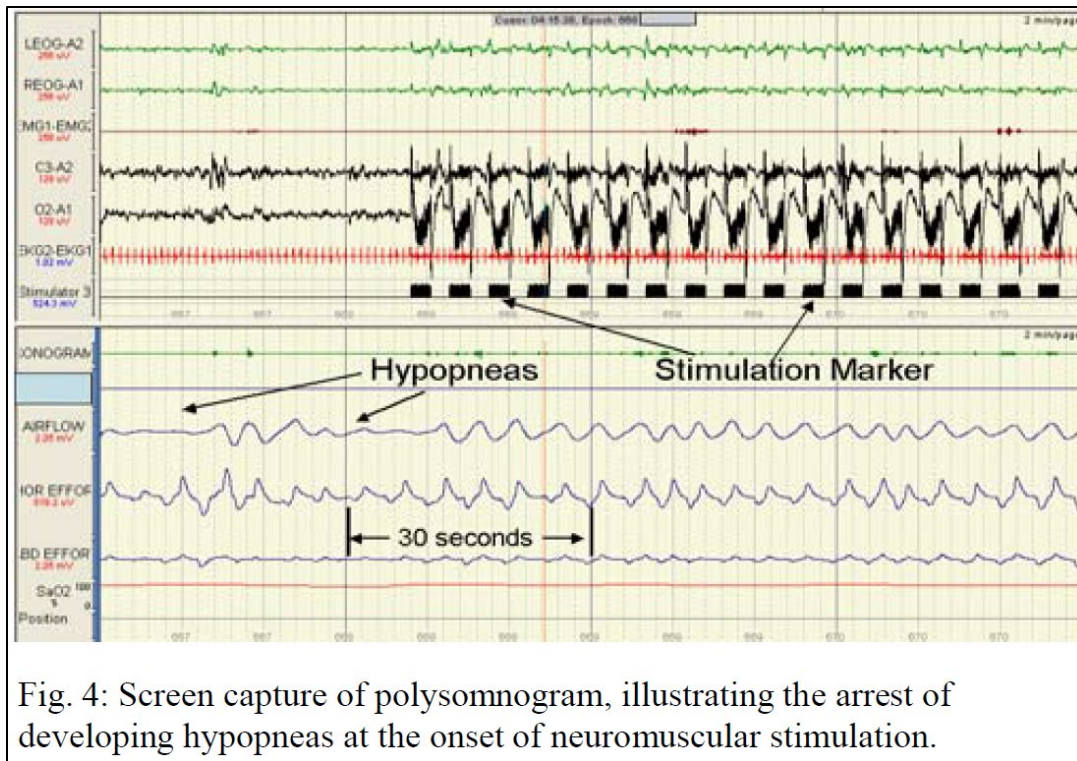


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010, p.4289, FIG. 4; EX-1003 ¶¶241.

A POSITA understood that a 30% duty cycle would correspond to a total duration of stimulation via the first stimulation protocol during a treatment period to be greater than 30% of the total duration of the treatment period. EX-1003 ¶¶242-243. A POSITA would be motivated to modify the teachings of Headley to include the first stimulation protocol during a treatment period is greater than 30 percent of the total duration of the treatment period as taught by Tran for the reasons discussed in X.B.3. EX-1003 ¶¶191-199, 242-243

Headley-Tran renders obvious claim 4. EX-1003 ¶¶243-244.

d. Claim 5

- i. [5] The device of claim 1, wherein the duration of the stimulation period comprises at least 50 percent of a duration of the stimulation cycle.*

Headley in view of Tran discloses claim 5 for the reasons discussed above with respect to claim 4. X.B.4.c; EX-1003 ¶245. Specifically, Headley discloses the total stimulation/on period [*total duration of stimulation*] may range from about 8% (e.g., on/off period of 5/60) to about 92% (e.g., on/off period of 60/5), and Tran discloses a 50% duty cycle. EX-1003 ¶¶245-246.

Headley-Tran renders obvious claim 5. EX-1003 ¶¶246-247.

e. Claim 6

- i. [6] The device of claim 1, wherein the duration of the stimulation period comprises at least 50 percent of a duration of the reference respiratory cycle.*

Tran discloses a five-second respiratory rate for a sleeping patient based on observing the patient during sleep. EX-1009 p.377. FIG. 4 of Tran-II illustrates a treatment protocol with a duty cycle of approximately 50%, such that stimulation is applied [*stimulation period*] 50% of the patient's respiratory rate [*reference respiratory cycle*].

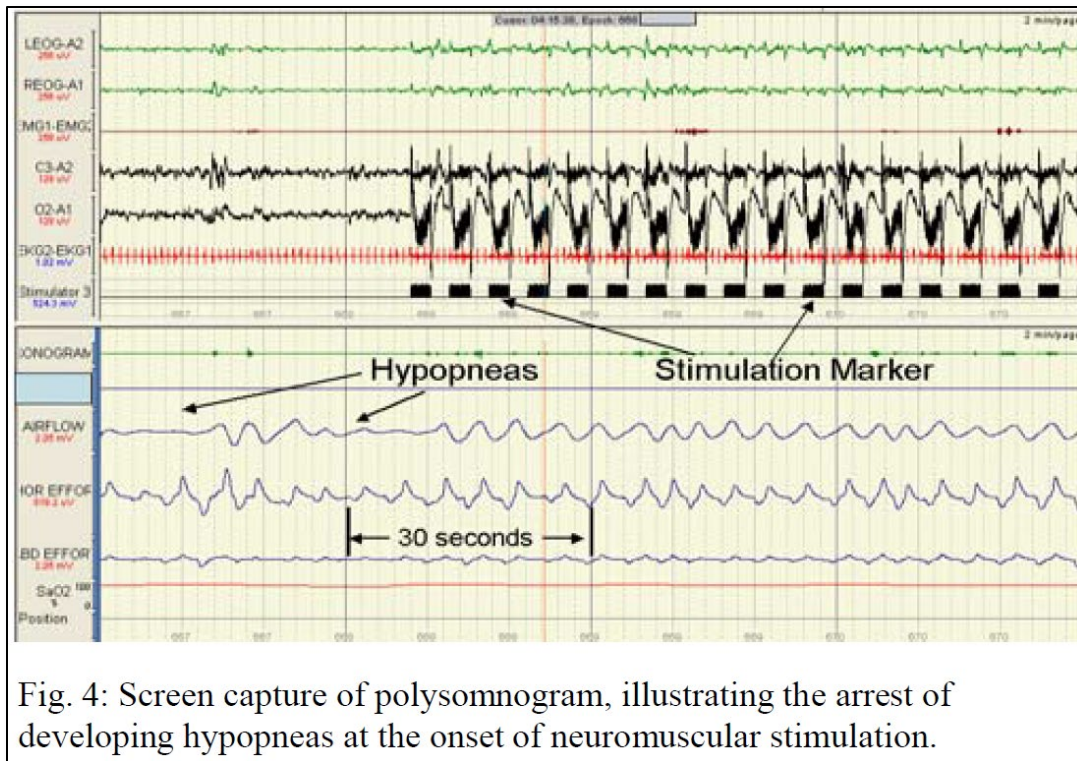


Fig. 4: Screen capture of polysomnogram, illustrating the arrest of developing hypopneas at the onset of neuromuscular stimulation.

EX-1010, FIG. 4; EX-1003 ¶¶248-249.

As detailed above, Headley discloses that the period of stimulation/on period [*stimulation period*] may range from 8% (e.g., on/off period of 5/60) to about 92% (e.g., on/off period of 60/5) of a stimulation cycle. X.B.4.c. Thus, a POSITA would have been motivated to modify Headley's teaching to provide a stimulation cycle in which the duration of the period of stimulation/on period [*stimulation period*] comprises at least 50% of a duration of the patient's respiratory rate [*reference respiratory cycle*] as taught by Tran for the reasons discussed in X.B.3 the Motivation to Combine section. EX-1003 ¶¶191-199, 250-251.

Headley-Tran renders obvious claim 6. EX-1003 ¶¶251-252.

f. Claim 7

- i. [7] The device of claim 1, wherein the duration of each respective stimulation cycle is less than the duration of the reference respiratory cycle, and a duration of the stimulation period exceeds the duration of the non-stimulation period by a factor of at least 3.*

Headley discloses that a stimulation cycle may be as short as two seconds, which is less than the five-second reference respiratory cycle disclosed by Tran. EX-1008 ¶48; EX-1003 ¶253. Headley further discloses duty cycles in which the stimulation/on period [*stimulation period*] is 12 times greater than the rest/off period [*non-stimulation period*] (e.g., 60 on/5 off), which is greater than 3. EX-1008 ¶48; EX-1003 ¶¶254-255.

Headley-Tran renders obvious claim 7. EX-1003 ¶¶255-256.

g. Claim 8

- i. [8] The device of claim 1, wherein the duration of each respective stimulation cycle is greater than the duration of the reference respiratory cycle.*

Headley discloses that the intermittent periods [*stimulation cycle*] may be as long as 240 seconds (e.g., 120 seconds on/120 seconds off), which is greater than the five-second reference respiratory cycle disclosed by Tran. EX-1008 ¶48; EX-1003 ¶257. A six-second stimulation cycle, which is in the range disclosed by Headley, also is greater than a five-second reference respiratory cycle disclosed by

Tran [*each respective stimulation cycle is greater than the duration of the reference respiratory cycle*]. EX-1008 ¶48; EX-1003 ¶¶257-258.

Headley-Tran renders obvious claim 8. EX-1003 ¶¶258-259.

h. Claim 9

- i. [9] The device of claim 8, wherein the stimulation period and the non-stimulation period are in a proportion of at least 1.5 to 1.***

Headley discloses duty cycles in which the stimulation/on period [*stimulation period*] and the rest/off period [*non-stimulation period*] are in a proportion of at least 1.5:1 (e.g., 60 on/5 off). EX-1008 ¶48; EX-1003 ¶¶260-261.

Headley discloses claim 9. EX-1003 ¶¶261-262.

i. Claim 10

- i. [10] The device of claim 8, wherein the duration of the stimulation cycle is less than a duration of two consecutive reference respiratory cycles.***

Headley discloses that intermittent periods [*stimulation cycle*] may range from 2-240 seconds. EX-1008 ¶48; EX-1003 ¶263. A six-second stimulation cycle, which is in the range disclosed by Headley (i.e., 3 seconds on/3 seconds off), is greater than a five-second reference respiratory cycle disclosed by Tran while being less than a duration of two consecutive five-second respiratory cycles (i.e., ten seconds) [*less than a duration of two consecutive reference respiratory cycles*]. EX-1003 ¶¶264-265.

Headley-Tran renders obvious claim 10. EX-1003 ¶265-266.

j. **Claim 12**

i. **[12.a] *The device of claim 1, comprising:
a processor; and***

Headley discloses that the pulse generator of the receiver includes a microprocessor [*processor*]. EX-1008 ¶30; EX-1003 ¶267.

Headley discloses [12.a]. EX-1003 ¶268.

ii. **[12.b] *a non-volatile computer readable medium
storing instructions, executable on the processor,
to implement the non-cardiac stimulation element
and to perform the first stimulation therapy
protocol.***

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 intermittent treatment [*first stimulation therapy protocol*]. For example, Headley describes that the controller could be programmed with the stimulation parameters which a POSITA understood would be stored in a non-volatile computer readable medium. EX-1008 ¶30; VIII.A; EX-1003 ¶¶269-270.

Headley discloses [12.b] and renders obvious claim 12. EX-1003 ¶271.

k. **Claim 13**

- i. ***[13.a] The device of claim 1, comprising:
a sensing element to at least periodically actively
sense respiratory information to obtain the
actively-sensed respiratory information unrelated
to stimulation synchronization,***

Headley discloses sound-activation-means and oxygen-sensing means
[*sensing element*] to at least periodically sense the patient snoring and/or low
oxygen levels [*actively sense respiratory information*].

In another preferred embodiment, the medical device further comprises
alternatively sound-activation-means for allowing the power unit to
turn on when the sound of snoring is received from the patient thus
allowing the device to be utilized only during times when the patient
may actually experience the apneic episodes, and/or oxygen-sensing
means and auto-start means for having the device turn on when the
patient's oxygen concentration as measured by transcutaneous receiver
placed on the antenna over the patient's skin would detect an oxygen
concentration of less than 96%.

EX-1008 ¶¶14, 44-45; EX-1003 ¶272.

A POSITA understood that either of the sound or oxygen activation means
disclosed by Headley would periodically actively sense respiratory information
(e.g., presence of snoring) but this information was not used to synchronize
simulation with the patient's respiratory cycle. EX-1003 ¶¶215-216, 273.

Headley discloses [13.a]. EX-1003 ¶¶273-274.

- ii. **[13.b] wherein the non-cardiac stimulation element is activated for stimulation upon the sensing element identifying, via at least the actively-sensed respiratory information, obstructive sleep apnea behavior which meets or exceeds a severity threshold and wherein the non-cardiac stimulation element is deactivated upon the sensing element identifying, via at least the actively-sensed respiratory information, that the obstructive sleep apnea behavior is less than the severity threshold.**

A POSITA understood that the sound-activation-means [*sensing element*] disclosed by Headley would activate the pulse generator of the receiver and electrodes stimulation [*activate the non-cardiac stimulation element*] if the snoring sound [*actively-sensed respiratory information identifying OSA behavior*] was at or above a severity threshold. EX-1008 ¶¶14, 44-45; EX-1003 ¶275. This is especially true given that Headley expressly discloses using a severity threshold (i.e., 96%) when discussing the oxygen sensing means. EX-1008 ¶¶14, 45; EX-1003 ¶276.

A POSITA also understood the electrical stimulation applied by the pulse generator of the receiver and electrode [*non-cardiac stimulation element*] would be deactivated when the snoring or oxygen level [*actively-sensed respiratory information*] is less than the severity threshold because Headley expressly discloses only providing stimulation when needed. EX-1003 ¶277. Indeed, Headley discloses that these sensing means “allow[] the device to be utilized **only**

during times when the patient may actually experience the apneic episodes” and further discloses a threshold (i.e., 96%) above which the electrical stimulation need not be applied [*deactivation of non-cardiac stimulation element*], which a POSITA understood as conserving battery. EX-1008 ¶¶14, 44-45; EX-1011 25:30-42; EX-1024 32:10-67; EX-1033, p.384; EX-1003 ¶277.

Headley discloses [13.b] and renders obvious claim 13. EX-1003 ¶278.

I. Claim 15

- i. [15] The device of claim 1, wherein the stimulation period and the non-stimulation period are in a proportion of at least 1.5 to 1.*

Headley discloses the limitations of claim 15 for the same reasons discussed with respect to claim 9. EX-1003 ¶279.

Headley renders claim 15 obvious. EX-1003 ¶280.

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 '709 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. 11,806,526 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 Claim and requests the Board institute *inter partes* review and then cancel the Challenged Claim as unpatentable.

Respectfully submitted,

DUANE MORRIS LLP

BY: /Jarrad M. Gunther/

Petition for *Inter Partes* Review of U.S. Patent No. 10,898,709

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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. 10,898,709 and all supporting exhibits were served via Federal Express, postage prepaid, to the Patent Owner by serving the correspondence address of record for the '709 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 13,997 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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