DOCUMENT HISTORY

REV	DCN	DESCRIPTION	EFFECTIVE DATE
AA	0596	Initial Release of Document	18-Apr-2014
AB	0687	Changed protocol in agreement with FDA per Q140608	08-Aug-2014
AC	0689	Exclusion Criteria: Add "Currently diagnosed with Obesity-Hypoventilation Syndrome (OHS)." Update Table 8 to include assessment of Adverse Events for Screening Evaluations #1 & #2.	15-Aug-2014
AD	0726	Updated document to address FDA questions from G140158.	06-Oct-2014
AE	0751	Revised wording to address FDA clarifications.	10-Nov-2014
AF	0753	Revised wording to address FDA additional recommendations from attached approval letter dated 06Nov14.	17-Nov-2014

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1 Contact Information

1.1 Principal Investigator and Co-Investigators

The sponsor will maintain a document with the contact information for all investigators participating in the study. The information maintained will include full names, addresses, telephone and fax numbers, and, if available, email addresses and mobile phone numbers for the following:

- Principal investigator
- Co-investigator(s)
- Study coordinators
- Hospital
- Sleep Laboratory
- Institutional Review Board chairperson

1.2 Sponsor

The sponsor will maintain a document with the contact information for all clinical study personnel participating in the study. The information maintained and provided to each site will include full names, addresses, telephone and fax numbers, and email addresses for the following:

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2 Clinical Investigational Plan Synopsis

Purpose of the Investigation	Published evidence strongly suggests that people diagnosed with obstructive sleep apnea (OSA) should be treated, and that untreated moderate or severe OSA is associated with morbidity and mortality, cardiovascular, metabolic, neurocognitive, and oncologic consequences. Positive airway pressure (PAP), if used regularly and as prescribed, likely treats/mitigates many of the symptoms and the health risks associated with OSA. However, poor PAP adherence and few acceptable alternative therapies leave a large OSA patient population untreated and at risk. The purpose of this study is to evaluate the benefits and risks of hypoglossal nerve stimulation with the ImThera Medical aura6000 System as a potential therapeutic option for individuals with moderate to severe OSA that have failed or do not tolerate PAP.
Device Tested	ImThera Medical, Inc. aura6000 System <u>Implantable components:</u> • ImThera Implantable Pulse Generator (IPG) - Model 100.0100 • ImThera Lead with Cuff Electrode (Lead) - Model 300.0100 <u>External components:</u> • ImThera Remote Control and Charger Kit (RCC) - Model 500.0100 • ImThera aCM Clinical Manager Software – Model 700.0100
Study Objectives	The objectives of this study are to evaluate the safety and effectiveness of the aura6000 System for the treatment of moderate to severe obstructive sleep apnea (OSA) in individuals who have failed or do not tolerate positive airway pressure (PAP) therapy or have failed or are intolerant of or refuse indicated alternative OSA treatments (such as oral appliances, positional devices and conventional sleep surgeries). PAP failure is defined as an inability to eliminate OSA (AHI > 20 despite PAP usage) and PAP intolerance is defined as: 1) inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night); or 2) unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it). The results of this study are anticipated to provide reasonable assurance of the safety and effectiveness of the aura6000 System when used as intended and to support the application for FDA Premarket Approval of the system.
Study Design	Multi-center, prospective, randomized, parallel, two-arm, controlled clinical study.
Study Population	Individuals with moderate to severe obstructive sleep apnea (OSA) that have failed or do not tolerate positive airway pressure (PAP) therapy or have failed or have declined indicated alternative OSA treatments such as oral appliances, positional devices and conventional sleep surgeries. aura6000 Therapy will be studied as a treatment for OSA when the outcome of PAP therapy is inadequate, such as when the patient is intolerant of PAP, or PAP therapy is unable to effectively treat OSA.
Number of Centers	Up to 20 clinical investigative sites
Randomization	Subjects will be randomized in a 2:1 ratio to the Treatment Group or the Control Group after implantation and prior to the Week 2 visit.
Treatment Group	The Treatment Group will be implanted with the aura6000 System and have therapy turned ON at the Month 1 follow-up visit.
Control Group	The Control Group will be implanted with the aura6000 System and receive treatment-as-usual, (i.e. any non-PAP, non-surgical OSA treatment including oral appliances and positional devices being used prior to enrollment in the study) until 14 days (washout period) prior to the Month 4 visit. At the Month 4 + 1 day follow-up visit, subjects in the Control Group will have therapy turned ON for the duration of the study.
Study Duration	The duration of the study is estimated to be 20 months from the time of first enrollment to completion of the Month 12 visit, and six years from the time of first enrollment to completion of the five year follow-up. Subjects will be followed to the five year post-implant follow-up visit.
Sample Size	The planned total sample size for the study is 141 subjects randomized 2:1 (94 Treatment Group and 47 Control Group). This sample size accounts for an assumed attrition rate of up to 10% at Month 4 and 15% at Month 12. An interim analysis with sample size assessment is planned at Month 4.

Inclusion/Exclusion Criteria	Individuals with moderate to severe obstructive sleep apnea (OSA) who have failed or do not tolerate positive airway pressure (PAP) therapy, have failed, or have rejected indicated alternative OSA treatments. The specific inclusion and exclusion criteria for the study are: Inclusion Criteria Candidates who meet all of the following criteria may be given consideration for inclusion in this clinical investigation: 1. Willing and capable of providing informed consent 2. Willing and capable of receiving the implant and utilizing the remote control and charger to activate the therapy and charge the implant 3. Willing and capable of returning for all follow-up evaluations and sleep studies 4. Willing and capable of completing all questionnaires 5. Is ≥ 18 years old 6. Has failed or does not tolerate PAP therapy 7. Has failed or refuses alternative OSA treatments (e.g. surgery, oral appliances, and behavioral treatments) 8. AHI ≥ 20 (moderate to severe OSA) based on in-lab polysomnography studies conducted no more than 45 days prior to aura6000 system implantation Exclusion criteria The subject must not meet any of the following exclusion criteria: *General* 1. Implanted with another active implantable device. 2. Actively enrolled in a clinical study of a different medical device or drug. *Concomitant Medications* 3. Taking opioids, narcotics, medications or supplements that in the opinion of the investigator may alter consciousness, the pattern of respiration, sleep architecture, or with known effect on sleep-wake function or alertness. *Medical History* 4. Currently receiving treatment for severe cardiac valvular dysfunction, NYHA Class III or IV heart failure, unstable angina or recent (< 6 month) myocardial infarction or cardiac arrhythmias. 5. Moderate to severe pulmonary hypertension defined as WHO Group II or higher. 6. Persistent uncontrolled hypertension (defined as systolic pressure ≥160 mm Hg or a diastolic pressure of ≥ 100 mm Hg) despite medications. 7. Neurodegenerative disorders or intrinsic neuromuscular disease or other neurologic deficits (e.g., multiple sclerosis, muscular dystrophy, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy, transient ischemic attack or cerebrovascular accident). 8. Active psychiatric disease (psychotic illness, major depression or acute anxiety attacks) that in the opinion of the investigator could prevent subject compliance with the requirements of the investigational study testing 9. Previous upper respiratory tract (URT) surgery (e.g., uvula, soft palate or tonsils) < 60 days prior to Screening PSG #1 10. Chronic obstructive pulmonary disease (FEV1 : FVC ratio < 70) or vital capacity of < 80% predicted) 11. Active history of pulmonary disease (including COPD, emphysema, and asthma) 12. Need for chronic supplemental oxygen therapy for any reason, PaO2 < 70 mm Hg 13. Other sleep disorders that confound functional assessments of sleepiness, such as narcolepsy with cataplexy, idiopathic hypersomnolence, insomnia, REM sleep behavior disorder, or sleep movement disorders, such as restless leg syndrome or periodic limb movement, producing sleep disturbances unrelated to OSA. *Lifestyle / Work* 14. Excessive use of alcohol, tobacco, caffeine, or recreational drugs. 15. Unwilling or unable to refrain from consumption of alcoholic beverages for 24 hours prior to the start of each PSG study 16. Unwilling or unable to refrain from use of PAP, oral appliances for OSA, positional devices, OSA surgery, or medications for OSA from enrollment through the completion of the Month 12 follow-up visit (except as permitted in the Control Group). 17. Subject has sleep hygiene behavior(s) that would substantially interfere with measurement outcomes during an overnight PSG study 18. Subject has an occupation for which untreated OSA presents a substantial risk to safety 19. Presence of occupational (shift work) or anticipation of shift changes (during the next two years) 20. Residing at, or planning to move within 2 years to a location where the subject would no longer be willing or capable of returning for all follow-up evaluations and sleep studies. *Physical Exam*

	21. BMI ≥ 35 kg/m2 22. Active systemic infection 23. Pedal edema grade ≥ 2+ 24. Clinical evidence of renal insufficiency, acute or chronic renal failure, or undergoing dialysis or expected to institute dialysis within 6 months 25. Clinical evidence of immunodeficiency 26. Life expectancy of < 2 years 27. Any condition likely to require future MRI, diathermy or other procedure producing strong RF fields 28. Pregnant or planning to become pregnant in the next year (must have a negative serum or urine pregnancy test within 14 days prior to implant and maintain adequate contraception during the study) 29. Any reason for which, in the judgment of the investigator, the subject is considered to be a poor surgical or study candidate, which may include, but is not limited to: any medical, social, or psychological problems that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study *Upper Airway Exam* 30. Tonsil grading system 3 and 4 31. Lingual Tonsil Hypertrophy Grading System (LTH) 3 and 4. 32. Friedman Tongue Position (FTP) IV 33. Hypoglossal nerve palsy (limited tongue movement or inability to move the tongue), tongue dysfunction, atrophy, hypertrophy, fasciculation, or problems swallowing or speaking. *Surgical Consult* 34. Rhinitis or nasal obstruction that is not well-controlled by medication or prior surgery 35. Severe mandibular deficiency/retrognathia or syndromic craniofacial abnormalities. 36. Prior surgery interfering with surgical exposure or implant safety 37. Previous surgical resection or radiation therapy for cancer or congenital malformations in the larynx, tongue, or throat. 38. ASA Status ≥ 4 39. Subject has torticollis or neck or facial spasm that could increase the risk of dislodgement 40. Any reason for which, in the judgment of the investigator, the subject is considered to be a poor surgical or study candidate, which may include, but is not limited to: any medical, anatomical, social, or psychological problems that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study *PSG Criteria* 41. AHI ≥ 65 on Screening PSGs 42. Apnea Index (AI) > 30 events per hour on Screening PSGs 43. SaO2 >10% falls index > 15 events per hour on Screening PSGs 44. ≥ 10% central apnea events as a proportion of the sum of apnea and hypopnea events per hour on Screening PSGs 45. Positional OSA as defined by: non-supine AHI < 10 on Screening PSGs 46. Predominantly REM OSA as defined by: non-REM AHI < 20 and > 50% difference in AHI between the REM and non-REM sleep on Screening PSGs 47. Evidence of Cheyne-Stokes breathing.
Primary Safety Endpoint	Estimate the incidence of adverse events (AEs) related to the aura6000 device or procedure through 365 days post-implant, including any unanticipated adverse device effects.
Responder Definitions	AHI Responder: A subject that has an apnea-hypopnea index (AHI) ≤ 20 and ≥ 50% reduction in AHI as compared to Baseline. ODI Responder: A subject that has a ≥ 25% reduction in oxygen desaturation index 4% (ODI 4%) as compared to Baseline
Primary Effectiveness Endpoints	Co -primary Effectiveness Endpoint #1 Proportion of subjects who experience improvement in the apnea-hypopnea index (AHI) at the Month 4 visit as defined above in the AHI Responder definition. It is hypothesized that the observed responder rate in the Treatment Group will be significantly greater than the responder rate in the Control Group at 4 months post-implant. Co-primary Effectiveness Endpoint #2 Proportion of subjects who experience improvement in the oxygen desaturation index 4% (ODI 4%) at the Month 4 visit as defined above in the ODI Responder definition. It is hypothesized that the observed responder rate in the Treatment Group will be significantly greater than the responder rate in the Control Group at 4 months post-implant. Co -primary Effectiveness Endpoint #3

	Proportion of subjects in the Treatment Group that experience clinically meaningful long-term improvements at Month 12 compared to Baseline in the apnea hypopnea index as defined above in the AHI responder definition. It is hypothesized that the observed AHI responder rate in the Treatment Group at 12 months post-implant will be numerically > 45%. <u>Co-primary Effectiveness Endpoint #4</u> Proportion of subjects in the Treatment Group that experience clinically meaningful long-term improvements at Month 12 compared to Baseline in the oxygen desaturation index as defined above in the ODI responder definition. It is hypothesized that the observed ODI responder rate in the Treatment Group at 12 months post-implant will be numerically > 45%.
Secondary Effectiveness Endpoints	• Improvement in Epworth Sleepiness Scale (ESS) • Improvement in Functional Outcomes of Sleep (FOSQ) • Improvement in EuroQol 5 Dimensional (EQ-5D)
Study Timeline	Subjects will be assessed at Screening; undergo aura6000 System implant; and will be followed regularly at two weeks, one month (Treatment Group only), two months, three months(Treatment Group only), four months, four months + 1 day (Control Group only), five months (Control Group only), ten months, twelve months, and annually through 60 months post-implant.
Study Oversight	Study oversight will be provided by: • An independent Clinical Events Committee (CEC) • An independent Data Safety and Monitoring Board (DSMB)

3 Investigational Device Description

3.1 Model and Manufacturer

The aura6000 System components to be used in this study are listed in Table 1. Devices will bear the following caution with regard to investigational use status:

Caution: Investigational Device. Limited by United States Law to Investigational Use

aura6000 Implantable Pulse Generator Kit (IPG)	Model 100.0100
aura6000 Lead Kit (Lead)	Model 300.0100
aura6000 Remote Control and Charger Kit (RCC)	Model 500.0100
aura6000 Clinical Manager Software (aCM)	Model 700.0100
Charging Antenna (CA)*	Model 500.0300
Remote Control Power Cord*	Model 500.04XX

*If necessary, these products may be used to replace components that are lost or damaged.

Table 1 - Components of the aura6000 System

3.2 aura6000 System Description and Use

The aura6000 System is intended to unilaterally stimulate the hypoglossal nerve which innervates the muscles of the tongue. The aura6000 System stimulates the hypoglossal nerve cyclically and continuously during sleep to maintain muscle tone of the tongue and upper airway during sleep. Stimulation is generated by a programmable, multi-current source,

implantable neurostimulator (IPG) and delivered to the hypoglossal nerve by a lead with multi-contact cuff electrode (lead). The IPG and lead are shown Figure 1 and Figure 2.

Figure 1: aura6000 Implantable Pulse Generator

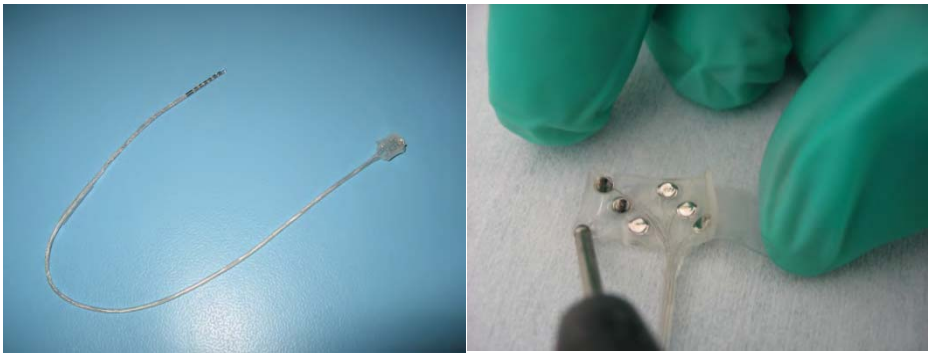


Figure 2: aura6000 Lead

The IPG is designed to operate for several days from its internal rechargeable battery before being transcutaneously recharged. The IPG is recharged using the remote control and charger (RCC) in combination with the Charging Antenna shown in Figure 3.

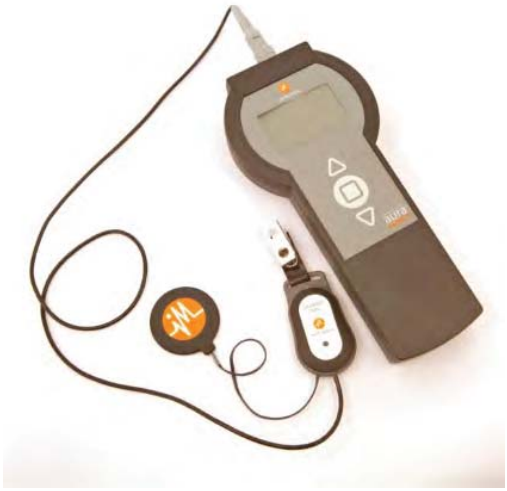


Figure 3: aura6000 Remote Control and Charger (RCC)

The RCC is a handheld device for controlling the IPG. The device allows the patient to start/stop/pause stimulation, charge the IPG, adjust various patient preference settings, adjust amplitude within physician-prescribed limits, and complete diagnostic tests of the system. The

RCC is housed in a plastic enclosure and uses a rechargeable battery pack. The RCC is recharged by attaching a mains power cord to the RCC. A connector on the top surface of RCC connects to the charging antenna for charging the IPG.

The RCC also has a mini USB connector which is used to connect it to a PC computer running the aura6000 Clinical Manager software (aCM) so that the aCM can send commands to the IPG via the RCC. The aCM software application can be installed on any PC computer running Windows® 7 or 8, and is used to set the stimulation parameters of the IPG.

The aCM is organized into a series of screens that correspond to the surgical implant procedure, the titration procedure (during which stimulation levels are defined) and the patient follow-up procedure (during which comfort adjustments are made).

Generally, the IPG is implanted in a subcutaneous pocket inferior to the collarbone over the pectoralis fascia, typically on the right side. A cuff electrode on the distal end of the lead is implanted on a proximal section of the hypoglossal nerve (HGN) in the submandibular region ipsilateral to the IPG. The proximal end of the lead is tunneled under the skin to the IPG. Figure 4 depicts the system configuration of the implanted components, post-implant.

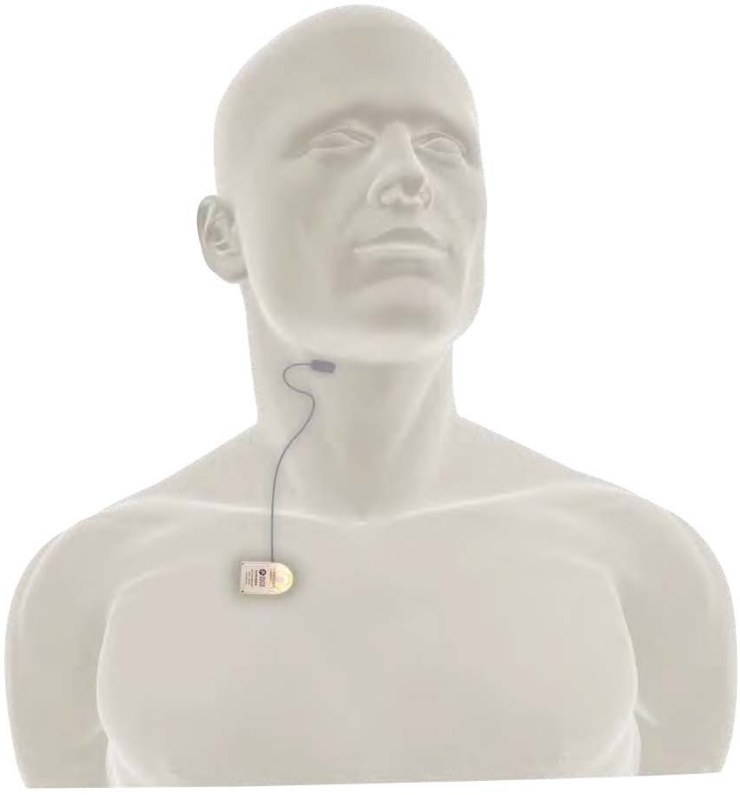


Figure 4: aura6000 System as Implanted

3.3 Instructions for Use (IFU) and Labeling

Copies of the following aura6000 labeling will be provided to all participating sites as part of the site initiation process:

- aura6000 Implant Manual
- aura6000 User's Manual
- aura6000 aCM Operator's Manual
- Patient Identification Cards
- Patient Information Brochure

Additional copies of all labeling included in the device package will be available and provided to the sites upon request.

3.4 Proposed Indication for Use

The aura6000 System is indicated for the reduction of sleep related apneas and/or hypopneas in adult patients with moderate to severe obstructive sleep apnea who have failed or are unwilling to use positive airway pressure (PAP) treatment.

4 Background and Significance

4.1 Overview of Obstructive Sleep Apnea (OSA) Epidemiology

Population based studies of diverse adult populations have identified a high prevalence of obstructive sleep apnea (Lee W 2008). Moderate to severe OSA (AHI ≥ 15) is estimated to occur in one in fifteen adults (Young T 2002) to 9% of middle aged men and 4% of women (Al Lawati 2009). OSA with or without symptoms is frequently under-diagnosed by physicians and unrecognized by patients (Fletcher EC, 1985; Logan AG 2001). Risk factors for developing OSA include obesity, alcohol consumption, smoking, nasal congestion, genetics and hormonal changes during menopause (Marcus JA 2014; Schwartz AR 2008; Foster GD 2009; Larkin AK 2005 & 2008; Vgontzas AN 2001). The presence of OSA is linked to other serious comorbidities such as hypertension, cardiovascular and cerebrovascular disease, diabetes and increased mortality (Marcus JA 2014; Leger B 2012; Bradley TD 2008; Sassani A 2004; Floras JS 2009 & 2013; Brenner 2008; Shahar E 2001; Yaggi HK 2005; Good DC 1996; Cappuccio FP 2010; Polotsky VY 2008; Botros N 2009; Meslier N 2003). In addition, untreated OSA contributes to an increased risk of motor vehicle and occupational accidents. The age-related progression of OSA is not well understood. However, the available epidemiological data suggest that in adults, OSA can progress over time (Gangwich JE 2008).

4.2 OSA Pathology

OSA is a common disorder characterized by repeated episodes of pharyngeal (upper) airway collapse or narrowing during sleep (Remmers JE 1978; Eckert DJ 2014). In people with OSA, pharyngeal muscles relax during sleep and gradually allow the pharynx to collapse. The level of pharyngeal collapse varies among patients, but most often occurs at the velopharyngeal level (e.g., palate) and/or the hypopharyngeal level (retroglossal airway, e.g., tongue). Collapse of the pharyngeal airway can block airflow (apnea) or significantly restrict airflow (hypopnea), both of which may cause oxyhemoglobin desaturation and/or arousals (Remmers 1978). An

episode of apnea or hypopnea is terminated by a brief arousal or a lighter stage of sleep, accompanied by activation of the upper airway dilator muscles and restoration of airway patency (White DP 2006). This cycle of repeated episodes of muscle relaxation, airway collapse, compromised airflow, arousal and/or oxyhemoglobin desaturation, and restored airway patency occurs repeatedly throughout the night. OSA may result in daytime hypersomnolence, excessive fatigue, and long term comorbidities (Corsonello A 2011; ViJayan VK 2012).

4.3 OSA Anatomy and Physiology

In general, people with OSA have an anatomically narrow upper airway (e.g., due to obesity or anatomical variation), and a narrow airway is more prone to collapse (Eckart DJ 2008; Taranto ML 2014). During wakefulness, people with OSA reflexively compensate for their more collapsible airway with increased airway dilator muscle activity. During sleep, however, their airway dilator muscle activity is decreased, and negative airway pressure induced by inspiration can result in airway collapse (Eckert DJ 2008). Collapse frequently occurs at the end of expiration, emphasizing the importance of sustained tonic activity in upper airway muscles. Pre-clinical animal and human studies demonstrate that hypoglossal nerve stimulation decreases airway collapsibility, increases airway patency, and stabilizes ventilation during sleep (Schwartz AR 2014).

In people who have OSA, the neuromuscular activity of the tongue is diminished or absent during sleep, contributing to airway collapse.

The muscles of the tongue are innervated by the hypoglossal nerve (cranial nerve XII; Netter FH 1997). The hypoglossal nerve predominantly contains efferent (motor) fibers, such that stimulation of the nerve activates the muscles of the tongue with minimal or no afferent (sensory) feedback. The aura6000 System stimulates the hypoglossal nerve to activate the muscles of the tongue to provide muscle tone and mitigate upper airway collapse during sleep (Zaidi FN 2013).

4.4 Management Alternatives for Obstructive Sleep Apnea

The diagnosis of OSA generally involves a physical examination, a medical history review, and an assessment of risk factors, symptoms and comorbidities, but a positive finding requires polysomnography (PSG), also called a sleep study. The indicated treatments for OSA are often based on OSA severity, symptoms, causal factors, and risk factors for comorbidities. The treatment options available to people with OSA exist on a spectrum from lifestyle changes to tracheotomy (Epstein LJ 2009). With the exception of tracheotomy (which is generally reserved for emergency situations), and maxilla-mandibular advancement surgery (which is generally reserved for people with retrognathia), no treatment option is as effective as positive airway pressure, the most common of which is continuous positive airway pressure (CPAP). Despite its effectiveness, patient adherence with CPAP is low, leaving a substantial population of OSA sufferers untreated or undertreated.

4.4.1 Lifestyle and Behavior Management

Some people with OSA can make lifestyle changes to reduce OSA severity, but they are not always successful (Heatley EM 2013). Examples of such lifestyle changes include: losing weight; avoiding alcohol, caffeine, and heavy meals within two hours of sleep; eliminating the use of sedatives; and changing sleep position to lay on the side or stomach (MayoClinic.com, Obstructive sleep apnea: Life style and home treatments).

4.4.2 Positional Therapy

Positional therapy, consisting of a method that attempts to keep the patient in a non-supine position, may be an effective secondary therapy or can be a supplement to primary therapies for OSA in patients who have a low AHI in the non-supine versus that in the supine position (Morgenthaler TI 2006). Examples of positional devices used to keep a person in a non-supine sleeping position include an alarm, pillow, backpack, or tennis ball. However, not all patients normalize breathing during sleep with these devices and many have difficulty sleeping with or cannot tolerate such devices.

4.4.3 Medical Management

Medical treatments (e.g., pharmaceuticals) may be used as part of an overall OSA treatment plan, but they are not a primary treatment option for OSA (Morgenthaler TI 2006; Mason M 2013).

Examples of medical treatments include:

Nasal sprays and decongestants may temporarily alleviate OSA by promoting nasal breathing, but only in instances where temporary nasal congestion (e.g., due to allergy or cold) is a causal or contributing factor for OSA. Some nasal decongestants can be habit-forming and should only be used for a limited period of time. Nasal sprays are ineffective when there is permanent narrowing of the nasal passages.

Alertness-promoting medications are sometimes prescribed to help OSA patients stay awake during the day, but they only treat a symptom of OSA and do not cure it or otherwise eliminate associated health risks.

Supplemental oxygen can help correct low oxygen levels caused by OSA, but it generally is not an adequate treatment option taken alone.

4.4.4 Oral Appliances

Oral appliances (also called dental devices) are considered primarily for people with mild-to-moderate OSA. Most oral appliances fit inside the oral cavity, although some devices fit around the head and mandible (Chen H 2013). Oral appliances are designed to open the airway by bringing the mandible and/or tongue forward during sleep. Two common types of oral appliances are mandibular repositioning devices and tongue retaining devices. Potential side effects include mouth soreness, joint or tongue pain, temporary or permanent misalignment of the jaw, excessive salivation and drooling, and nausea. In general, oral appliances are not

considered as effective as CPAP in treating OSA and some patients have difficulty wearing an oral appliance throughout the night (Ferguson KA 2006).

4.4.5 Positive Airway Pressure

Continuous positive airway pressure (CPAP) is the preferred treatment option for OSA (Gay P 2006). CPAP is indicated for people with moderate to severe OSA, and people with mild OSA plus daytime hypersomnolence (American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research 1999). Research shows that CPAP decreases daytime sleepiness, especially in those with moderate to severe OSA (Wright J 2000 & 2002; Hansley M 2004). Research also shows that if CPAP is used regularly and properly, it is associated with reduced likelihood of premature death (Young 2008).

Although CPAP has been shown to be effective in treating OSA when used and adjusted properly, many patients have a difficult time tolerating CPAP. Claustrophobia, patient anxiety, irritation of the nose and throat, air swallowing, and bed partner issues are among the many factors that contribute to poor patient tolerability and compliance on CPAP (Catcheside PG 2010). Objective measures of patient adherence (e.g., CPAP machines that record usage) suggest that patient adherence is less than 50% even with an arbitrarily low threshold for adherence (defined as ≥ four hours CPAP use per night for 70% of nights; Kribbs NB 1993).

4.4.6 Surgery

Surgical treatments may be considered for OSA patients when other less invasive treatment options have failed or have been found intolerable by the patient (Kotecha BT 2014). Surgery may also be considered for patients that have an anatomical abnormality that is a causal factor for their OSA (e.g., nasal restriction or obstruction; unusually large soft palate, tonsils or adenoids; unusually large tongue relative to oral cavity; retrognathia, etc.).

Under current practice, the type of surgical intervention indicated for a particular patient depends largely on anatomical considerations such as the level of airway obstruction. Levels of obstruction include nasal or nasopharyngeal (e.g., nose), oropharyngeal (e.g., palate), and hypopharyngeal (e.g., tongue). Surgical interventions are often combined, recognizing that obstructions may occur at more than one level or that a new level of obstruction may arise post surgically. In addition, airway bypass is sometimes used and is usually indicated for emergency situations where no alternative is immediately available to establish adequate airflow. An example of this is tracheotomy.

A recent meta-analysis (Table 2) of multiple surgical procedures to modify the upper airway for treatment of obstructive sleep apnea found that the literature was too limited to make recommendations for surgical treatments for OSA. For example, in an analysis of 15 studies in the published literature, uvulopalatopharyngoplasty (UPPP) surgery, the most commonly performed procedure, was associated with an average AHI reduction of a 33% (range 23% -

42%), which is less than the criteria for success (i.e. an AHI reduction of at least 50%) typically used for surgical procedures (Caples SM 2010).

SURGERY	SUCCESS CRITERIA	SUCCESS RATE (Ref)
Palatal Implants	Post surgical AHI ≤ 10 AHI reduction ≥ 50%	50% (Nordgard S 2007)
UPPP – oropharyngeal obstruction only	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	52.3% (Sher AE 2002)
UPPP – hypopharyngeal obstruction or hypopharyngeal obstruction + oropharyngeal obstruction	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	5.3% (Sher AE 2002)
Genioglossus Advancement (GA)	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	62% (Kezirian EJ 2006)
Motorized Genioplasty	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	48% (Kezirian EJ 2006)
Tongue Radiofrequency Ablation	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	35% (Kezirian EJ 2006)
Midline Glossectomy (MG)	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	50% (Kezirian EJ 2006)
Hyoid Suspension (HS)	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	50% (Kezirian EJ 2006)
Tongue Stabilization	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	35% (Kezirian EJ 2006)
Tongue Base Suspension + UPPP	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	20% (Miller FR 2002)
MG + UPPP	Post surgical RDI reduction ≥ 50%	41.7% (Sher AE 2002)
Lingualplasty + UPPP	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	77% (Sher AE 2002)
GA + Hyoid Myotomy + UPPP	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	67% (Sher AE 2002)
Maxillo-Mandibular Advancement + UPPP	Post surgical RDI ≤ 20 RDI reduction ≥ 50%	97.8% (Sher AE 2002)
Tracheotomy	Resolution EDS	83-100% (Sher AE 2002)

Table 2: Success rates of the common surgical interventions for OSA, generally in order of increasing invasiveness. (AHI=apnea-hypopnea index, RDI=respiratory distress index, EDS=Excessive Daytime Sleepiness)

4.5 Untreated OSA – Consequences and Comorbidities

OSA causes fragmented sleep and can lead to daytime hypersomnolence and excess fatigue, resulting in an increased risk for motor vehicle accidents (Mulgrew AT 2008), occupational accidents and lost productivity (Lindberg E 2001), and decreased quality of life (Akashiba T 2002).

OSA is also associated with an increased risk of stroke (Yaggi HK 2005) and hypertension (Peppard PE 2000). Recent large population based studies have confirmed an association between OSA and coronary artery disease (Shahar E 2001), congestive heart failure (Shahar E 2001, type 2 diabetes (Reichmuth KJ 2005) and death (Young T 2008). Table 3 shows the increased risk factor for each of these conditions for people with moderate-to-severe OSA.

Condition Increased Risk	(Odds ratio)
Motor Vehicle Accidents	2.0 – 6.7
Occupational Accidents	2.2
Coronary Artery Disease	1.2 – 5.4
Stroke	1.6 – 3.1
Hypertension	2.9
Congestive Heart Failure	2.4
Type 2 Diabetes	1.5
Death	1.5 – 5.2

Table 3: Odds Ratios for Persons with Moderate to Severe OSA

4.6 Unmet Medical Need

Published evidence strongly suggests that people diagnosed with OSA should be treated, and that untreated severe OSA can be fatal (Young T 2008). CPAP, if used regularly and as prescribed, likely prevents many of the health risks identified above including premature death. However, poor PAP adherence (Kreivi HR 2014) and few acceptable alternatives leave a large OSA patient population untreated, at risk, and searching for a new therapy.

4.7 Clinical Rationale for Hypoglossal Nerve Stimulation for Treatment of OSA

Patients with moderate to severe OSA who have failed or otherwise do not tolerate PAP therapy are at increased risk of significant health problems and death. Hypoglossal nerve stimulation has shown potential as a safe and efficacious therapy for patients with moderate to severe OSA, when the outcome of PAP therapy is inadequate (such as when the patient is intolerant of PAP, or PAP therapy is unable to effectively treat OSA; Kreivi HR 2014), and may mitigate the associated health risks. For these patients, the aura6000 System is intended to offer a treatment option that is effective, easy to use and tolerate (unlike PAP), and reversible (unlike OSA surgeries) thereby preserving other treatment alternatives.

In summary, the aura6000 System has the potential to be a safe and effective therapy option for people with moderate to severe OSA who have failed or cannot tolerate PAP. The risks associated with untreated OSA are expected to outweigh the risks believed to be associated with implanting and using the aura6000 System.

5 Summary of Report of Prior Investigations

5.1 Synopsis

There is an extensive body of literature that supports the acute and chronic safety of nerve stimulation in general and hypoglossal nerve stimulation in particular. Earlier work involved acute stimulation first in animals, and then in humans. The successful demonstration of safety and effectiveness in acute studies motivated the progression to studies of chronically implanted devices in humans.

To date, there are multiple papers reporting the use of acute and chronic hypoglossal nerve stimulation in over 250 cumulative subjects. The effectiveness data from these studies show a reduction in the apnea hypopnea index by approximately 50%-70% with the use of a variety of hypoglossal nerve stimulators. Additionally, patients noted significant decreases in their daytime sleepiness symptoms, significant improvements in intensity of snoring, significant improvements in their daily functioning, and significant improvements in their overall quality of life. Adverse events have generally been unremarkable and occur at rates similar to, or below those of other neurostimulators. Evidence from studies of these and other closely-related neurostimulation devices supports the assertion that for well-selected patients, the likely benefits of hypoglossal neurostimulation outweigh the risk of the therapy and the risks associated with untreated OSA.

5.2 Acute Genioglossus Muscle Stimulation

Acute direct genioglossus muscle stimulation has been studied as a surrogate for hypoglossal nerve stimulation, given that the hypoglossal nerve innervates the genioglossus muscle and controls tongue protrusion, which is believed to be a major contributor to airway patency (Mann 2002). Investigators have largely found that therapeutic electrical stimulation of the tongue muscle during sleep can be achieved without arousal or any other remarkable adverse events. The present literature search identified more than 80 human and 65 animal papers concerning acute direct stimulation of various retrusor and protrusor tongue muscles. Of these 24 and 17 papers involved genioglossus muscle stimulation experiments in humans and animals respectively.

More recently, methods were developed to selectively stimulate the genioglossus muscle (the main muscle of tongue protrusion) in patients with OSA (Schwartz 1996, Oliven 2003). The electrical stimulation of the genioglossus muscle has been demonstrated to reduce or eliminate the collapse of the upper airway during sleep in OSA patients. Decker et. al. reported in 1993 a study that involved eleven subjects, of which seven were OSA subjects. This study, in which surface electrodes were placed submentally and fine wire electrodes were placed on the genioglossus muscle, found that subjects tolerated higher stimulus parameters during sleep than wakefulness. However, the fine wire stimulation only removed 23 % of apneic events.

Similarly, in 1996, Schwartz et. al., in a study that involved nine subjects with OSA, found that therapeutic electrical stimulation of the genioglossus could be delivered without causing arousal as measured by EEG, EMG, heart rate, and airflow. They also showed that stimulation reduced AHI, over thirty minutes, from 65.6± 11.5 to 9.0±5.8 episodes/hour. Mann et. al. reported, in 2002 a study that involved 14 healthy subjects where fine wire electrodes were placed in the genioglossus muscle, that the subjects tolerated the stimulation well and that no adverse events related to the procedure occurred other than transient mild neck tenderness related to the electrode insertion. They also showed that direct genioglossus stimulation significantly increased (+133%) upper airway diameter as measured using endoscopic techniques.

In 2003, Oliven et. al. placed bipolar fine wire electrodes bilaterally in nine OSA subjects and found that direct genioglossus stimulation decreased the critical closing pressure of the subjects' upper airway by 3.18 ± 1.7 cmH2O. They also found that the site of collapse (oropharynx vs. velopharynx) did not influence the response to direct genioglossus electrical stimulation. Oliven et. al. also performed a study in 2007 that involved 32 OSA subjects and found that substantial improvement in pharyngeal patency could be observed in half of the subjects. They found that therapeutic response was related to the magnitude of forward displacement of the tongue and that direct stimulation of the genioglossus muscle decreased collapsibility by enlarging the pharynx. In 2008, Lianggang Hu et. al., studied the effect of stimulation of the genioglossus with percutaneous biphasic electrical pulses on 22 OSA patients with obstructive sleep apnea syndrome (OSAS). During polysomnography (PSG), whenever sleep apnea was detected, the genioglossus was stimulated with percutaneous biphasic electrical pulses that were automatically regulated by a microcontroller to achieve the optimal effect relieving the glossopharyngeal airway obstruction. The study concluded that the OSAS patient's apnea time decreased ($P < 0.01$), RDI decreased ($P < 0.01$), and SaO2 increased ($P < 0.01$). No tissue injury or major discomfort was noticed during the trial (Lianggang Hu 2008).

Feasibility studies targeting both tongue protrusor and retrusor muscles showed remarkable improvements in OSA, but also in overall quality of life (Schwartz 2001, Eastwood 2010). Oliven et. al. (2007) evaluated the effect of co-activation of tongue protrusors and retractors on pharyngeal patency in patients with OSA. The effect of genioglossus (GG), hyoglossus (HG), and coactivation of both on nasal pressure, flow relationships was evaluated in a sleep study (n = 7) and during a propofol anesthesia study (n = 7). The study concluded that the beneficial effect of coactivation depends on the pattern of GG fiber recruitment: although surface stimulation of GG failed to protrude the tongue, it prevented the occlusive effect of the retractor, thereby improving pharyngeal patency during coactivation. Another study by Schwartz et. al. showed that airway obstruction was alleviated not solely by the genioglossus muscle but also when the tongue retrusor muscles were activated in conjunction with the genioglossus muscle (Schwartz AR 1996). Suggesting that both protrusor and retrusor tongue muscles contribute to upper airway patency and can be targeted for stimulation (Oliven 2007).

5.3 Chronic Hypoglossal Nerve Stimulation

To date >250 cumulative patients (in more than eight different studies) have been implanted with a hypoglossal nerve stimulation system for treatment of obstructive sleep apnea. These studies show a reduction in the apnea hypopnea index by approximately 50%-70% with the use of a variety of hypoglossal nerve stimulators (Table 4). Additionally, the studies also reported significant decreases in daytime sleepiness symptoms, significant improvements in intensity of snoring, significant improvements in daily functioning, and significant improvements in overall quality of life (Walsh 2011, Van de Heyning 2012, Mwenge GB 2013, Eastwood 2010, Strollo P 2014).

Owners	Study	Subjects (N)	Duration	AHI Improvement
Apnex Medical, Inc.	Apnex I (Eastwood P, 2011)	21	6 M	55%
	Apnex II (Kezirian EJ, 2014)	32	12M	45%
Inspire Medical System	Inspire 1 (Schwartz AR, 2001)	8	6M	59% -66%
	Inspire 2/Group I (Van de Heyning PH, 2012)	22	6M	10% - 70%
	Inspire 2/Group II (Van de Heyning PH, 2012)	9	6M	74%
	STAR-IDE (Strollo PJ Jr, 2014)	126	12M	51%
ImThera Medical, Inc.	THN1 (Mwenge GB, 2013)	13	12M	53%
Percutaneous HN Stimulation	Percutaneous biphasic electrical stimulation (Lianggang Hu, 2008)	22	Single PSG	60% (RDI)

Table 4: Significant Hypoglossal Nerve Stimulation Studies

The feasibility of chronic hypoglossal nerve stimulation and its potential as a therapeutic approach for the treatment of OSA have been previously demonstrated by Schwartz et. al. in 2001. Eight patients with moderate-to-severe OSA participated in a study of chronic unilateral stimulation of the hypoglossal nerve during inspiration while asleep. An implantable pulse generator (IPG) was placed in a subcutaneous pocket over the pectoralis fascia. The half-cuff stimulating lead was tunneled between the IPG and the hypoglossal nerve. A pressure-sensing lead, used to track respiration, was tunneled from the IPG and implanted into the manubrium of the sternum. Information from this lead was used to trigger the onset of stimulation during the inspiratory phase of the respiratory cycle.

For the eight patients implanted with the device, sleep and breathing patterns at baseline (pre-implant) were compared to averaged results obtained at 1, 3, and 6 months follow-up post-implant. Comparisons were made for the entire night as well as for periods of time with maximal synchrony of stimulation to inspiration. Table 5 summarizes the mean results for apnea-hypopnea indices (AHI) and the lowest oxyhemoglobin saturations (SaO_2%) reported in the Schwartz 2001 study, for both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.

Time point	Avg. AHI		Avg. Low SaO_2%	
	REM	NREM	REM	NREM
Baseline	48.2	52.0	88.7	89.7
Entire Night	16.6	22.6	91.6	91.7
Continuous Stimulation	12.0	15.5	92.6	92.4

Table 5: Clinical Results of Chronic HGN Stimulation (Schwartz et. al.. 2001).

AHI was significantly reduced from baseline for both REM and non-REM sleep. In addition, the

severity of oxyhemoglobin desaturation was reduced significantly. Along with these improvements in sleep apnea, the authors observed a trend toward deeper stages of non-REM sleep. Finally, the authors reported that patients were able to tolerate long-term stimulation and had no adverse effects from stimulation of the hypoglossal nerve. The Schwartz et. al. study utilized the Inspire I system (Figure 5 - Illustration of the device used in Schwartz et. al., 2001.) made by Medtronic (Minneapolis, MN, USA), which was reported to have performed well in terms of safety, despite a number of technical problems with the system including failure of the electrode and sensor in some cases (Eisele DW 2003). Although the cause(s) for these technical problems are not reported in the clinical literature, pre-clinical studies using the same stimulation lead (model 3990) and sensor (model 4322) were reported to have similar problems (Goding GS 2001).

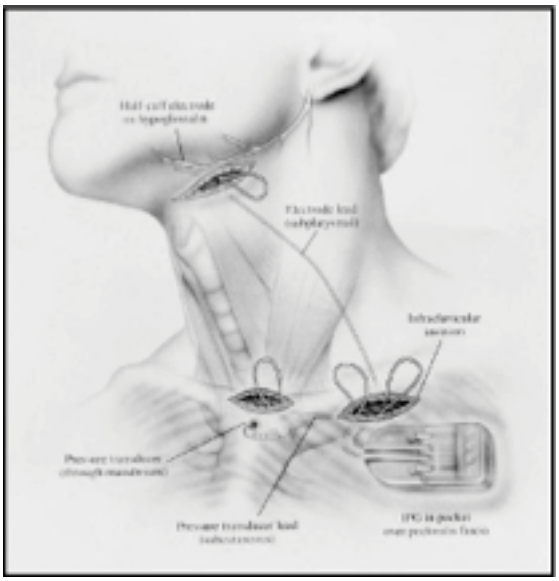


Figure 5 - Illustration of the device used in Schwartz et. al., 2001.

More recently, Strollo et. al. 2014, evaluated the clinical safety and effectiveness of upper-airway stimulation at 12 months for the treatment of moderate-to-severe obstructive sleep apnea in 126 patients. Using a multicenter, prospective, single-group, cohort design, upper-airway stimulation device were surgically implanted in patients with obstructive sleep apnea who had difficulty either accepting or adhering to CPAP therapy. The primary outcome measures were the apnea-hypopnea index and oxygen desaturation index. Secondary outcome measures were the Epworth Sleepiness Scale, the Functional Outcomes of Sleep Questionnaire (FOSQ), and the percentage of sleep time with the oxygen saturation less than 90%. Consecutive participants with a response were included in a randomized, controlled therapy-withdrawal trial. The study included 126 participants; 83% were men. The median AHI score at 12 months decreased 68%, from 29.3 events per hour to 9.0 events per hour (P<0.001); the ODI score decreased 70%, from 25.4 events per hour to 7.4 events per hour (P<0.001). Secondary outcome measures showed a reduction in the effects of sleep apnea and improved quality of life. In the randomized phase, the mean AHI score did not differ significantly from the 12-month score in the nonrandomized phase among the 23 participants in the therapy-maintenance group (8.9 and 7.2 events per hour, respectively); the AHI score was significantly higher

(indicating more severe apnea) among the 23 participants in the therapy-withdrawal group (25.8 vs. 7.6 events per hour, P<0.001). The ODI results followed a similar pattern. The rate of procedure-related serious adverse events was less than 2%.

Similarly, Mwenge et. al. performed a prospective, single center, feasibility study to assess the safety and preliminary efficacy of the ImThera aura6000 Targeted Hypoglossal Neurostimulation System (Figure 6) (Mwenge GB 2013).

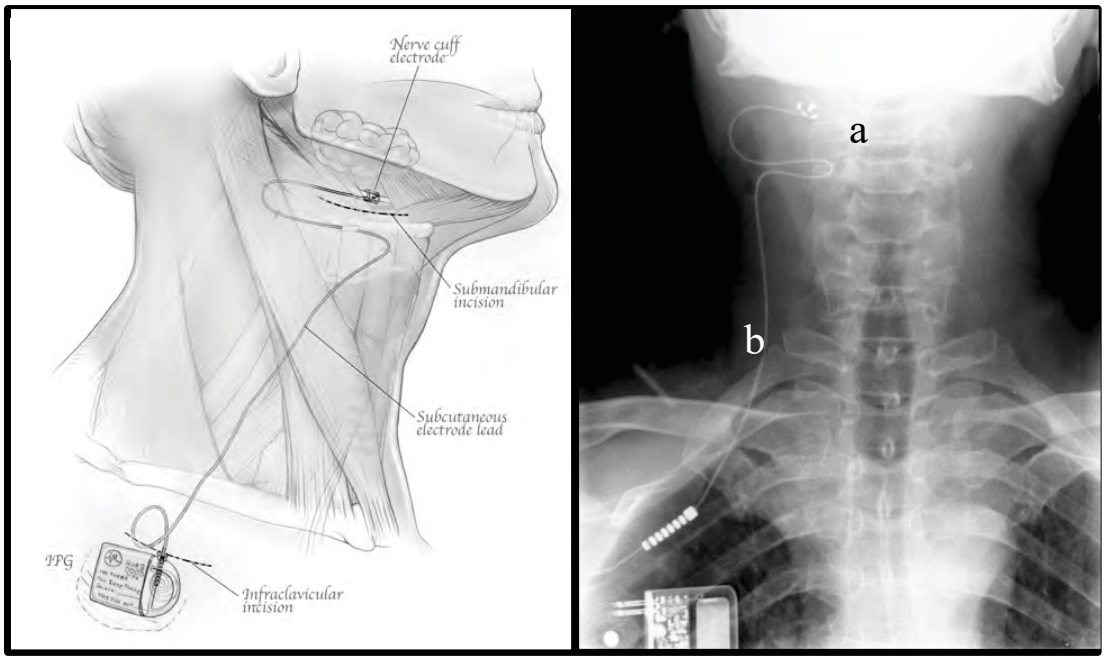


Figure 6: ImThera Medical device illustration and the X-Ray used in Mwenge et. al., 2013 (a: position of the cuff, b: lead and c: IPG).

In the thirteen subjects with data at 12 months, the mean AHI was reduced (improved) from 45.2 ± 17.8 at baseline to 21.7 ± 19.9 at Week 12 (52.1% mean improvement), and to 21.0 ± 16.5 at 12 months (53.5% mean improvement). Similarly, the mean oxygen desaturation index (ODI) was reduced from 29.2 ± 19.6 at baseline to 14.2 ± 16.7 at Week 12 (51.4% mean improvement), and to 15.3 ± 16.2 at 12 months (47.6% mean improvement). The study also reported that three of the patients implanted in the study did not meet inclusion/exclusion criteria and should not have been enrolled due to a large uvula, BMI >37, or excessive central sleep apnea. Excluding these 3 patients, 9 patients (90%) experience AHI reduction >50% and 8 patients (80%) met the pre-defined responder criteria (AHI reductions >50% and AHI<20) at 12 months. In this responder subgroup AHI improved from 41.5 ± 13.1 at baseline to 14.3 ± 8.8 at 12 weeks (65.5% mean improvement), and to 13.2 ± 5.5 at 12 months (68.2% mean improvement); and ODI improved from 23.1 ± 10.2 at baseline to 7.6 ± 4.1 at 12 weeks (67.1% mean improvement) and to 7.8 ± 5.3 at 12 months (66.2% mean improvement).

Earlier, Eastwood et. al. conducted a single-arm, open-label study has been completed in four sites in Australia using the HGNS device manufactured by Apnex Medical, Inc. in 2011. Twenty-one subjects were assessed at baseline, 3 months, and 6 months post-implant. Therapy

compliance was assessed by nightly hours in use. Symptoms were assessed using the Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), Calgary Sleep Apnea Quality of Life Index (SAQLI) and the Back Depression Inventory (BDI). The results showed significant improvement (all $P < 0.05$) from baseline to 6 months in: AHI (43.1 ±17.5 to 19.5 ± 16.7), ESS (12.1 ± 4.7 to 8.1 ± 4.4), FOSQ (14.4 ± 2.0 to 16.7 ± 2.2), SAQLI (3.2 ± 1.0 to 4.9 ± 1.3), and BDI (15.8 ± 9.0 to 9.7 ± 7.6). Two serious device-related adverse events occurred. The authors concluded that the device demonstrated favorable safety, efficacy, and compliance. Subjects with predominate hypopnea-based OSA experienced a significant decrease in OSA severity and OSA-associated symptoms.

Kezirian et. al. in 2010 presented results from eight obstructive sleep apnea patients with a fully implanted system for hypoglossal nerve stimulation, demonstrating an improvement in upper airway collapsibility and obstructive sleep apnea severity. Eastwood et. al. in 2010 examined the safety and effectiveness of the hypoglossal nerve stimulation system as a potential treatment alternative for OSA. Eighteen CPAP non-compliant OSA subjects underwent surgical implantation of the HGNS system in a feasibility study. Clinical data at 3 months post-implant in twelve (12) subjects (8 male), age 55.4±10.5 yrs. (means); suggested a 56% reduction in mean AHI (49.3/hr. to 21.6/hr.), with eight subjects (67%) experiencing an AHI reduction of 50% or more (mean AHI 53.6/hr. to 16.8/hr.). In addition, there was improvement in symptoms based on the ESS, FOSQ, SAQLI, PSQI, and BDI scores. Adherence was 92% (11/12).

Later in 2014 Kezirian et. al. examined the safety, feasibility and efficacy of a novel hypoglossal nerve stimulation system for 12 months in 31 subjects (35% female, age 52.4 ` 9.4 years) with moderate to severe obstructive sleep apnea. There was a significant improvement ($P < 0.001$) from baseline to 12 months in apnea–hypopnea index (45.4 ± 17.5 to 25.3 ± 20.6 events/h) and Functional Outcomes of Sleep Questionnaire score (14.2 ± 2.0 to 17.0 ± 2.4), as well as other polysomnographic and symptom measures. Outcomes were stable compared with 6 months following implantation. Three serious device-related adverse events occurred: an infection requiring device removal; and two stimulation lead cuff dislodgements requiring replacement. There were no significant adverse events with onset later than 6 months following implantation. Hypoglossal nerve stimulation demonstrated favorable safety, feasibility and efficacy.

5.4 Clinical Experiences with Other Neurostimulation Devices

The present literature search revealed that implantable neurostimulators and leads have a long history of safe clinical use. For example, neurostimulators are used for chronic stimulation of, the sacral nerve for urinary incontinence (Scriener et. al. 2013) and fecal incontinence, spinal cord for pain (Kapural 2014, Tanabe 2014), the diaphragm/phrenic nerve for respiratory control (Podnar 2013), brain for Parkinson's disease (Little et. al.., 2013), and vagus nerve for epilepsy and depression (Beekwilder, 2010). In these applications, as with the aura6000 therapy, a stimulation lead is implanted near the nerve/muscle, and then tunneled to a subcutaneous pocket and connected to an implanted neurostimulator. These systems are similar in many

aspects to cardiac pacemakers and cardiac defibrillators, which also have a long history of safe clinical use.

Other than the system used for chronic hypoglossal nerve stimulation in the studies described above (Schwartz et. al.. 1996, 2001, Walsh 2011, Van de Heyning 2012, Mwenge GB 2013, Eastwood 2010, Malhotra A 2014), implantation of the Cyberonics vagus nerve stimulator (VNS) system is probably the most similar to hypoglossal neurostimulation in terms of the type of surgeon that implants the system, the type of components implanted, and the location of the implanted components. In the Cyberonics procedure, the stimulation lead is placed around the vagus nerve via a neck dissection, tunneled down the neck to a subcutaneous pocket in the chest, and connected to the neurostimulator. Although very similar in other aspects, exposure of the vagus nerve for implanting the VNS system is more invasive (e.g., involves dissection near the carotid artery and jugular vein, requires resection within the carotid sheath, etc.) than dissection of the hypoglossal nerve. Nevertheless, implantation of the VNS system is reported to be straightforward, and implantation of electrodes in the neck is considered safe (Santos 2004). For example, a clinical trial conducted by Cyberonics in which 454 patients were implanted VNS Therapy System, resulted 13 surgery related SAE in 13 (4.1%) patients and 4 stimulation related SAE in 4 (1.2%) patients (http://dynamic.cyberonics.com/manuals/?lang=English-US). Although a total of 9 patients died, none of these deaths were attributed by the investigators to the VNS Therapy System. In another Cyberonics study for the treatment of patients with treatment-resistant depression (D-21; http://dynamic.cyberonics.com/manuals/?lang=English-US), ten out of 331 patients had a total of 12 SAEs that were considered definite, possibly or probably related to the implant procedure (dyspnea, chest pain, incision site reaction, device site reaction, hemorrhage, device site pain and infection [6 patients]). Seven patients had a total of 8 SAEs that were considered possibly related to stimulation (suicide attempt, abdominal manic reaction [2 patients] and depression [4 patients]). There were 6 unrelated deaths.

Similarly, other studies (sponsored by companies with various neurostimulation devices) suggest that implantable systems are reliable and that the probable benefits to health from the use of such devices outweigh any probable injury or illness from such use. “Summary of Safety and Effectiveness Data” provided to FDA by ANS/St. Jude Genesis system (http://www.accessdata.fda.gov/cdrh_docs/pdf/P010032b.pdf), summarizes the risks sixteen studies (table below), demonstrating the safety of the Genesis (IPG) Neurostimulation System. Their analysis from 13 studies reviewed (in 1253 patients; Table 6), suggests that the largest risk, i.e. lead breakage, occurs in 17.2% of patients.

Risks	# Patients	# Events	% Patients
Lead Migration	1059	144	13.6
Infection	1253	37	3
Epidural Hemorrhage	1253	0	0
Seroma	1253	0	0
Hematoma	1253	5	0.4
Paralysis	1253	1	0.1
CSF Leak	1253	6	0.5
Over/Under Stim	1059	27	2.6
Intermittent Stim	1059	0	0
Pain over Implant	1059	12	1.1
Allergic Reaction	1059	2	0.2
Skin Erosion	1059	1	0.1
Lead Breakage	1059	182	17.2
Hardware Malfunction	1059	32	3
Loose Connection	1059	10	1
Battery Failure	911	17	1.9
Other	1059	24	2.3

Table 6: Summary of Adverse Events Reported in Thirteen Spinal Cord Stimulator Studies

Surgical dissection to the hypoglossal nerve for implanting a hypoglossal neurostimulator is similar to submandibular gland resection surgery, which is a simple surgical procedure (indicated for salivary gland neoplasms) that otolaryngologists are trained in during residency. The hypoglossal nerve lies deep to the submandibular gland and retraction of the gland involves exposing the proximal trunk of the hypoglossal nerve proximal to the branching point of the nerve. The cuff of the stimulation lead is placed on the nerve immediate distal to the superior root of ansa cervicalis. To date, no major surgical complications resulting in death or life-threatening illness or permanent impairment have been reported in any hypoglossal nerve stimulation study. The adverse events have typically been minimal and quickly, completely, and safely resolved. One of the largest clinical study conducted by Strollo PJ et. al. (2014) documented the overall rate of procedure related SAE to be less than 2% (Table 7). Likewise, procedure related SAE were quite comparable to other studies as well (4 events in THN1-Mwenge GB et. al., 2013, Eastwood PR et. al., 2011 and 11 events in APNEX II-Kezirian EJ et. al., 2014).

Adverse Events	Apnex II			Inspire IDE			THN1		
	# Events	# Subjects	% Subjects	# Events	# Subjects	% Subjects	# Events	# Subjects	% Subjects
All Serious Adverse Event (SAE)	11	7	22%	9	8	6%	4	3	23%

Table 7: Summary of Adverse Events Reported in Significant Hypoglossal Neurostimulation Studies.

5.5 Summary

Patients with moderate to severe OSA who have failed or otherwise do not tolerate PAP therapy are at increased risk of significant health problems and death. Hypoglossal nerve stimulation has shown potential as a safe and efficacious therapy for patients with moderate to severe OSA, when the outcome of PAP therapy is inadequate (such as when the patient is intolerant of PAP, or PAP therapy is unable to effectively treat OSA), and may mitigate the associated health risks. The present literature review has identified and studied the bibliography of all publications, whether adverse or supportive, that are directly or indirectly relevant to an evaluation of the safety and effectiveness of hypoglossal nerve stimulation using implantable stimulators. The literature provides reasonable assurances of risk/benefit, with the caveat that long-term effects are not currently known. Therefore, chronic implant effects can only be derived from clinical experiences of other neurostimulation devices which have been on the market for many years now. In summary, the literature search suggests that risks associated with untreated OSA outweigh the risks believed to be associated with implanting and using a hypoglossal nerve stimulation system like the aura6000 System.

6 Study Protocol

6.1 Overall Study Objectives

The objectives of this study are to evaluate the safety and effectiveness of the aura6000 System for the treatment of moderate to severe obstructive sleep apnea (OSA) in individuals who have failed or do not tolerate positive airway pressure (PAP) therapy or have failed or are intolerant of or refuse indicated alternative OSA treatments (such as oral appliances, positional devices and conventional sleep surgeries). PAP failure is defined as an inability to reduce OSA (AHI > 20 despite PAP usage) and PAP intolerance is defined as: 1) inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night); or 2) unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it).

6.2 Study Design

This is a multi-center, prospective, randomized, parallel, two-arm, controlled, study. The study is designed to evaluate the safety and effectiveness of the aura6000 System when used as intended.

6.3 Study Duration

The study will be initiated upon Investigational Device Exemption (IDE) approval, and site Institutional Review Board (IRB) or Medical Ethics Committee (EC) approval at each site. The duration of the study is estimated to require 20 months from the time of first enrollment to completion of the Month 12 follow-up, and six years from the time of first enrollment to completion of the five-year follow-up. Subjects will be followed to the five-year post-implant follow-up visit.

6.4 Investigative Sites

This study will be conducted at up to 20 investigative sites. Each investigative site must include a surgical center/surgeon qualified to perform the implant procedure, and a sleep medicine center / certified sleep medicine physician, qualified to diagnose and treat obstructive sleep apnea patients. In the event that the sleep medicine center and the surgical center are affiliated with different institutions, and two reviewing IRBs/ECs must approve the study, the site will be counted as one investigative site because the two sites will be responsible for enrolling and following the same cohort of patients. For overall study oversight, one investigator will be identified as the site's principal investigator, as required by 21 CFR 812, and the other(s) will be co-investigator(s).

6.5 Study Patient Population

Subjects participating in the study will be individuals who have failed or do not tolerate positive airway pressure (PAP) therapy or have failed or are intolerant of or refuse indicated alternative OSA treatments (such as oral appliances, positional devices and conventional sleep surgeries). PAP failure is defined as an inability to eliminate OSA (AHI > 20 despite PAP usage) and PAP intolerance is defined as: 1) inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night); or 2) unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it). Only subjects who have signed an informed consent form and who have met all inclusion and exclusion criteria via specified testing will be implanted. Subjects will not be excluded based on gender or minority status.

6.6 Randomization

Subjects will be randomized to the Treatment Group or the Control Group in a 2:1 ratio via permuted block randomization with separate randomization schedules generated for each clinical site. Random block sizes of 3 and 6 within sites will be used to maintain the 2:1 randomization allocation. Randomization will occur after implantation surgery and before the

Week 2 follow-up visit. Subjects and investigators will be informed of the subjects' group assignment by the Week 2 follow-up visit.

6.6.1 Treatment Group

The Treatment Group will be implanted with the aura6000 System and have stimulation therapy turned ON at the Month 1 follow-up visit and will continue to have stimulation therapy turned ON for the duration of the study.

6.6.2 Control Group

The Control Group will be implanted with the aura6000 System and stimulation therapy will be delayed (remain OFF) through the Month 4 follow-up visit. Prior to the Month 4 follow-up visit, subjects in the Control Group may use treatment-as-usual, (i.e. any non-PAP, non-surgical OSA treatment including oral appliances and positional devices being used prior to enrollment in the study)until 14 days (washout period) prior to the Month 4 visit. At the Month 4+1 day follow-up visit, subjects in the Control Group will have stimulation therapy turned ON for the duration of the study.

6.6.2.1 Control Group Justification

Randomization to the therapy OFF Control Group ensures that causal inferences about effectiveness of the therapy can be made. Data from the Control Group are used to address the study's primary effectiveness endpoints as well as the primary safety endpoint. The randomized comparison between aura6000 therapy ON (Treatment Group) and therapy OFF (Control Group) isolates the risks associated with stimulation therapy. The Control Group also contributes to the estimate of procedure and device-related adverse events.

A randomized trial design effectively controls for both known and unknown baseline factors that may affect subjects' change in severity of obstructive sleep apnea (selection bias) and provides an unbiased estimate of treatment effect size. Importantly, subjects in either the Treatment or Control Groups may make lifestyle changes during the course of the study that affect their weight and physical fitness, and randomization controls for such important confounders as the baseline propensity for lifestyle changes. The presence of a Control Group also allows for a comparison of confounding outcomes such as weight loss. The randomized design enhances the scientific soundness of the study and helps to ensure the study objectives are met in a timely and efficient manner (minimizes loss to follow-up, maximizes subject recruitment).

Subjects' risk to participation in the study, both the Treatment and Control subjects, has been minimized to as low as possible. Control Group subjects may use treatment-as-usual (any non-PAP, non-surgical OSA treatments being used prior to enrollment in the study) throughout the 4 month therapy OFF period, except during the 14 day washout period preceding the Month 4 Endpoint PSG. Fourteen days is an adequate duration to washout the effects of non-surgical therapies. The risks to subjects are acceptable and are balanced by the potential benefits to subjects of aura6000 therapy.

Societal risk is not increased by the use of a therapy OFF Control Group. The study specifically excludes individuals that have an occupation for which untreated OSA presents a substantial risk to safety, and the Control Group may use treatment-as-usual (i.e. any non-PAP, non-surgical OSA therapy being used prior to enrollment in the study) until 14 days prior to the Month 4 visit.

The clinical need for alternative OSA therapeutic modalities indicates there is sufficient ethical justification to study the effectiveness of aura6000 therapy. Given that the effectiveness of the therapy is not yet proven, and that the Control Group may use treatment-as-usual (i.e any non-PAP, non-surgical OSA therapy being used prior to enrollment in the study) until 14 days prior to the Month 4 visit, there is no added ethical concern for the Control Group above and beyond that of a Treatment Group.

6.6.3 Blinding

Subjects and investigators in the study will not be blinded to treatment assignment. Due to the sensation of stimulation and the requirement for both therapy titration and recharging of the device, blinding of subjects and investigators is not possible. The CEC will be blinded to randomization allocation through the Month 4 visit.

The core lab will not be blinded to treatment assignment. It is not possible to blind this information as the aura6000 stimulation artifact is visible on one or more channels of the PSG montage. To minimize bias in the ascertainment of the primary effectiveness endpoints, PSG studies will have identifying information removed relating to reason for the sleep study.

Lack of blinding does not affect the primary safety endpoints as all adverse events will be reported, and procedures for reporting adverse events are the same in both groups. In addition, both groups have exposure to the same surgical procedure and therapy. Effectiveness endpoints are based on results of polysomnography (PSG), which is an objective measurement and not based on subjects' self-reports of symptoms or improvements. Scoring of PSGs has an element of subjectivity in the evaluation of obstructive sleep apnea events. However, standard guidelines for counting apneas and hypopneas are being used, and an independent core lab, will derive all PSG measures. The core lab will be blinded to the randomization assignment. This will minimize any investigator bias in the evaluation of the Month 4 and Month 12 effectiveness endpoints. Finally, the pre-specified analysis plan for the study eliminates any endpoint ascertainment bias that could be introduced if the selection of analysis methods or decisions about the inclusion of subjects' data in the analysis could be influenced by knowledge of subjects' group assignment.

6.7 Study Inclusion/Exclusion Criteria

Patients will be screened in conformance with the inclusion/exclusion criteria. The Investigator is responsible for screening all patients to determine the appropriateness of enrollment in the study, with the exception of criteria based on the Screening PSGs which will be assessed by the PSG Core Lab.

6.7.1 Inclusion Criteria

Candidates who meet all of the following criteria may be given consideration for inclusion in this clinical investigation:

1. Willing and capable of providing informed consent
2. Willing and capable of receiving the implant and utilizing the remote control and charger to activate the therapy and charge the implant
3. Willing and capable of returning for all follow-up evaluations and sleep studies
4. Willing and capable of completing all questionnaires
5. Is ≥ 18 years old
6. Has failed or does not tolerate PAP therapy
7. Has failed, refuses or is not indicated for alternative OSA treatments (e.g. surgery, oral appliances, and behavioral treatments)
8. AHI ≥ 20 (moderate to severe OSA) based on in-lab polysomnography studies conducted no more than 45 days prior to aura6000 system implantation

6.7.2 Exclusion criteria

The subject must not meet any of the following exclusion criteria:

General

1. Implanted with another active implantable device.
2. Actively enrolled in a clinical study of a different medical device or drug.

Concomitant Medications

3. Taking opioids, narcotics, medications or supplements that in the opinion of the investigator may alter consciousness, the pattern of respiration, sleep architecture, or with known effect on sleep-wake function or alertness.

Medical History

4. Currently receiving treatment for severe cardiac valvular dysfunction, NYHA Class III or IV heart failure, unstable angina or recent (< 6 month) myocardial infarction or cardiac arrhythmias.
5. Moderate to severe pulmonary hypertension defined as WHO Group II or higher.
6. Persistent uncontrolled hypertension (defined as systolic pressure ≥160 mm Hg or a diastolic pressure of ≥ 100 mm Hg) despite medications.
7. Neurodegenerative disorders or intrinsic neuromuscular disease or other neurologic deficits (e.g., multiple sclerosis, muscular dystrophy, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy, transient ischemic attack or cerebrovascular accident).
8. Active psychiatric disease (psychotic illness, major depression or acute anxiety attacks) that in the opinion of the investigator could prevent subject compliance with the requirements of the investigational study testing
9. Previous upper respiratory tract (URT) surgery (e.g., uvula, soft palate or tonsils) < 60 days prior to Screening PSG #1
10. Chronic obstructive pulmonary disease (FEV1 : FVC ratio < 70) or vital capacity of < 80% predicted)

11. Active history of pulmonary disease (including COPD, emphysema, and asthma)
12. Need for chronic supplemental oxygen therapy for any reason, PaO2 < 70 mm Hg
13. Other sleep disorders that confound functional assessments of sleepiness, such as narcolepsy with cataplexy, idiopathic hypersomnolence, insomnia, REM sleep behavior disorder, or sleep movement disorders, such as restless leg syndrome or periodic limb movement, producing sleep disturbances unrelated to OSA.

Lifestyle / Work

14. Excessive use of alcohol, tobacco, caffeine, or recreational drugs.
15. Unwilling or unable to refrain from consumption of alcoholic beverages for 24 hours prior to the start of each PSG study
16. Unwilling or unable to refrain from use of PAP, oral appliances for OSA, positional devices, OSA surgery, or medications for OSA from enrollment through the completion of the Month 12 follow-up visit (except as permitted in the Control Group).
17. Subject has sleep hygiene behavior(s) that would substantially interfere with measurement outcomes during an overnight PSG study
18. Subject has an occupation for which untreated OSA presents a substantial risk to safety
19. Presence of occupational (shift work) or anticipation of shift changes (during the next two years)
20. Residing at, or planning to move within 2 years to a location where the subject would no longer be willing or capable of returning for all follow-up evaluations and sleep studies.

Physical Exam

21. BMI ≥ 35 kg/m2
22. Active systemic infection
23. Pedal edema grade ≥ 2+
24. Clinical evidence of renal insufficiency, acute or chronic renal failure, or undergoing dialysis or expected to institute dialysis within 6 months
25. Clinical evidence of immunodeficiency
26. Life expectancy of < 2 years
27. Any condition likely to require future MRI, diathermy or other procedure producing strong RF fields
28. Pregnant or planning to become pregnant in the next year (must have a negative serum or urine pregnancy test within 14 days prior to implant and maintain adequate contraception during the study)
29. Any reason for which, in the judgment of the investigator, the subject is considered to be a poor surgical or study candidate, which may include, but is not limited to: any medical, social, or psychological problems that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study

Upper Airway Exam

30. Tonsil grading system 3 and 4
31. Lingual Tonsil Hypertrophy Grading System (LTH) 3 and 4.

32. Friedman Tongue Position (FTP) IV
33. Hypoglossal nerve palsy (limited tongue movement or inability to move the tongue), tongue dysfunction, atrophy, hypertrophy, fasciculation, or problems swallowing or speaking.

Surgical Consult

34. Rhinitis or nasal obstruction that is not well-controlled by medication or prior surgery
35. Severe mandibular deficiency/retrognathia or syndromic craniofacial abnormalities.
36. Prior surgery interfering with surgical exposure or implant safety
37. Previous surgical resection or radiation therapy for cancer or congenital malformations in the larynx, tongue, or throat.
38. ASA Status ≥ 4
39. Subject has torticollis or neck or facial spasm that could increase the risk of dislodgement
40. Any reason for which, in the judgment of the investigator, the subject is considered to be a poor surgical or study candidate, which may include, but is not limited to: any medical, anatomical, social, or psychological problems that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study

PSG Criteria

41. AHI ≥ 65 on Screening PSGs
42. Apnea Index (AI) > 30 events per hour on Screening PSGs
43. SaO2 >10% falls index > 15 events per hour on Screening PSGs
44. ≥ 10% central apnea events as a proportion of the sum of apnea and hypopnea events per hour on Screening PSGs
45. Positional OSA as defined by: non-supine AHI < 10 on Screening PSGs
46. Predominantly REM OSA as defined by: non-REM AHI < 20 and > 50% difference in AHI between the REM and non-REM sleep on Screening PSGs
47. Evidence of Cheyne-Stokes breathing.

6.7.3 Inclusion and Exclusion Criteria Assessed by Polysomnography (PSG)

Among the above listed inclusion and exclusion criteria are a number of criteria that require assessment by overnight PSG sleep studies. Following informed consent and prior to the aura6000 System implant, each subject will undergo two pre-implant Screening PSG studies.

The Screening PSGs must be conducted within 14 days of each other, and the final Screening PSG must be conducted no more than 45 days prior to aura6000 System implantation.

The pre-implant screening PSG studies will be scored by an independent core laboratory.

Subjects that fail to meet the AHI inclusion/exclusion criteria, and central apnea, AI and SaO2 falls exclusion criteria in both Screening PSGs will be excluded. The core laboratory determination will be communicated to the sponsor and the investigator.

6.7.4 Determination of Baseline PSG Score

The scores of the two pre-implant Screening PSG studies will be averaged to generate the Baseline PSG score.

6.8 Subject Recruitment

It is the responsibility of site personnel to ensure adequate recruitment into the study. Potential study subjects will be sought from a variety of sources, which will be different from site to site depending on capabilities and resources. Site personnel will be required to track recruiting and screening efforts on a per patient basis and will be required to submit this information to the Sponsor at regular intervals during the screening and enrollment phase.

6.9 Subject Enrollment

Enrollment will commence only after the study has received IDE approval from the FDA, and local IRB/EC approval.

An individual will be considered enrolled in the study after the individual has signed the informed consent. If, after signing the informed consent form, it is determined via specified testing that the individual does not meet all the inclusion and exclusion criteria, the individual will not be implanted, and exited from the study. The specific inclusion and/or exclusion criteria that were not met, or the reason that the individual was exited will be documented.

No one investigative site shall randomize more than 15% of the total randomized subjects in the study.

Subjects will be randomized following the implantation of their first complete aura6000 system (IPG and Lead) in accordance with the randomization plan. If an enrolled subject is not randomized for any reason, the subject will be exited from the study and replaced to allow for randomization of 141 randomized subjects. The specific reason that the individual was exited will be documented.

If for any reason a subject undergoes an attempted surgery to implant the aura6000 System, but is not subsequently implanted with the full system for any reason, that subject will not be randomized but will be followed up at one week and one month following surgery for safety only. The subject will be exited from the study and replaced to allow for randomization of 141 subjects. The event of undergoing anesthesia and not receiving the implant will be recorded as an adverse event and counted in the intent-to-treat population.

6.10 Primary Endpoints

6.10.1 Primary Safety Endpoints

The primary safety endpoint is:

- Estimate the incidence of adverse events related to the aura6000 System implant procedure or device through 365 days post implantation, including any unanticipated adverse device effects.

6.10.2 Primary Effectiveness Endpoints

6.10.2.1 Co-primary Effectiveness Endpoint #1

The first co-primary effectiveness endpoint is the proportion of subjects that experience clinically meaningful improvements at Month 4 compared to Baseline in the apnea-hypopnea index (AHI) as defined below (AHI responder rate). An AHI responder is a subject that has:

- An AHI ≤ 20 and ≥ 50% reduction in AHI

It is hypothesized that the observed AHI responder rate (as defined above) in the Treatment Group will be significantly greater than the AHI responder rate in the Control Group at 4 months post implant of the aura6000 System.

The apnea hypopnea index (AHI) is the current gold standard for assessment of obstructive sleep apnea severity. The AHI responder definition is based on published sleep medicine literature that have evaluated alternative therapies for OSA, such as surgery.

6.10.2.2 Co-primary Effectiveness Endpoint #2

The second primary effectiveness endpoint is the proportion of subjects that experience clinically meaningful improvements at Month 4 compared to Baseline in oxygen desaturation index (4%) (ODI 4%) as defined below (responder rate). A responder is a subject that has:

- A ≥ 25% reduction in ODI 4%

It is hypothesized that the observed ODI responder rate (as defined above) in the Treatment Group will be significantly greater than the ODI responder rate in the Control Group at Month 4 post implant of the aura6000 System.

The ODI responder definition is based on ODI 4% which has been independently associated with risk of cardiovascular disease (Punjabi 2008).

6.10.2.3 Co-primary Effectiveness Endpoint #3

The third co-primary effectiveness endpoint is the proportion of subjects in the Treatment Group that experience clinically meaningful long-term improvements at Month 12 compared to Baseline in the apnea hypopnea index as defined above (AHI responder rate), i.e. the "Long-term AHI responder rate".

It is hypothesized that the observed Long-term AHI responder rate (as defined above) in the Treatment Group will be significantly greater than 45% at 12 months post implant of the aura6000 System.

6.10.2.4 Co-primary Effectiveness Endpoint #4

The fourth co-primary effectiveness endpoint is the proportion of subjects in the Treatment Group that experience clinically meaningful long-term improvements at Month 12 compared to Baseline in the oxygen desaturation index as defined above (ODI responder rate), i.e. the "Long-term ODI responder rate".

It is hypothesized that the observed Long-term ODI responder rate (as defined above) in the Treatment Group will be significantly greater than 45% at 12 months post implant of the aura6000 System.

6.11 Secondary Endpoints

6.11.1 Secondary Effectiveness Endpoints

Four pre-specified secondary effectiveness endpoints were identified in planning the study sample size to ensure that these endpoints can be analyzed statistically with sufficient Type 1 (alpha < 0.05) and Type 2 (beta < 0.20) error control.

6.11.1.1 Epworth Sleepiness Scale (ESS)

The ESS is a validated, self-report instrument that rates a subject's tendency to fall asleep in eight common daily situations.

The change in ESS scores from Baseline to Month 4 will be compared between groups. It is hypothesized that the improvement in the Treatment Group will be significantly greater than the improvement in the Control Group at 4 months post implant of the aura6000 System.

6.11.1.2 Functional Outcomes of Sleep (FOSQ)

The FOSQ is a quality of life questionnaire specifically designed to evaluate the impact of excessive sleepiness disorders on activities of daily living, such as activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcomes.

The change in FOSQ scores from Baseline to Month 4 will be compared between groups. It is hypothesized that the improvement in the Treatment Group will be significantly greater than the improvement in the Control Group at 4 months post implant of the aura6000 System.

6.11.1.3 EuroQol 5D (EQ-5D)

The EQ-5D is a standardized measure of general health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal.

The change in EQ-5D scores from Baseline to Month 4 will be compared between groups. It is hypothesized that the improvement in the Treatment Group will be significantly greater than the improvement in the Control Group at 4 months post implant of the aura6000 System.

6.11.1.4 Additional Ancillary Data Collection

The following pre-specified ancillary analyses will be performed. Variables assessed will be tabulated and summarized with appropriate descriptive statistics as described in Section 10.1. Data will be presented at each follow-up time point and by randomized group as appropriate.

- Utilization of therapy: hours per night, percent of nights used
- OSA Severity Shift (Mild, Moderate, Severe) – shift in proportion of subjects in each category
- Arousal Index (number of EEG arousals per hour slept)
- Blood Pressure
- Pulse Transit Time (PTT) and Pulse Wave Velocity (PWV)
- Sleep Architecture measures, e.g. Sleep Stages, Sleep latency, Sleep Efficiency
- Incidence of new onset co-morbidities: hypertension, cardiovascular disease, stroke, obesity/weight, type 2 diabetes
- Subgroup analyses of primary and secondary endpoints: subgroups based on gender, baseline OSA severity, BMI, prior palate surgery, investigational site
- Therapy effect on snoring through patient reported survey
- Subject Satisfaction with therapy
- Follow-up visit necessity

6.11.2 Definitions of AHI and ODI 4% for Baseline and Endpoints

The following definitions will be used to document AHI and ODI 4% for Baseline and Endpoint PSGs.

Apnea-hypopnea index (AHI) is the number of apnea and hypopnea events per hour of sleep. Apnea and hypopnea events are defined by the AASM 2007 Recommended criteria:

- Apnea is defined as a drop of thermistor sensor signal amplitude by ≥ 90% of baseline and lasting for 10 seconds or more.
- Hypopnea is defined as a decrease in nasal pressure signal amplitude (flow) by ≥ 30% of baseline and lasting for at least 10 seconds with a ≥ 4% desaturation from pre-event baseline.

Oxygen desaturation index 4% (ODI 4%) is defined as the number of oxygen desaturations per hour of sleep that are ≥ 4% as measured by pulse oximetry with a maximum acceptable signal averaging time of three (3) seconds.

Reference: Iber C, Ancoli-Israel S, Chesson A, Quan S; for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.

6.12 Sample Size

The overall sample size for the study is driven by the third and fourth primary effectiveness endpoints for the Treatment Group, and the first and second primary effectiveness endpoints for the Control Group. Sample size was estimated using SAS Version 9.3. The planned total sample size for the study is 141 implanted subjects randomized in a 2:1 ratio (94 Treatment : 47 Control).

The minimum required sample size of the Treatment Group was computed under the following assumptions:

- 85% power
- One-sided 0.025 alpha
- Expected Treatment Group responder rate at Month 12: 62.5%
- Performance Goal of 45%
- 15% loss to follow up at Month 12

Under these assumptions, 79 evaluable Treatment Group subjects will provide at least 85% power for the first secondary effectiveness endpoint. Randomizing 94 subjects to the Treatment Group will result in at least 80 evaluable subjects at attrition rates up to 15% at Month 12.

The minimum required sample size of the Control Group was computed under the following assumptions:

- 85% power
- One-sided 0.025 alpha
- Expected Treatment Group responder rate at Month 4: 67.5%
- Expected Control Group responder rate at Month 4: 35.0%
- 10% loss to follow up at Month 4

Under these assumptions, 108 evaluable subjects (72 Treatment: 36 Control) will provide at least 85% power for the primary effectiveness endpoints. Randomizing 47 subjects to the Control Group will result in at least 42 evaluable subjects at attrition rates up to 10% at Month 4.

At the assumed responder rates and attrition rates, 141 subjects is estimated to provide greater than 80% power overall to demonstrate a statistically significant result at the 0.025 alpha level. This sample size is estimated to provide adequate power for the four secondary endpoints.

The expected treatment responder rate at Month 12 is based on data observed from the THN1 and THN2 feasibility studies. Among the feasibility subjects meeting similar inclusion/exclusion criteria for this study, the observed rates in THN1 and THN2 were 77% and 89%, respectively. These estimates are based on smaller sample sizes than the study, however a responder rate of 62.5% is considered a conservative, clinically meaningful responder rate that accounts for variability around the estimates from THN1 and THN2.

6.13 Adverse Event Reporting

Any adverse event (AE) that occurs between the time a subject is enrolled in the study and the time the subject departs the study after the Month 60 follow-up visit will be captured and recorded. All AEs will be recorded in the participant's medical records and/or other source documents. The occurrence of all adverse events will be reviewed at each scheduled and unscheduled follow-up visit with the subject. AEs will be followed in a timely manner by the investigator to resolution. An independent Clinical Events Committee will review, adjudicate, and categorize all adverse events. Events will be reported as:

- All Non-serious Adverse Events
  - Related to the Procedure
  - Related to the Device
  - Unrelated to the Device or Procedure
- All Serious Adverse Events
  - Related to the Procedure
  - Related to the Device
  - Unrelated to the Device or Procedure
- Unanticipated Adverse Device Effects

6.14 Flow of Subjects From Enrollment through Completion

The flow of subjects through the study from enrollment to completion of the 5-year follow-up visit is shown in Figure 7.

Subjects who have signed an informed consent form will undergo screening. Screening consists of 4 main parts: medical screening (medical history and physical examination), surgical consultation, upper airway exam with endoscopy, and screening PSGs.

Subjects who meet all inclusion/exclusion criteria via specified testing will continue on to be implanted. If, after signing the informed consent form, it is determined that the subject does not meet all the inclusion and exclusion criteria, the screening will be terminated and the specific inclusion and/or exclusion criteria that were not met, or the reason that the subject was not implanted will be documented.

Randomized subjects will continue through the schedule of study assessments according to their randomized group.

6.15 Schedule of Study Assessments and Procedures

An overview of the schedule of required assessments and procedures that must be completed at each study visit is presented in Table 8 and Table 9. Each study visit must be completed within a specified window of time. Corresponding data for each visit must be reported on appropriate study case report forms.

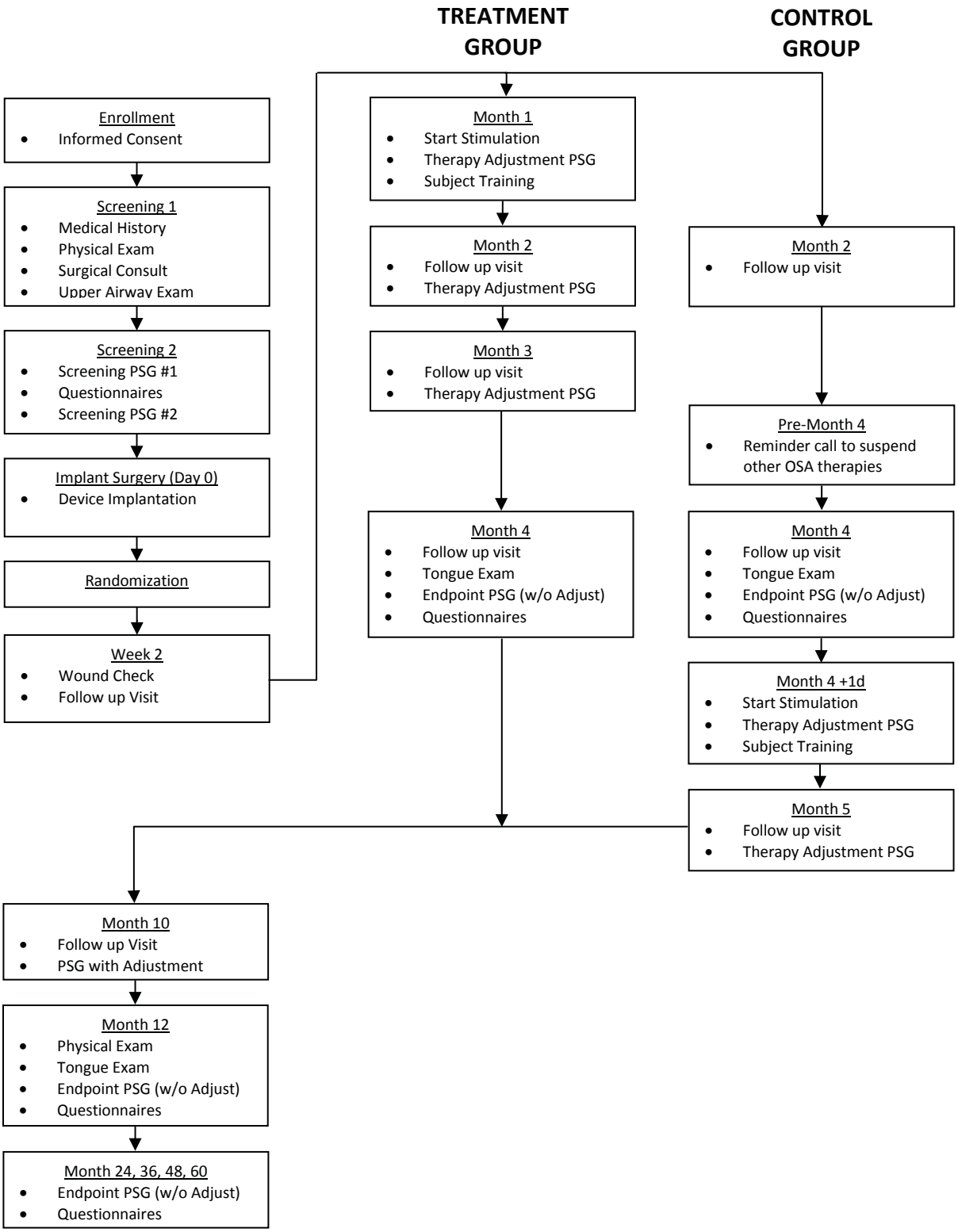


Figure 7: Study Flowchart

	All Subjects								
	Enroll	**Medical Screening**	**Surgical Consult**	**Up. airway exam**	**Screening PSG1**	**Screening PSG2**	**Implant**	**Random-ization**	**Week 2**
Visit Window (days post-implant)		**Prior to PSGs**			**≤ 14 days prior to PSG#2**	**≤ 45 days prior to implant**	**Day 0**	**Day 0 to Week 2**	**Day 7 – 14**
Informed Consent	X								
Inclusion / Exclusion		X	X	X	X	X			
Medical History		X							
Physical Exam		X							
Vital Signs		X			X	X	X		X
Concomitant Meds		X			X	X	X		X
Adverse Events		X			X	X	X		X
Surgical Consultation			X						
Upper Airway Exam				X					
Screening PSG #1					X				
Screening PSG #2						X			
ESS						X			
FOSQ						X			
EQ-5D						X			
Snoring Survey						X			
Urine Pregnancy Test							X		
Implant Surgery							X		
Randomization								X	
Wound Check									X

Table 8: Required Assessments and Procedures –Part 1

	Treatment Group				Control Group				All Subjects		
	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 2**	**Month 4**	**Month 4 +1d**	**Month 5**	**Month 10**	**Month 12**	**Month 24, 36, 48, 60**
Visit Window (days post-implant)	**25-35 days**	**50-70 days**	**80-100 days**	**110 - 130 days**	**50-70 days**	**110-130 days**	**1-15 days after M4**	**140-160 days**	**285–325 days**	**350-375 days**	**± 30 days**
Physical Exam										X	
Tongue Exam				X		X				X	
Vital Signs	X	X	X	X	X	X		X	X	X	X
Concomitant Meds	X	X	X	X	X	X		X	X	X	X
Adverse Events	X	X	X	X	X	X		X	X	X	X
Therapy Initiation	X						X				
Subject Training	X						X				
Therapy Adjust. PSG	X	X	X				X	X	X		
Endpoint PSG				X		X				X	X
Device Interrogation									X	X	X
ESS				X		X				X	X
FOSQ				X		X				X	X
EQ-5D				X		X				X	X
Snoring Survey				X		X				X	X
Subject Satisfaction Survey				X						X	X

Table 9: Required Assessments and Procedures, Part 2

6.16 Description of Assessments

Assessments conducted at the study visits are described in this section.

6.16.1 Medical History

At the first Screening visit, the investigator will review and document the subject's general medical history and current known conditions to help determine eligibility for the study. It is recommended that the subjects provide a recent history and physical documentation from their primary care or other provider. Complete medical history will include history of disease (major past diseases as well as all current conditions) and treatment, current symptoms, current medications, known drug allergies, and an assessment of allergy, cardiovascular, neurologic, psychiatric, respiratory, and surgical history. Demographics and medical insurance information will also be collected.

6.16.1.1 OSA and Respiratory History

As part of the medical history, the following OSA and respiratory history information will also be collected:

- Subject-reported date of first OSA symptoms observed
- Subject-reported date of first PSG and reported AHI
- Factors that exacerbate OSA for each subject
- OSA treatment history, past and current
- Sleep hygiene
- Inventory of OSA comorbidities
- History of any pulmonary disease (e.g. COPD, emphysema, asthma)
- Need for chronic supplemental oxygen

6.16.1.2 Lifestyle and Work Status

As part of the medical history, the following information will also be collected:

- Use of alcohol, tobacco and recreational drugs
- Subject occupation and occupation plans
- Subject plans for changing residence, or pregnancy

6.16.2 Physical Examination

A complete physical examination will include an assessment of the abdomen, ears, nose, throat, mouth, tongue, lymph nodes, extremities, eyes, head and neck (including thyroid), heart, lungs, musculoskeletal, neurologic (reflexes), skin, and other applicable system(s). The data collected and recorded on the case report form from the physical examination will include whether the body system has any abnormalities and, if so, a description of the abnormalities.

6.16.3 Follow Up Visits

A follow up visits consist of collecting vital signs, documenting concomitant medication and assessing adverse events.

6.16.3.1 Vital Signs

Vital signs required to be collected will include heart rate, weight, height, and blood pressure. These measurements will be assessed as noted below:

- Heart Rate – heart rate will be measured one time after the subject has been seated for at least five (5) minutes.
- Weight – body weight will be measured using the clinic's balances or electronic scales.
- Height – body height will be measured without shoes using the clinic's routinely used stadiometer. Height will only be measured at the medical screening visit.
- Blood pressure – Blood pressure measurements will be measured one time after the subject has been seated for at least five (5) minutes. BP will be measured at each clinic follow-up, scheduled or unscheduled.

6.16.3.2 Concomitant Medications

It is required that the subject's medication usage be provided and documented at Screening and throughout the study. This includes all prescription and over-the-counter drugs and supplements taken by the subject in the relevant time period. Emphasis is given to medications that affect sleep or may affect other endpoints being evaluated in the trial as noted in the categories below:

- Antidepressants
- Antiarrhythmics
- Sedating antihistamines
- Medications containing caffeine
- Medications containing alcohol
- Sedative/Hypnotics
- Hypertension Medications
- Corticosteroids
- Nicotine patches
- Sympathomimetic stimulants
- Theophylline
- Thyroid hormones
- Any Other Medications

At the Screening evaluation, the generic and brand name, start date, and dosage of all prescribed or over-the-counter medications that the subject is currently taking will be recorded according to category on the appropriate study case report form. If any such medications are

started or stopped during the course of the study, those medications and the start/stop dates will also be recorded.

6.16.3.3 Assessment of Adverse Events

At each visit the site personnel will assess if any adverse events have occurred. Adverse events may be detected through a conversation with the subject or a family member, examination of the subject, coordinator telephone follow-up, changes in therapy, notification of hospitalization or physician visit, or medication change, etc. All adverse events will be recorded in the subject's medical record and/or other source document and reported on the appropriate case report form(s).

6.16.4 Surgical Consultation

During the surgical consultation, the subject meets with the surgeon to discuss the implantation surgery. A review is conducted of the subject's previous and current surgeries and procedures. The surgeon also assesses the subject medical, anatomical, social, and psychological status.

6.16.5 Upper Airway Examination

An investigator will evaluate the subject's tonsil size, tongue function, tongue position, upper airway anatomy, and lingual tonsils (using endoscopy) at the visit.

6.16.5.1 Tonsil Size

Tonsil size will be assessed and will be classified according to the Tonsil Grading System as follows (Brodsky L 1989). Patients who have Size 3 or Size 4 tonsils according to the Tonsillar Grading System are excluded from participation in the study. Figure 8: Tonsillar Grading Scale illustrates each of the classifications of tonsil size.

- Size 0, tonsils absent (including previous tonsillectomy)
- Size 1, tonsils within the pillars.
- Size 2, tonsils extend to the pillars.
- Size 3, tonsils extend past the pillars.
- Size 4, tonsils extend to the midline.

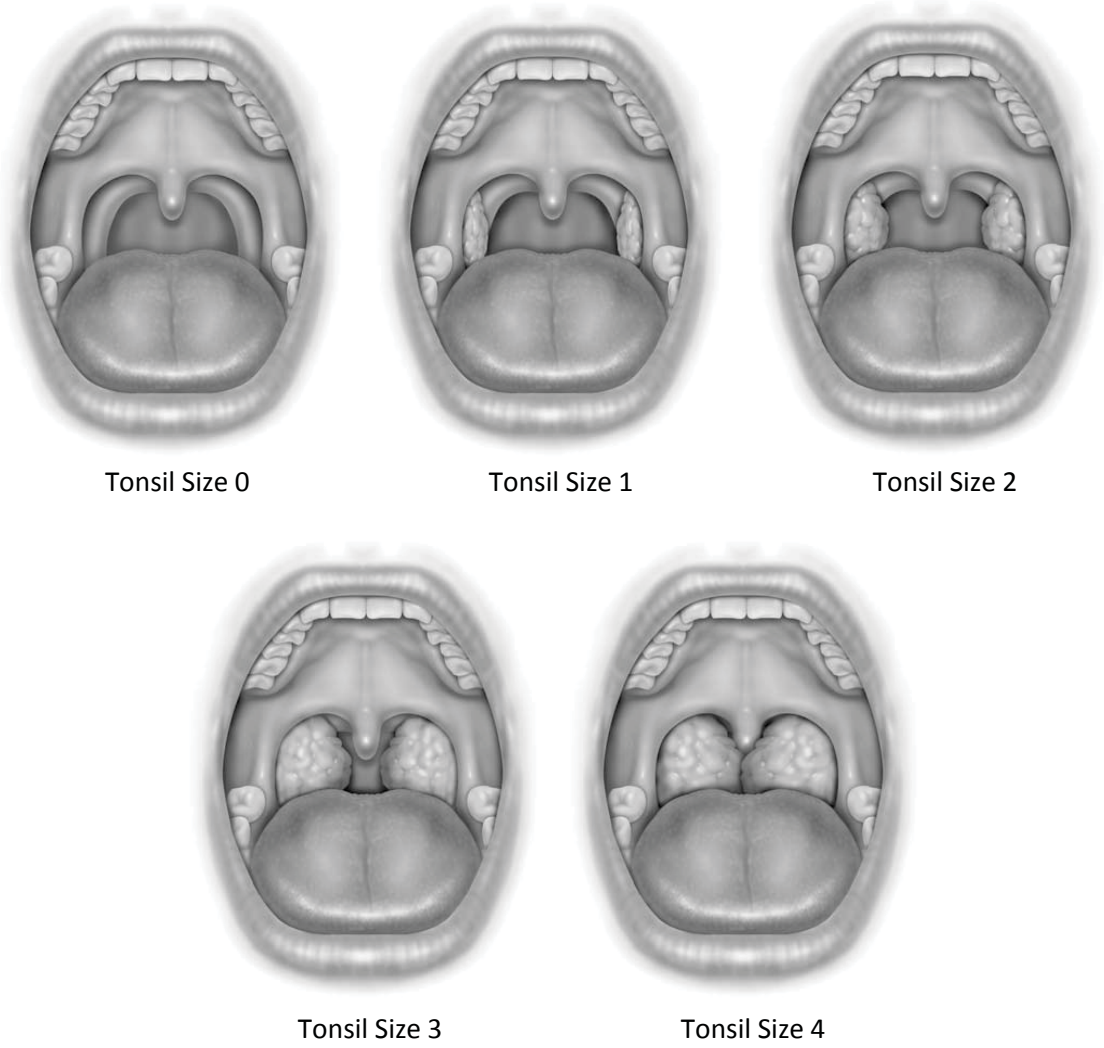


Figure 8: Tonsillar Grading Scale

6.16.5.2 Clinical Assessment of Tongue Function

A clinical assessment of the tongue function will be completed during the screening phase. This will include assessment of presence (with characterization) or absence of the following with the tongue protruded in a central position:

1. tongue abnormalities
2. pain
3. numbness

A functional tongue assessment should evaluate the following:

1. Tongue movements to the left and right
2. Difficulty/alteration in swallowing, e.g. a glass of water
3. Difficulty/alteration in speech, e.g. clear spelling of words with lingual consonants such as T, D, J, and G

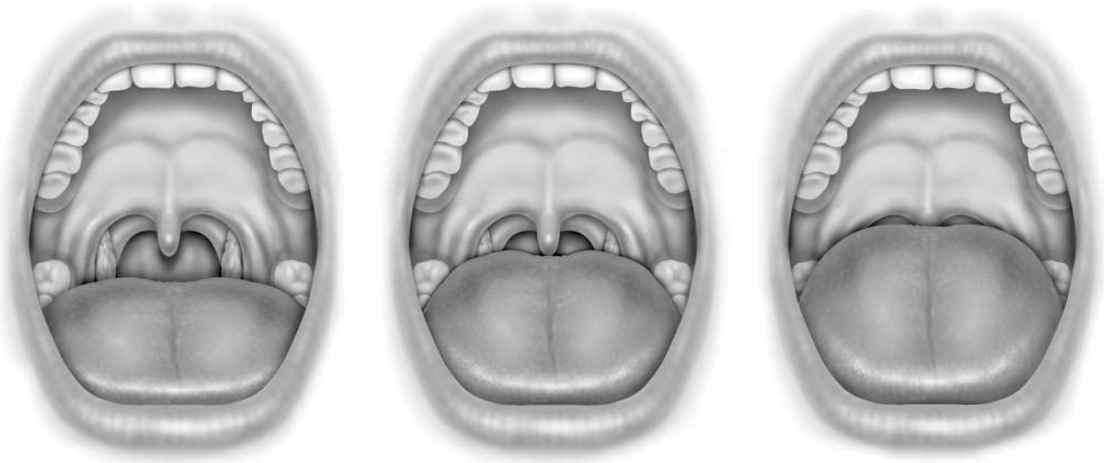
6.16.5.3 Friedman Tongue Position

Tongue position will be assessed and will be classified according to the Friedman Tongue Position (FTP) as follows. The FTP was previously called Friedman Palate Position (Friedman 2004). Subjects who have a FTP III or FTP IV are excluded from participation in the study. Figure 9 illustrates each of the classifications of tongue position.

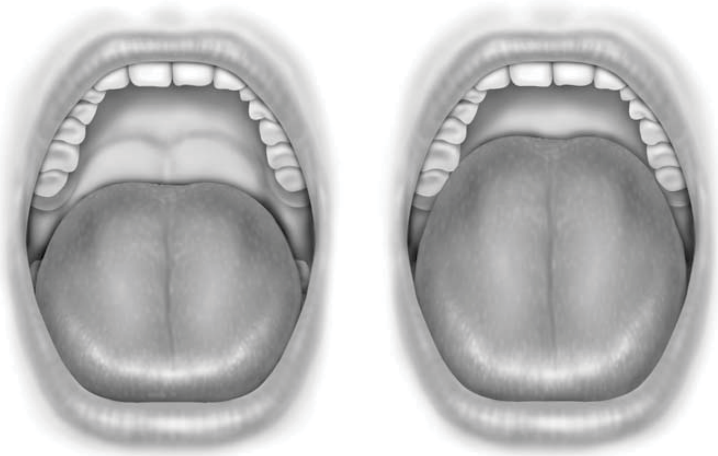
- FTP I visualizes uvula and tonsils/pillar
- FTP IIa visualizes most of uvula, no tonsils/pillar
- FTP IIb visualizes entire soft palate to uvula base
- FTP III shows some of soft palate with absent distal end
- FTP IV visualizes only the hard palate

The FTP shall be documented photographically. This requires 2 photos: one with the tongue in neutral position(in mouth); and one with the tongue depressed to show the soft palate and tonsils.

The FTP will be scored by the site and by an independent otolaryngologist reviewer. If either score meets the exclusion criteria, the subject will be exited from the study.



FTP I FTP IIa FTP IIb



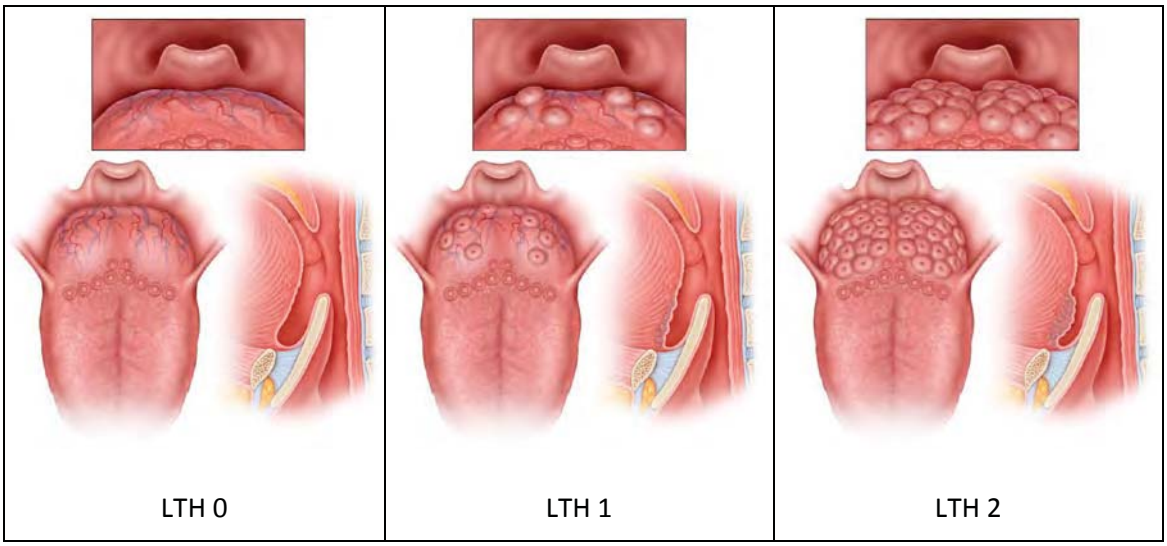
FTP III FTP IV

Figure 9: Friedman Tongue Position

6.16.5.4 Lingual tonsils

Oral endoscopy will be used to assess and classify lingual tonsil size according to the Lingual Tonsil Hypertrophy Grading System (LTH) as follows (Friedman M 2014). Patients who have LTH 3 or LTH 4 are excluded from participation in the study. Figure 10 illustrates each of the classifications of lingual tonsil hypertrophy from LTH 0 to LTH 4.

- LTH 0: no lymphoid tissue
- LTH 1: scattered lymphoid tissue
- LTH 2: covering entire tongue base, limited vertical thickness
- LTH 3: entirety of tongue base, significant vertical thickness approximately 5-10 mm
- LTH 4: entire tongue base, rising to or above tip of epiglottis, approximately 1 cm in height



LTH 0 LTH 1 LTH 2

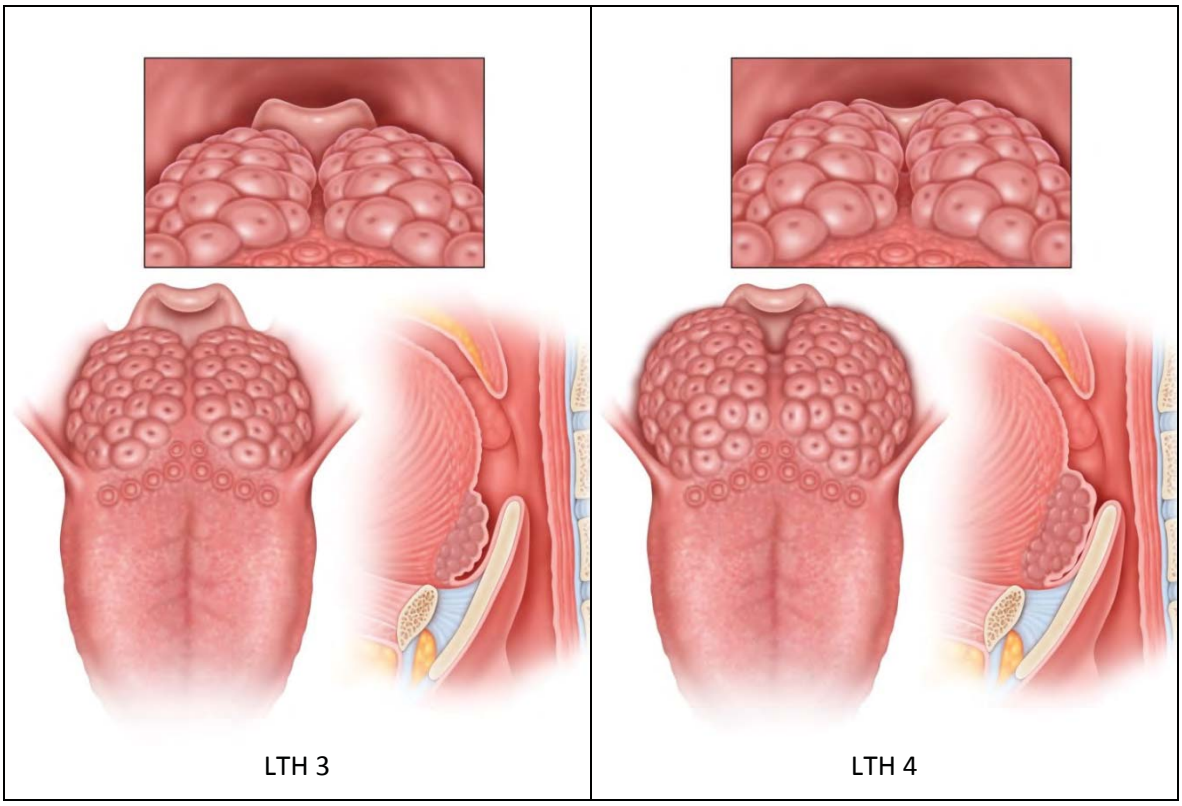


Figure 10: Lingual Tonsil Hypertrophy Grading Scale

6.16.6 Pregnancy Test

For women of child bearing potential, a negative urine or serum pregnancy test must be completed prior to, and within 14 days of surgery. Subjects with a positive pregnancy test cannot be implanted in the study. Female subjects of child bearing potential should use a method of contraception agreed upon with the investigator for the first 12 months of the study.

6.16.7 PSG Studies

6.16.7.1 Screening PSG Studies

The Screening PSG studies used for inclusion into the study are expected to be two overnight sessions within 14 nights of each other but may include repeat nights if neither PSG provides sufficient data to assess the subject's eligibility. The final Screening PSG must occur within 45 days of the implantation of the aura6000 system.

Subjects using any other OSA therapy must be instructed to discontinue and complete a 14 day washout period prior to any Screening PSG study.

6.16.7.2 Therapy Adjustment PSG (PSG with Adjustment)

Therapy Adjustment PSGs are described below in the aura6000 Programming and Therapy Titration section.

6.16.7.3 Endpoint PSG (PSG without Adjustment)

Endpoint PSG studies are performed at Month 4, Month 12, and annually thereafter until Month 60 for all subjects.

Endpoint PSGs are expected to be one overnight session but may include repeat nights if the PSG does not capture the required endpoint data. Clinician-programmed therapy settings must remain constant for 7 days prior to any Endpoint PSG study. If therapy settings are re-programmed within 7 days of an Endpoint PSG study, the Endpoint PSG study must be rescheduled.

It is expected that study subjects with stimulation therapy ON will not be using alternative or concomitant OSA therapies prior to any Endpoint PSG. Study subjects will be instructed to not use any alternative or concomitant OSA therapy during the 14 days prior to any Endpoint PSG. At each follow-up visit, subjects will be asked if they used alternative or concomitant therapies and, if so, the reason and extent of the use. If a subject does utilize an alternative or concomitant therapy, it is required that they discontinue that therapy for 14 days prior to any Endpoint PSG study. Therapy adjustments will not be permitted during the Endpoint PSGs.

6.16.7.4 PSG Montage

While the specific technical requirements for PSG recordings will be defined by the PSG Core Lab, all PSGs should be conducted according to current standards of practice. In general, multiple channels of physiologic data will be collected during each PSG, which must include, at a minimum:

- Electroencephalogram (EEG, C3-M2 or C4-M1)
- Electroencephalogram (EEG, O2-M1 or O1-M2)
- Electroencephalogram (EEG, F3-M2 or F2-M1)
- Electrooculogram (EOG, E1 – M2)
- Electrooculogram (EOG, E2– M2)
- Electromyogram (EMG, chin /submental)
- Electromyogram (EMG, anterior tibialis- LAT, RAT)
- ECG (Lead II – heart rate and arrhythmias, if present)
- Pressure-based nasal airflow signal
- Thermal based oro-nasal airflow signal
- Thoracic effort
- Abdominal effort
- Oxygen saturation
- Body position

All Screening PSG and Endpoint PSG studies must have a total recording time (TRT) as defined by Lights OFF to Lights ON of between six and eight hours (360-480 minutes).

For all Endpoint PSGs except Control Group Month 4, stimulation must be turned on for the duration of the PSG. Endpoint PSG's must have a total stimulation time (TXT) as defined by

Stimulation ON to Stimulation OFF of no less than 5 hours (300 minutes). Screening PSGs and Endpoint PSGs that do not meet these criteria must be repeated.

Additional guidance for conducting PSGs will be provided to the sites as determined by the Core Lab and the Sponsor.

6.16.8 Subject Questionnaires

Subject assessment of daytime sleepiness and the effect of sleepiness on daily activities will be reported via the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ). Subject assessment of their general health status will be reported via the EuroQol (EQ-5D) questionnaire. Subject assessment of snoring severity and subject's satisfaction with aura6000 therapy will be documented via questionnaire.

Study subjects will complete these questionnaires at Screening PSG #2 and all Endpoint visits to serve as a measure against which changes in symptoms can be assessed. The questionnaires may be completed up to 24 hours before or after the corresponding Screening PSG and Endpoint PSGs.

6.16.8.1 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered, eight question survey in which subjects are asked to evaluate their level of sleepiness in various daytime situations. The ESS will take the study subject approximately five minutes to complete.

6.16.8.2 Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a self-administered questionnaire with 30 items designed to assess the impact of OSA on multiple activities of daily living. The FOSQ will take approximately 15 minutes for the subject to complete.

6.16.8.3 EuroQol 5 Dimensional (EQ-5D)

The EQ-5D is a standardized measure of general health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. EQ-5D is designed for self-completion by subjects, and takes approximately five minutes to complete.

6.16.8.4 Snoring Survey

The Snoring Survey is a self-reported measure of snoring severity as reported by the subject and the subject's bed partner. The Snoring Survey will take approximately five minutes for the subject to complete.

6.16.8.5 Subject Satisfaction Survey

This Subject Satisfaction Survey will assess subjects' satisfaction with the aura6000 System. It will take approximately five minutes to complete. The questions will focus on ease of use and overall subject satisfaction.

6.16.9 Device Interrogation

A device interrogation will be performed at the Month 10 and Month 12 PSG visits and the device event log downloaded. The Programming Guide for the aura6000 System describes the procedure for device interrogation.

In addition, as clinically indicated to troubleshoot or document aura6000 System performance, the following may take place:

- Radiographic or other imaging (computed tomography, ultrasound, fluoroscopy or x-ray) via standard institution procedures, to evaluate the location or integrity of the implanted system components
- Oral and/or nasal Endoscopy as clinically indicated

6.16.10 Subject Training

Subject training must occur prior to sending a subject home with the RCC to initiate use of aura6000 therapy. Instruction also may be provided at any visit as needed. Information for subject training is in the aura6000 User's Manual. Subject training consists of a description of the system and its functionality, training on use of the RCC controller, and troubleshooting questions regarding device therapy, charging, etc.

6.16.11 aura6000 Programming and Therapy Titration

6.16.11.1 Overview of Therapy Titration Process

Therapy titration is an iterative process in which the subject becomes accustomed to the sensation of stimulation, and therapy settings are systematically adjusted with the goal of maintaining adequate airway patency to minimize apneas and hypopneas without directly causing discomfort or arousal from sleep. Maximal inspiratory airflow during sleep is used as an acute measure of airway patency (Gold AR 1996, McWhorter AJ, 1999). Therapy settings are systematically evaluated for their effect on respiratory events, airflow and arousal until optimal settings are found. The therapy settings, which result in sufficient airflow and a minimum number of disordered breathing events, without evidence of causing arousal from sleep, are selected as the therapeutic settings.

In-lab sleep titration studies and therapy adjustments are used to adjust therapy settings over time. Following initiation of nighttime use of therapy at home, additional in-lab sleep titration sessions are allowed as needed to guide further therapy adjustments. All programming changes, reason for therapy adjustments, and therapy settings must be documented.

6.16.11.2 Therapy Adjustment Nights

Prior to each therapy adjustment PSG, an awake stimulation will be conducted to generate an initial assessment of the sensory limits, or stimulation amplitude for each contact utilized, beyond which the subject reports that stimulation becomes uncomfortable.

Following the evaluation of sensory limits in wakefulness the subject will undergo an in-lab PSG therapy adjustment night. Hypnotics (such as Ambien® 10mg) may be used as necessary to aid sleep during therapy adjustment nights. During the therapy adjustment night, a range of contacts and amplitude settings will be evaluated at various durations and frequency combinations. Stimulation contacts will be selected for their ability to preserve or improve airflow and/or result in the reduction/elimination of obstructive events without causing arousals. The process is iterative throughout the night and culminates with the selection of optimum settings for therapy at home. Multiple nights may be needed to identify the best set of stimulation parameters.

An ImThera Medical field clinical representative will be present at all therapy adjustment nights to train on-site personnel and provide support to the investigator and sleep technicians performing the PSG, and to assist with troubleshooting any technical problems or with questions that might arise during the visit.

An in-lab therapy adjustment PSG assessment will occur at the Month 1, Month 2, Month 3, and Month 10 follow-up visits for the Treatment Group, and the Month 4+1 day, Month 5, and Month 10 follow-up visit for the Control Group. The results of the therapy adjustment assessment will be used to evaluate the stability of the subject's therapeutic settings, and adjust therapy settings, as needed.

Additional unscheduled therapy adjustment PSG nights may be conducted at the discretion of the investigator at any time during the course of the study to assess and/or adjust therapy.

All therapy adjustment nights, scheduled and unscheduled, will be documented on appropriate case report forms.

6.16.11.3 Programming and Titration Plan

At the conclusion of the initial therapy adjustment night at the Month 1 visit for the Treatment Group and at the Month 4+1 day visit for the Control Group, the subject will be sent home with the device settings adjusted for the subject and ready to be used at home during the night.

Additional programmable options also may be enabled to manage subjects' tolerance and comfort level with stimulation. The investigator should refer to the ImThera Medical Programming Guide and consult with the ImThera field clinical representative for additional guidance on the use of these settings.

6.16.11.4 Programming Adjustments

When the subject returns for follow-up visits, the investigator may make programming adjustments based on:

- subject feedback,
- subject compliance with therapy,
- results from prior therapy adjustment or Endpoint PSG, or
- the occurrence of any adverse events.

All programming changes, reasons for therapy adjustment, and therapy settings will be documented on the appropriate case report forms.

Clinician-programmed therapy settings must remain constant for 7 days prior to any Endpoint PSG study. If stimulation settings are reprogrammed by a clinician within 7 days prior to an Endpoint PSG study, the Endpoint PSG study must be rescheduled.

6.17 Assessments/Procedures by Visit

6.17.1 Enrollment

The subject is given the chance to ask questions and signs the informed consent.

6.17.2 Medical Screening

After the subject signs the informed consent document, the following assessments will be conducted to collect Screening data to verify that the individual is an eligible study candidate who meets all medical history and physical examination inclusion criteria and does not meet any exclusion criteria. The Medical Screening visit may occur in one or more office visits, and it may be performed by one or more site personnel.

- Informed consent
- Medical history
- Physical examination
- Vital signs
- Pregnancy test, if applicable
- Concomitant medications
- Assessment of adverse events

6.17.3 Surgical Screening

After the subject signs the informed consent document, the following assessments will be conducted to collect Screening data to verify that the individual is an eligible study candidate who meets all surgical inclusion criteria and does not meet any exclusion criteria. The Surgical Screening evaluation visit must be performed by a study surgeon.

The Surgical Screening should only be performed after the Medical Screening, on candidates who meet all Medical Screening criteria.

6.17.4 Upper Airway Examination

After the subject signs the informed consent document, the following assessments will be conducted to collect Screening data and verify that the individual is an eligible study candidate who meets all upper airway and tongue criteria and does not meet any exclusion criteria.

The upper airway examination can be performed by a sleep medicine physician or surgeon.

The Upper Airway Examination should only be performed after the Medical Screening, on candidates who meet all Medical Screening criteria.

- Assessment of tonsil size
- Assessment of tongue, speaking and swallowing functions
- Assessment of tongue position
- Assessment of lingual tonsils (with oral endoscopy)

6.17.5 Screening PSGs

If the subject meets all other inclusion and no exclusion criteria, the following assessments will be conducted to complete the subject screening.

- Concomitant medications
- Assessment of adverse events
- Screening PSG #1
- Questionnaires (excluding Subject Satisfaction Survey)
- Screening PSG #2

Subjects must suspend use of any other OSA treatments at least 14 days prior to a Screening PSG. Screening PSG #2 must occur: i) within 14 days of Screening PSG #1; and ii) no more than 45 days before IPG implantation surgery.

If the subject meets all other inclusion and no exclusion criteria, including criteria determined through Screening PSGs, the subject may be scheduled for system implantation.

6.17.6 System Implantation

6.17.6.1 Implant Procedure

The specific technique for surgical placement of the aura6000 System and intra-operative system testing is described in the aura6000 Implant Manual.

At discharge, the patient will be instructed to refrain from any physical activity that could disturb the electrode's position around the nerve or the passage of the lead to the implanted stimulator or the implanted stimulator's position within its pocket in the chest.

Technical and/or clinical research personnel from the sponsor will be present for system implants. All adverse events will be documented.

The following device and surgical procedure information must be recorded at the time of the initial implant or replacement procedure and provided to the sponsor:

- Device tracking information
- Anesthesia type, route and duration information
- Length of procedure
- Vital Signs
- Concomitant medications
- Assessment of adverse events

6.17.7 Randomization

Subjects will be randomized after the implantation of the aura6000 system per Section 6.6.

6.17.8 Week 2 Visit

At approximately two weeks after the implant procedure (7 to 14 days post-implant) the following assessments will be completed:

- Wound Check
- Vital signs
- Concomitant medications
- Assessment of adverse events

6.17.9 Month 1 Visit (Treatment Group Only)

At approximately one month after the implant procedure (25 to 35 days post-implant) the following assessments will be completed:

- Start Stimulation
- Vital signs
- Concomitant medications
- Assessment of adverse events
- Therapy adjustment PSG
- Subject Training

6.17.10 Month 2 Visit

At approximately two months following implant (50 to 70 days post-implant) the following assessments will be completed:

- Vital signs
- Concomitant medications
- Assessment of adverse events
- Therapy adjustment PSG (Treatment Group only)

6.17.11 Month 3 Visit (Treatment Group Only)

At approximately three months following implant (80 to 100 days post-implant) the following assessments will be completed:

- Vital signs
- Concomitant medications
- Assessment of adverse events
- Therapy adjustment PSG

6.17.12 Pre-Month 4 Contact (Control Group Only)

Approximately 15 to 20 days before the Month 4 Endpoint PSG, Control Group subjects will be contacted and reminded to suspend use of all non-surgical OSA therapies for 14 days prior to Month 4 PSG study.

6.17.13 Month 4 Visit

At approximately four months following implant (110 to 130 days post-implant) the following assessments will be completed:

- Vital signs
- Concomitant medications
- Assessment of adverse events
- Assessment of tongue, speaking and swallowing functions
- Endpoint PSG Study (without adjustment)
- Questionnaires

6.17.14 Month 4 + 1 Day Visit (Control Group Only)

At approximately 1 to 14 days after the Month 4 visit the following assessments will be completed:

- Start Stimulation
- Therapy Adjustment PSG
- Subject Training

6.17.15 Month 5 Visit (Control Group Only)

At approximately five months following implant (140 to 160 days post-implant) the following assessments will be completed:

- Vital signs
- Concomitant medications
- Assessment of adverse events
- Therapy adjustment PSG

6.17.16 Month 10 Visit

At approximately ten months following implant (285 to 325 days post-implant) the following assessments will be completed:

- Vital signs

- Concomitant medications
- Assessment of adverse events
- Therapy adjustment PSG
- Device Interrogation

6.17.17 Month 12 Visit

At approximately twelve months following implant (350 to 375 days post-implant) the following assessments will be completed:

- Physical examination
- Vital signs
- Concomitant medications
- Assessment of adverse events
- Assessment of tongue, speaking and swallowing functions
- Endpoint PSG Study (without adjustment)
- Device Interrogation
- Questionnaires

6.17.18 Month 24, 36, 48, and 60 Visits

At approximately 24, 36, 48, and 60 months ± 30 days following implant the following assessments will be completed:

- Vital signs
- Concomitant medications
- Assessment of adverse events
- Endpoint PSG Study (without adjustment)
- Device Interrogation
- Questionnaires

6.17.19 Unscheduled Visits

Subjects may return to the investigator at any time. If a subject returns for an unscheduled visit, any or all of the following procedures may be performed as needed based on the purpose of the visit:

- Vital signs
- Concomitant medications
- Assessment of adverse events
- Device Interrogation
- Awake stimulation assessment
- Therapy adjustment PSG
- Other assessments as clinically indicated
- Review treatment and therapy adherence with subject

6.17.20 System Revision and Replacement or Explant

It may be necessary to revise or explant some or all of the aura6000 System due to an adverse event, such as infection, or due to the development of a new medical condition requiring treatment contraindicated for use with aura6000, or electively, for a non-medical reason such as subject preference. Lead revisions are most likely to occur in the first few weeks following system implantation and may require surgical intervention to reposition the cuff around the nerve. All aura6000 System revisions, replacements, and explants will be documented on appropriate study case report form(s) as adverse events. The information recorded during the revision procedure is similar to the information recorded for the initial system implantation including date of surgery, vital signs, procedure information, and device information. Following a system revision, subjects will continue to be followed per protocol unless the subject chooses to withdraw from the study. If the subject withdraws from the study, all attempts will be made to followed the subject for 30 days for safety. If any component of the system is explanted, the Sponsor will be notified immediately and the explanted device returned to the Sponsor for analysis. The Sponsor will provide instructions/materials to return the product.

6.18 Termination of Participation

6.18.1 Anticipated Study Completion

At the end of the Month 60 follow-up the subjects' participation in the study will be completed.

6.18.2 Loss to Follow-Up

Reasonable attempts must be made to have each subject complete the follow up visit schedule following enrollment. A subject will not be considered lost-to-follow-up unless efforts to obtain follow-up are unsuccessful. At a minimum, the effort to obtain follow-up information must include three documented attempts to make contact via telephone or email. If contact is not successful, then, a certified letter from the principal investigator must be sent to the subject's last known place of residence.

6.18.3 Subject Withdrawal

All study subjects have the right to withdraw their consent at any time during the study. Whenever possible, the site staff should obtain written documentation from the subject that wishes to withdraw consent for future study participation. If the site's staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded.

A study investigator also may withdraw a subject from the study without regard to the subject's consent if the investigator has a concern for the subject or investigative site staff's rights, safety, or welfare.

6.18.4 Study Exit

Completion of a Study Exit case report form, documenting reason for study exit, will be required for all subjects when exiting the study for any reason. It is anticipated that subjects will continue in the study through the scheduled Month 60 follow-up visit.

6.19 Deviations to the Investigation

The principal investigator, co-investigators and study staff must avoid protocol deviations to the maximum extent possible. The investigators should not implement any deviation from, or changes to, the investigational plan without prior review and documented approval by the site's IRB/EC and the sponsor. Any emergency deviations (deviations from the protocol to protect the life or physical well-being of a subject) that occur must be reported to the sponsor, the FDA and the site IRB/EC as soon as possible but no later than five days after the emergency deviation occurs. Non-emergency, unplanned deviations or instances of inadvertent protocol noncompliance will be reported to the sponsor as soon as the site becomes aware of the deviation. Non-emergency protocol deviations will be reported to the FDA as part of the annual reporting process.

The sponsor of the study will seek FDA approval through an IDE supplement for any changes to the study protocol that might affect the rights, safety or welfare of the subjects or scientific soundness of the study.

6.20 Device Malfunctions

Device malfunctions may occur during the study. A device malfunction occurs when any part of the aura6000 System does not perform as intended when used in accordance with device labeling. The malfunction may be due to defects within the device or components. Examples of device malfunctions may include:

- lead fracture
- unintended loss of stimulation
- unintended stimulation of nerve or muscle structures due to extraneous electrical field produced by the aura6000 System
- premature battery depletion
- random component failure
- unintended delivery of stimulation at unscheduled times and/or settings other than programmed
- patient controller fails to correctly stop, pause or start therapy when buttons are pressed correctly
- inability of the charger to charge the implant
- inability of the programmer software/hardware to set and/or detect programmed device settings

A device malfunction may occur before, during or after implantation. If the malfunction is discovered while the packaging is still intact or the packaging is opened but the contents have

not been used, the details of the device malfunction will be recorded on the appropriate case report form. If the device has been used or the device is explanted, either incidental to or as a result of the malfunction, the details of the device malfunction will be recorded on the appropriate case report form and the procedures for return of contaminated product will be followed.

A device malfunction may or may not be accompanied by an adverse event. Device malfunctions will be reported regardless of whether or not an adverse event is associated with the malfunction. If a device malfunction results in an adverse event, this adverse event must be reported in addition to the device malfunction. For all device malfunctions, information regarding the nature of the malfunction, date the malfunction was detected, suspected cause of the malfunction (if known), and action taken, including device removals, revisions, and replacements, and outcome will be recorded.

6.21 Subject Lack of Response and Rescue Therapy

After a subject has completed the Month 12 follow-up visit, in the event that the subject is a non-responder and receiving incomplete or no benefit from the device after all attempts to optimize therapy programming have been exhausted, adjunctive therapy options should be attempted before permanently turning OFF the aura6000 therapy or deciding to explant the device.

Adjunctive therapy alternatives should be considered based on the investigator's clinical judgment and the subject's preferences. These may include:

- Adjunctive positional therapy
- Adjunctive oral appliances
- Adjunctive PAP
- Adjunctive oxygen
- Adjunctive palate surgery

6.22 Continued Use of aura6000 System Following Completion of Study

Subjects residing in the United States that require a replacement aura6000 System or system component prior to FDA approval and U.S. commercial release of the device will be provided the device(s) free of charge. After U.S. commercial release of the aura6000 System subjects will be responsible for the cost of replacement devices.

6.23 Adverse Events

6.23.1 Recording and Reporting

An adverse event (AE) is any undesirable medical occurrence in a study subject whether or not considered related to the investigational device or procedure, that is identified or worsens during the clinical study. The investigator or designee will follow AEs until they are resolved, normalized, or the subject withdraws from the study.

The investigator will assess and document AEs at all study visits. All suspected AEs must be recorded in the subject's medical record and/or other source document, and reported on the appropriate case report form(s). Each AE should be reported as soon as possible after the investigational site's knowledge of the event.

All initial AE reports must contain the date of onset of the adverse event, a brief description of the event, the severity, the treatment provided, the outcome, the date of resolution (if applicable) and the relationship to the surgical procedure or device.

A serious adverse event (SAE) is an adverse event that involves an occurrence that:

1. Results in death
2. Is life threatening (Any event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
3. Requires inpatient hospitalization (>24 hours) or prolongation of an existing hospitalization
4. Results in persistent or significant disability/incapacity (Any event that results in a substantial disruption of a person's ability to conduct normal life functions)
5. Results in a congenital anomaly or birth defect

All SAEs, whether anticipated or unanticipated, whether related or unrelated to the aura6000 procedure or device must be reported to the sponsor within 24 hours of the investigator learning of the event. SAEs should be reported to the IRB/EC per the site's reporting guidelines; at a minimum in the annual report.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the Investigational Plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. This definition includes any effect that meets the criteria above and results from insufficiencies or inadequacies in the instructions for use or the development of the device. This definition also includes any effect that meets the criteria above and is a result of user error.

All UADEs will be reported by the investigator to the sponsor within 24 hours of learning of the effect. The investigator will also report the effect to the supervising IRB/EC as soon as possible, but in no event later than 10 working days from the date the investigator first learns of the effect. The sponsor will conduct an immediate evaluation of a reported UADE. The results of the evaluation will be reported to the Food and Drug Administration (FDA), all reviewing IRB/ECs and all principal investigators within 10 working days after the sponsor first receives notice of the effect.

Adverse events will be reviewed by a Clinical Events Committee and a Data Safety Monitoring Committee as outlined in Section 12.1 and 12.2. The investigational site will provide source

documentation for all AEs and SAEs to facilitate review by the sponsor and adjudication by the CEC.

6.23.2 Death

The investigator should obtain a copy of the death certificate and a copy of the autopsy report, if available. Any other source documents relied upon to make a determination of death classification and cause of death must be provided for CEC review. In the event that no source documents are available, the investigator will write a memo describing the verification and circumstances of the subject's death.

6.23.3 Adverse Event Severity

The investigator will provide an assessment of the severity of each AE using the following categories: mild, moderate, and severe. For example, a headache can be mild, moderate or severe but usually does not meet the definition of serious because it is not life threatening and does not result in an inpatient hospitalization. It is important to recognize that severity is not equivalent to event seriousness. Severity of an event refers to the intensity of an event, while seriousness refers to the outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as described above.

Severity is a subjective judgment and the investigator should use medical judgment to compare the reported AE to similar types of events observed in clinical practice. Recommended guidelines for the assessment of severity are:

- Mild: symptom(s) the subject is aware of signs or symptoms, but they are easily tolerated and cause no loss of time from normal activities; symptoms may be associated with mild discomfort. Signs and symptoms are transient and resolved without medical intervention. Adjustment of stimulation parameters may or may not be required.
- Moderate: symptoms cause the subject moderate discomfort. The AE causes some limitation in the subject's performance or functioning. Minimal medical intervention may be needed to resolve the event.
- Severe: symptoms cause the subject severe discomfort and/or cause marked limitations in the subject's everyday functioning and invasive medical or surgical intervention, or permanent cessation of aura6000 therapy is needed to resolve the event.

6.23.4 Adverse Event Relatedness

Related adverse events are defined as any adverse events that are considered by the CEC to be related to the surgical procedure or device (aura6000 System or stimulation therapy), with consideration of the strength of the temporal relationship to the surgical procedure and the presence or performance of the device, and the presence or absence of an alternative etiology such as the underlying disease, co-morbidities, and concomitant drugs/treatments.

Assessment of relatedness to the study treatment is based on:

- the strength of the temporal relationship to the surgical procedure or the presence or performance of the device,
- the likelihood that the symptom could have been produced by the participant's clinical state, underlying disease, comorbidities, the environment, or other interventions
- whether the participant's symptom course follows a known pattern of response to the intervention,
- whether the symptom disappears or decreases with therapy adjustments or cessation of intervention, and
- whether the symptom recurs with re-exposure to the intervention

Ratings will be made using the following nominal rating categories:

- Procedure Related: Occurs due to the surgical procedure.
- Device Related: Results from the presence of the device or the device components or the performance of the device.
- Unknown: Cannot be definitively determined to have or not have a causal relationship with the presence of the system or therapy delivered by the system or to the initial implantation or to a secondary procedure.
- Unrelated: Determined not to have a causal relationship with the presence of the system or therapy delivered by the system or to the initial implantation or a secondary procedure.

7 Data Management and Quality Assurance

7.1 Case Report Forms

Standardization of data collection and a documented audit trail will be achieved through the use of an electronic data capture system using electronic case report forms (eCRFs), which will be completed for each subject. All information recorded on the forms must be supported by documentation in the subject's file (clinic or hospital records, medical history, dated and signed notes and worksheets). The source documents in the subject file should include (but are not limited to) the following:

- enrollment number (Subject ID)
- diagnosis
- entries for all therapy/medications
- entries summarizing all clinic visits, including those for study purposes
- entries for all adverse events

The clinical monitor will verify eCRF entries against source documents. The sites will be provided with worksheets that can be considered source documentation if they are signed and dated by the appropriate personnel. These worksheets will be utilized by the sites to capture

data that would not normally be part of the subject's standard medical record. All eCRFs and all supporting information should be readily available for review during scheduled monitoring visits.

A final electronic copy of the eCRF will be provided to the investigator for retention at the investigator's site. Study specific case report form completion instructions will be distributed to the investigative sites to identify additional data collection requirements.

7.2 Study Data Requirements

Electronic case report form completion instructions (eCRFs) for each case report form will be provided in the study operations manual. In addition to eCRFs, PSG studies will be conducted and documented. All study data should be de-identified to remove subject related identifiers and use the Subject ID exclusively. Instruction regarding transfer of non-eCRF data to the Sponsor will be provided in the study operations manual.

7.3 Data Management Organizations

The Sponsor will be using third party data management organizations to facilitate data management and statistical functions. Data that is provided to/from these companies will be through a 21 CFR Part 11 and HIPAA compliant database for reporting functions. Contact information will be provided to the sites, as appropriate, and maintained in the study operations manual.

7.3.1 PSG Quality

PSG recording quality must meet minimum AASM standards for 100% of the total sleep time (five hours minimum). Specific quality requirements are specified in the PSG core laboratory manual. PSG studies of insufficient duration or that do not meet quality standards must be repeated. Backup electrodes should be placed according to AASM guidelines to allow display of alternate derivations if electrodes malfunction during the study.

7.3.2 PSG Core Lab

All scoring of the results of PSG will be performed by an independent PSG Core Laboratory. The PSG Core Lab will define the specific technical requirements and methodology for consistent PSG recordings at all investigational sites, the procedures to transfer electronic PSG data files from the investigational site to the PSG Core Lab, as well as the interpretation of the AASM 2007 PSG scoring definitions. The definitive scoring used to determine Screening PSG and Endpoint PSG values will be determined by the PSG Core Lab. The same scorers will be used for all studies. Core lab scoring reliability will be verified through periodic assessment of intra- and inter-scorer reliability.

PSG Core Lab materials and training will be provided to all sites prior to the start of the study. Contact information for core lab personnel will be provided to each site, and will be on file at the sponsor and will be available upon request.

7.4 Economic Data (USA Sites Only)

Wherever possible, the investigator and Institution will provide to the Sponsor, patient economic data relating to the implant procedure contained in UB04s, to be used by sponsor in support of submissions to Center for Medicare and Medicaid Services (CMS). The UB04s will include, at a minimum, the following fields of information: subject birth date, Admit date-discharge date, Date of procedure, ICD-9-CM code(s), ICD-9-CM diagnosis code(s), CPT code(s), total charges, Hospital name and ID, and Physician name and ID.

7.5 Device Accountability and Storage

The investigator shall maintain a log of all investigational devices received at the site and the subsequent disposition of each device (e.g., used, opened, returned to the sponsor, etc.). At a minimum, the disposition records should include dates, quantities, serial/lot numbers (as applicable), expiration dates (as applicable) and subject ID numbers associated with the device(s). All investigational devices will be stored in a controlled, locked cabinet or room until used in the clinical study. In addition, all implanted and opened devices utilized in the study will be recorded on the appropriate case report form. Any explanted investigational device must be returned to the sponsor for analysis. At the end of the study, all unused investigational devices will also be returned to the sponsor.

7.6 Amendments to the Clinical Investigational Plan

The Sponsor may request that the investigator submit an amendment to the Clinical Investigational Plan or a supplemental Clinical Investigational Plan for IRB/EC review if the sponsor or an investigator proposes a change in the Clinical Investigational Plan that may affect scientific soundness of the study or the rights, safety, or welfare of subjects. Any such amendment or supplement will be approved by FDA prior to implementation. These amendments must be signed by the investigator and sponsor and approved by the IRB/EC before implementation.

8 Study Monitoring Procedures

8.1 Monitoring Procedures

The Sponsor will be responsible for ensuring that appropriate monitoring of the study is performed. Monitoring activities will be in compliance with sponsor SOPs, good clinical practice (GCP) guidelines, FDA guidelines, and FDA regulations (21 CFR 312 and 812) which require monitors to verify that:

a) the rights and well-being of human subjects are protected;
b) reported study data are accurate, complete, and verifiable from source documents; and
c) the conduct of the study is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements.

Policies of other overseeing regulatory agencies will also be followed as applicable.

Monitors will conduct visits to the participating clinical sites to verify accuracy of data, timeliness of data submissions, adequate subject enrollment, investigational device accountability, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed investigator agreement, and compliance with IRB/EC conditions and guidelines. Any non-compliance with these items will be discussed with the sponsor and the site PI. The site PI will be responsible for ensuring that the non-compliance is adequately addressed with relevant corrective and preventative actions. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

Additional detail regarding specific monitoring procedures will be located in the study Monitoring Plan.

8.2 Monitoring Reports

Following each monitoring visit, the monitor will complete a report that will detail what monitoring activities were accomplished during that visit. This report may be generated in whole or in part from the electronic data capture system. Details of the report format will be included in the study Monitoring Plan. This report will be for internal information only. Information that is relevant to be shared with the site will be included in the follow-up letter.

8.3 Monitoring Follow-up Letters

After each monitoring visit, the monitor will compile and send to the applicable site personnel a letter summarizing the monitoring visit. The letter will include the date of the monitoring visit, the name of the monitor, findings and any required follow-up. The investigator will be responsible for ensuring that any follow-up actions needed to resolve issues are completed in an accurate and timely manner.

8.4 Site Closeout Visit

A final monitoring visit will be conducted at the close of the study. The purpose of the final visit is to collect all outstanding study data documents, ensure that the principal investigator's files are accurate and complete, review record retention requirements, ensure that device accountability records are finalized and all investigational product is returned to the sponsor, and ensure that all applicable requirements are met for the study.

9 Site Personnel Training

All investigational site personnel (investigators, co-investigators, study coordinators sleep technicians, and any site personnel designated to perform study related activities) will be trained on the study protocol and all applicable required procedures. Those directly involved with the subjects will also be trained on the investigational product and the surgical implant procedure, as applicable. Training will be timed to coincide with appropriate study milestones

to keep retraining to a minimum. As new study personnel are added at the investigational sites, they will be trained to the same standards prior to assuming study responsibilities.

Prior to implanting the aura6000 System, each implanting surgeon at each investigational site will complete surgical training. Additionally, each investigator or designee will be fully trained to use the aura6000 System including the RCC, and aCM programming software.

10 Statistical Analysis

10.1 General Statistical Methods

Standard summary statistics will be calculated for all study variables. For continuous variables, statistics will include means, standard deviations, ranges, medians, and inter-quartile ranges. Categorical variables will be summarized in frequency distributions. Statistical analyses will be conducted in SAS version 9.3 or above (SAS Institute, Cary, N.C.) or another validated software package.

10.2 Analysis of Primary Endpoints

10.2.1 Analysis of Primary Safety Endpoint

The primary safety endpoint is:

- Estimate the incidence of adverse events related to the aura6000 System implant procedure or device through 365 days post-implant, including any unanticipated adverse device effects.

CEC adjudicated adverse event classifications of events will be used for analysis of the primary safety endpoint. The primary safety endpoint will be summarized using descriptive statistics. No formal hypothesis testing will be performed. Adverse events related to the aura6000 System implant procedure or device through 365 days post-implant will be reported as proportions along with 95% confidence intervals. Results will be presented for all subjects with an attempted surgical implant procedure.

10.2.2 Analysis of Primary Effectiveness Endpoints

10.2.2.1 Analysis of Primary Endpoint #1

The first primary effectiveness endpoint is the proportion of subjects that experience clinically meaningful improvements at Month 4 compared to Baseline in the apnea-hypopnea index (AHI) as defined below. This endpoint is referred to as the “AHI responder rate”. An AHI responder is a subject that has:

- AHI ≤ 20 and ≥ 50% reduction in AHI

Statistical Analysis: AHI responder rates will be compared between randomized groups using an exact binomial test for two independent proportions.

Statistical Hypothesis: Let R_{treat} and $R_{control}$ denote the proportion of subjects in the randomized Treatment and Control Groups respectively that meet the AHI responder criteria.

$$H_o: R_{treat} \leq R_{control}$$

$$H_a: R_{treat} > R_{control}$$

Rejection of the null hypothesis will indicate a higher AHI responder rate in the Treatment group compared to the Control group. The one-sided test will be performed using the appropriate alpha level based on an O'Brien-Fleming type alpha spending function accounting for the interim analysis.

10.2.2.2 Analysis of Primary Endpoint #2

The second primary effectiveness endpoint is the proportion of subjects that experience clinically meaningful improvements at Month 4 compared to Baseline in the oxygen desaturation index (4%) (ODI 4%) as defined below. This endpoint is referred to as the "ODI responder rate". An ODI responder is a subject that has:

- ≥ 25% reduction in ODI 4%

Statistical Analysis: ODI responder rates will be compared between randomized groups using an exact binomial test for two independent proportions.

Statistical Hypothesis: Let R_{treat} and $R_{control}$ denote the proportion of subjects in the randomized Treatment and Control Groups respectively that meet the ODI responder criteria.

$$H_o: R_{treat} \leq R_{control}$$

$$H_a: R_{treat} > R_{control}$$

Rejection of the null hypothesis will indicate a higher ODI responder rate in the Treatment group compared to the Control group. The one-sided test will be performed using the appropriate alpha level based on an O'Brien-Fleming type alpha spending function accounting for the interim analysis.

10.2.2.3 Analysis of Primary Endpoint #3

The third primary effectiveness endpoint is the proportion of subjects in the Treatment Group who meet the definition of an AHI responder at Month 12 post implant of the aura6000 System. This endpoint is referred to as the "long-term AHI responder rate". This endpoint will ensure the therapy provides a clinically meaningful long-term benefit to a significant portion of the target population.

Statistical Analysis: The proportion of responders at Month 12 will be compared to the performance goal using an exact binomial test. This endpoint will be considered to have been met if the lower bound of the confidence interval for the responder rate in the Treatment Group at Month 12 post implant of the aura6000 System is > 45%.

Statistical Hypothesis: Let R_{treat} denote the proportion of subjects in the randomized Treatment Group that meet the AHI responder criteria. Let PG denote the performance goal of 45%.

$$H_o: R_{treat} \leq PG$$

$$H_a: R_{treat} > PG$$

Rejection of the null hypothesis will indicate the long-term AHI responder rate in the Treatment Group is above the performance goal. The one-sided test will be performed using the appropriate alpha level based on an O'Brien-Fleming type alpha spending function accounting for the interim analysis.

10.2.2.4 Analysis of Primary Endpoint #4

The third primary effectiveness endpoint is the proportion of subjects in the Treatment Group who meet the definition of an ODI responder at Month 12 post implant of the aura6000 System. This endpoint is referred to as the "long-term ODI responder rate". This endpoint will ensure the therapy provides a clinically meaningful long-term benefit to a significant portion of the target population.

Statistical Analysis: The proportion of ODI responders at Month 12 will be compared to the performance goal using an exact binomial test. This endpoint will be considered to have been met if the lower bound of the confidence interval for the ODI responder rate in the Treatment Group at Month 12 post implant of the aura6000 System is > 45%.

Statistical Hypothesis: Let R_{treat} denote the proportion of subjects in the randomized Treatment Group that meet the ODI responder criteria. Let PG denote the performance goal of 45%.

$$H_o: R_{treat} \leq PG$$

$$H_a: R_{treat} > PG$$

Rejection of the null hypothesis will indicate the long-term ODI responder rate in the Treatment Group is above the performance goal. The one-sided test will be performed using the appropriate alpha level based on an O'Brien-Fleming type alpha spending function accounting for the interim analysis.

10.3 Analysis of Secondary Endpoints

10.3.1 Change in Epworth Sleepiness Scale (ESS) from Baseline to Month 4

The first secondary endpoint is a comparison of the changes in ESS from Baseline to 4 months post-implant of the aura6000 System between randomized groups. It is hypothesized that the improvement in the Treatment Group will be significantly greater than the improvement in the Control Group at 4 months post implant of the aura6000 System.

Statistical Analysis: Mean changes in ESS will be compared using a two-sample t-test. In the event that the data are not normally distributed, a non-parametric Wilcoxon test will be used.

Statistical Hypothesis: The null hypothesis is that the improvement in ESS in the Treatment Group is less than or equal to the improvement in the Control Group. The alternative hypothesis is that the improvement in the Treatment group is greater than the improvement in the Control Group. The p-value will be compared to the appropriate alpha level based on an O'Brien-Fleming type alpha spending function accounting for the interim analysis. Successful rejection of the null hypothesis indicates a statistically significant improvement in ESS.

10.3.2 Change in FOSQ from Baseline to Month 4

The second secondary endpoint is a comparison of the changes in FOSQ from Baseline to 4 months post-implant of the aura6000 System between randomized groups. It is hypothesized that the improvement in the Treatment Group will be significantly greater than the improvement in the Control Group at 4 months post implant of the aura6000 System.

Statistical Analysis: Mean changes in FOSQ will be compared using a two-sample t-test. In the event that the data are not normally distributed, a non-parametric Wilcoxon test will be used.

Statistical Hypothesis: The null hypothesis is that the improvement in FOSQ in the Treatment Group is less than or equal to the improvement in the Control Group. The alternative hypothesis is that the improvement in the Treatment group is greater than the improvement in the Control Group. The p-value will be compared to the appropriate alpha level based on an O'Brien-Fleming type alpha spending function accounting for the interim analysis. Successful rejection of the null hypothesis indicates a statistically significant improvement in FOSQ.

10.3.3 Change in EuroQol 5 Dimensional (EQ-5D) from Baseline to Month 4

The third secondary endpoint is a comparison of the changes in EQ-5D from Baseline to 4 months post-implant of the aura6000 System between randomized groups. It is hypothesized that the improvement in the Treatment Group will be significantly greater than the improvement in the Control Group at 4 months post implant of the aura6000 System.

Statistical Analysis: Mean changes in EQ-5D will be compared using a two-sample t-test. In the event that the data are not normally distributed, a non-parametric Wilcoxon test will be used.

Statistical Hypothesis: The null hypothesis is that the improvement in EQ-5D in the Treatment Group is less than or equal to the improvement in the Control Group. The alternative hypothesis is that the improvement in the Treatment group is greater than the improvement in the Control Group. The p-value will be compared to the appropriate alpha level based on an O'Brien-Fleming type alpha spending function accounting for the interim analysis. Successful rejection of the null hypothesis indicates a statistically significant improvement in EQ-5D.

10.4 Alpha Control for Multiple Comparisons

Serial testing of the endpoints will be performed such that conditional on a successful test of the first endpoint, the next endpoint in the series will be tested. This process will repeat for the four primary effectiveness endpoints and three secondary effectiveness endpoints. This serial

gate-keeping strategy controls the study level alpha. The order of the testing of the effectiveness endpoints is as follows:

1. First primary effectiveness endpoint
    - Month 4 randomized comparison of AHI responder rates
2. Second primary effectiveness endpoint
    - Month 4 randomized comparison of ODI responder rates
3. Third primary effectiveness endpoint
    - Month 12 Treatment Group AHI responder rate
4. Fourth primary effectiveness endpoint
    - Month 12 Treatment Group ODI responder rate
5. First secondary effectiveness endpoint
    - Month 4 Improvement in ESS
6. Second secondary effectiveness endpoint
    - Month 4 Improvement in FOSQ
7. Third secondary effectiveness endpoint
    - Month 4 Improvement in EQ-5D

The study will be considered successful if the primary effectiveness endpoints are met based on the primary analysis of the full analysis set defined in Section 10.2.2.

10.5 Additional Ancillary Data Analyses

Section 6.11.1.5 provides a list of additional pre-specified ancillary analyses. There are no statistical hypotheses for these analyses. Variables assessed will be tabulated and summarized with appropriate descriptive statistics as defined in Section 10.1. Data will be presented at each follow-up time point as appropriate. Results will be presented for all randomized subjects, and additionally separately for the randomized groups.

10.6 Interim Analysis

One formal interim analysis will be conducted by the DSMB to allow an increase in study sample size, if necessary, or early trial termination due to futility. The interim analysis will be conducted when approximately 50% of each randomized group have completed the Month 4 follow-up visit. The observed Month 4 responder rate will also be used to inform assumptions made on the Month 12 responder rate. At the time of the interim analysis, a sample size re-estimation will be conducted via conditional power. This design will maintain 80% overall power. The Lan-DeMets approach to group sequential analysis using an O'Brien-Fleming type alpha spending function will be used to control the overall study type I error rate. The resulting approximate alpha levels for the planned interim analysis and final analyses are a one-sided $\alpha = 0.00153$ and $\alpha = 0.0245$, respectively. This interim analysis will indicate whether the original study sample size is sufficient, or additional subjects must be enrolled to maintain 80% power of the study. The original sample size will not be reduced given the results of this analysis, nor will it provide justification for early study termination as a result of positive effectiveness results. Conversely, should the interim analysis indicate that an excessive number of additional

patients are required to maintain 80% overall study power, it will strongly support the possible decision by the sponsor of early termination due to futility. A maximum of 260 total subjects may be successfully implanted in the study. If the sample size re-estimation concludes that more than 260 total successfully implanted subjects would be required to maintain 80% overall study power, then the study may be terminated. Formal statistical monitoring guidelines for stopping and adjusting sample size and details of the statistical analysis methods will be incorporated in a Statistical Analysis Plan (SAP). The results from the interim analysis will be for internal purposes only and will not be shared publicly to minimize potential bias in study conduct.

Since the first and second effectiveness primary endpoints drive the sample size of the control group and the third and fourth primary effectiveness endpoints drive the sample size of the treatment group, conditional power will be calculated for all four endpoints. For a better understanding of the sample size re-estimation process, consider the four hypotheses of interest:

Hypothesis 1 (AHI) – H_0: $R_{control} \geq R_{treat}$ vs H_a: $R_{control} < R_{treat}$

Hypothesis 2 (ODI) – H_0: $R_{control} \geq R_{treat}$ vs H_a: $R_{control} < R_{treat}$

Hypothesis 3 (AHI) – H_0: $R_{treat} \leq 45\%$ vs H_a: $R_{treat} > 45\%$

Hypothesis 4 (ODI) – H_0: $R_{treat} \leq 45\%$ vs H_a: $R_{treat} > 45\%$

The sample size re-estimation (if needed) will be performed per the following. The alpha levels are assuming the interim analysis is performed when 50% of each randomized group have completed the Month 4 follow-up visit:

10.6.1 Interim Analysis

- Test Hypothesis 1 at Alpha1 = 0.00153 (O'Brien-Fleming)
    - If H_0 (for Hypothesis 1) is not rejected: re-estimate sample size via conditional power. In particular re-estimate sample size via conditional power for each Hypothesis testing (i.e., 1,2, 3, and 4). Then keep the larger sample size.
        - If new sample size is greater than maximum allowed by the sponsor, then DSMB may recommend the sponsor consider stopping the trial.
        - If new sample size is lower than the original sample size, keep the original sample size.
    - If H_0 for Hypothesis 1 is rejected: test Hypothesis 2 at $Alpha_1 = 0.00153$
        - If H_0 (for Hypothesis 2) is not rejected: re-estimate sample size using conditional power exactly as in the previous step.
            - If new sample size is greater than maximum allowed by the sponsor, then DSMB may recommend the sponsor consider stopping the trial.
            - If new sample size is lower than the original sample size, keep the original sample size.

        - If H0 (for Hypothesis 2) is rejected: no need to re-estimate original sample size.
    - Continue following a similar pattern of calculations for all four primary effectiveness endpoints.

10.6.2 Final Analysis

- Test Hypothesis 1 at $Alpha_2 = 0.02450$ (O'Brien-Fleming)
    - If H_0 (for Hypothesis 1) is not rejected: no more formal testing needed and conclude fail to prove efficacy.
    - If H_0 (for Hypothesis 1) is rejected and co-primary endpoint is successful: test Hypothesis 2 at $Alpha_2 = 0.02450$.
        - If H_0 (for Hypothesis 2) is not rejected: conclude fail to prove efficacy.
        - If H_0 (for Hypothesis 2) is rejected: test Hypothesis 3 at $Alpha_2 = 0.02450$.
    - Continue with formal hypothesis testing in sequential order conditional on a successful test of the prior hypothesis

Conditional power will be computed using the results based on Chang's method (2008). The conditional power for the first two hypotheses will be computed for a one-sided two-sample proportion test per *PASS Sample Size Software, NCSS. Conditional Power of Two Proportions Tests, Chapter 202*. For hypotheses 3 and 4, the conditional power will be computed for a one-sided single proportion per *PASS Sample Size Software, NCSS. Conditional Power of One Proportions Tests, Chapter 101*. The sample size is computed by finding the minimum sample size where the conditional power is at least 80%.

10.7 Consistency of Results by Site and Subgroups

The poolability of the data across investigational sites will be assessed for the first and second primary effectiveness endpoints using Breslow-Day tests. Poolability will be assessed for the third and fourth primary effectiveness endpoints using logistic regression models. In the event that statistical evidence of a difference in primary efficacy endpoints between sites is found (evidenced by a p-value < 0.10), additional analyses will be conducted to assess the differences. In the event some sites have relatively small enrollments, grouping of sites may be employed.

10.8 Missing Data

Efforts will be made during the course of the trial to minimize the amount of missing data for the effectiveness endpoints. This will include intuitive design of data collection forms, extensive in person and electronic monitoring of case report forms, proper training of study sites, and standard operating procedures. Because missing data has the ability to reduce the validity of a study, statistical analyses will be performed to assess the impact of missing data on the results for the primary effectiveness endpoints.

The primary analysis for each Primary Effectiveness Endpoint will adhere to the principle of intent-to-treat (ITT), whereby all available data will be included and subjects will be analyzed according to their randomized group, irrespective of the treatment actually received. This follows the definition of "Full Analysis Set" of the E9 ICH Statistical Principles for Clinical Trials. For the primary endpoint ITT analyses, randomized subjects with missing data will be considered non-responders. Two additional sensitivity analyses will be performed for the first and second primary effectiveness endpoints. For effectiveness Endpoints #1 and 2, a best case scenario, worst case scenario, and tipping point analysis will be performed. The best case scenario will assume Treatment Group subjects with missing data are responders, and Control Group subjects with missing data are non-responders. The worst case scenario will assume Treatment Group subjects with missing data are non-responders, and Control Group subjects with missing data are responders. The tipping point analysis assesses all combinations of missing data. For the ITT analysis of effectiveness Endpoints #3 and 4 , subjects with missing data will be considered non-responders. The subject's Baseline value will be used in place of the missing follow-up value; this is equivalent to observing no change for the primary effectiveness endpoint and assuming that there is no treatment effect. A "last observation carried forward method" (LOCF) will also be performed. The LOCF method uses data from the previous PSG study in place of missing data; this is equivalent to observing a sustained response. Consistency of the sensitivity results with the primary intent-to-treat analysis will provide evidence that the results are not unduly influenced by missing data.

10.9 Analysis Cohorts

10.9.1 Full Analysis Set

The full analysis set will be based on all randomized subjects in the arm to which they were randomized, irrespective of the treatment actually received. This will be the basis of the primary analysis.

10.9.2 Access to Data

While the trial is ongoing, access to study data will be limited. Data on adverse events will be reviewed regularly by an independent Clinical Events Committee to adjudicate all adverse events. Data will be reported regularly to an independent Data Safety Monitoring Board to ensure subject safety. An independent Core Laboratory will provide scoring of sleep studies that are Endpoint PSGs. These independent bodies will help to prevent the introduction of bias into the study.

Aggregate study results will not be released to field personnel, study investigators or site personnel at any participating investigative center.

11 Scientific Soundness

This study is designed to provide valid scientific evidence to address the objectives of the study. It is expected that the results of this study will provide reasonable assurance of the safety and effectiveness of the aura6000 System for the treatment of moderate to severe obstructive sleep apnea in individuals that fail or do not tolerate PAP.

The study utilizes a multi-center, prospective, randomized, controlled, two-arm design. Procedures have been implemented to minimize bias and randomization provides a basis for causal inference and the validity of statistical hypothesis tests. Randomization to an untreated Control Group allows for the ability to discriminate between improvement in outcomes due to the investigational treatment, and that due to other possible factors.

Bias in patient selection is minimized by clearly defined enrollment criteria, and standard procedures to track and report subject recruitment and screening activities.

Specific, well-defined pre-specified study endpoints commonly reported in the sleep apnea literature will protect against endpoint ascertainment bias. Endpoint measurement error is minimized by selecting qualified professionals who are experienced in the diagnosis, assessment and treatment of obstructive sleep apnea to perform the endpoint evaluations, use of standard assessment tools that are known to be valid and reliable, and use of a central independent polysomnography core laboratory for assessment of key study endpoints.

Bias introduced by lack of blinding of subjects and investigators is minimized as all adverse events will be reported, and procedures for reporting adverse events are the same in both the Treatment and Control Groups. Bias due to lack of blinding subjects and investigators also is minimized because effectiveness endpoints are based on results of polysomnography (PSG), which is an objective measurement, obtained during sleep, that is not based on subjects' self-reports of symptoms or improvements. Scoring of PSG utilizes standard guidelines for counting apneas and hypopneas and an independent core lab will provide all PSG measurements. Although the aura6000 stimulation artifact is visible on the PSG traces and complete blinding of group assignment is not possible, the core laboratory will be unaware if the PSG study is from a titration, endpoint, or unscheduled visit. This uncertainty will minimize bias in the scoring of the PSGs.

Finally, the pre-specified analysis plan for the study eliminates any endpoint ascertainment bias that could be introduced if the selection of analysis methods or decisions about the inclusion of subjects' data in the analysis could be influenced by knowledge of subjects' treatment assignment. The sample size selected for this pivotal study provides adequate precision for estimating adverse event rates and adequate power for statistical hypothesis tests of key effectiveness endpoints. Statistical methods are pre-specified, defined based on standard methods that are in agreement with relevant guidance documents, and analysis will be performed with standard validated software.

An independent and experienced Data Safety Monitoring Board will provide ethical and scientific review of the ongoing study. The study will be conducted per the Code of Federal

Regulations, Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki. Study data and conduct and compliance with the protocol will be monitored on an ongoing basis.

Finally, the results will be carefully interpreted in light of the postulated mechanism of action of hypoglossal nerve stimulation to improve OSA, the expected risks and benefits of treatment with the aura6000 System, and the risks and benefits of incomplete treatment or no treatment.

12 Study Administration

12.1 Clinical Events Committee

A Clinical Events Committee (CEC) will be formed to review all adverse events, all device malfunctions, and all deaths. The committee will consist of a minimum of three (3) members, comprised of a sleep medicine (pulmonology and/or neurology) physician, a surgeon and an additional physician with experience in medical device implants/studies. The CEC will meet on an as-needed basis, at a minimum twice a year, to assess individual adverse events in the study.

Every adverse event will be classified according to the definitions in this Investigational Plan. An initial classification of the adverse event shall be obtained from data provided by the investigator. The CEC may reclassify an adverse event as reported. In this case, the adjudication of the CEC supersedes the investigator's classification of the event. When an adverse event is re-classified, the investigator involved will be notified of the committee's classification. In addition, the Data Safety Monitoring Committee will be provided with reports of the final CEC-adjudicated events including both investigator and CEC classifications.

Names and contact information for all CEC members will be on-file at the sponsor and available on request.

12.2 Data Safety and Monitoring Board

The Data Safety Monitoring Board (DSMB) will consist of a minimum of three (3) members, comprised of a sleep medicine (pulmonology and/or neurology) physician, a surgeon, and a biostatistician. The DSMB will meet on an as-needed basis, at a minimum annually, to assess the ongoing safety information collected during the study. Membership will include only independent members and therefore will not include a study investigator or a representative from the sponsor. The DSMB meetings will consist of open and closed sessions, denoting sponsor staff present and not present, respectively.

The sponsor will provide the DSMB with reports related to subject enrollment, procedural outcome, follow-up visits, adverse events (including adjudication by a Clinical Events Committee) and any other material the DSMB may deem necessary to carry out its responsibilities as established at the outset of the committee in the DSMB charter. The DSMB will assess if early evidence exists for dramatic benefit or harm for subjects while the clinical

study is in progress. The DSMB will make recommendations to the sponsor concerning continuation, modification or termination of the study.

Names and contact information for all DSMB members will be on-file at the sponsor and available on request.

12.3 Publication Committee

A publication committee will be formed that will be responsible for overseeing the development of the Publication Strategy, including the development of any multi-center trial manuscripts or abstracts and publication venues. Multi-center publications must be agreed to by the publication committee to ensure consistency of analysis methods, data integrity, and appropriate publication timing. Members of the publication committee may include but are not limited to the following individuals:

- Investigators from centers involved in the trial
- Representatives of the sponsor (e.g. statistician, manager of the trial)

Names and contact information for all Publication Committee members will be on-file at the sponsor and available on request.

12.3.1 Publication Strategy

The study will be registered with http://www.clinicaltrials.gov as required by the Food and Drug Administration (FDA) and International Committee of Medical Journal Editors.

When all subjects have completed the Month 4 follow-up visit and results have been submitted to FDA, an abstract reporting the results may be prepared and presented at major professional society meetings. A final primary multi-center manuscript will be prepared and submitted when all subjects have completed the Month 12 follow-up visit. Additional publications may arise from the study, as determined by the Publication Committee. All publications of study data will be reviewed and approved by the Publication Committee.

13 Clinical Risk/ Benefit Analysis

13.1 Potential Benefits of the aura6000 System

At this time, the clinical benefit of hypoglossal nerve stimulation therapy is unproven. Potential benefits to the subjects may include, but are not limited to, reducing the occurrence of obstructive events during sleep and symptoms related to OSA. The benefits of treating OSA for the reduction of associated risks are well documented. Preclinical evaluation has demonstrated that lingual muscle activation can be achieved through hypoglossal nerve stimulation. In addition, clinical evaluation published by Schwartz et al and Strollo et al has shown that hypoglossal nerve stimulation can reduce apnea and hypopnea events. Further, this effect also has been shown in two feasibility studies of the aura6000 System (ImThera Medical, Inc. IMT 2009-01/01/03 (“THN1”) and IMT 2012-01 (“THN2”).

13.2 Potential Risks of the aura6000 System

Potential adverse events from hypoglossal nerve stimulation may include but are not limited to the following. These events may result in hospitalization, prolongation of hospitalization, unanticipated surgery, tracheotomy, revision or replacement of system components, or death.

13.2.1 Risks Associated With the Implantation Procedure

It is anticipated that subjects participating in the study will be exposed to operative and postoperative risks similar to related surgical procedures involving the neck, and implantation of an implantable neurostimulator with associated lead. These surgical risks may include, but are not limited to:

- infection
- bleeding
- hematoma
- seroma
- scarring
- dysarthria
- lingual nerve or other surrounding structure injury
- excessive fibrotic tissue growth around the implanted device
- temporary or permanent hypoglossal or other nerve damage resulting in paresis (or weakness), paralysis or other dysfunction including impaired ability to swallow or speak
- temporary or permanent pain, paresthesia or numbness at the implant sites, tunneled path, or elsewhere
- complications from intubation, anesthesia or extended procedure time
- heart attack
- allergic or immune system response to the implanted materials
- component migration or erosion through the skin

13.2.1.1 Risks Related to aura6000 System Revisions, Replacements, Explants

One or more components of the aura6000 System may need to be replaced or explanted in the event of a device failure or serious adverse event such as an infection or another clinical indication for device removal. The potential risks of device explant are the same as the risks associated with the initial procedure, complicated by the presence of the device components and scar tissue which could result in failure to explant the entire system. Consequently, the risk of injury or damage to the hypoglossal nerve may be higher in revision or replacement procedures.

The IPG may need to be replaced when the battery is no longer able to hold a charge sufficient to deliver adequate therapy. The time to the elective replacement indicator (ERI) is estimated to be eleven (11) years and the time to end of life (EOL) is estimated to be fifteen (15) years or sooner if there is a neurostimulator failure. While the potential surgical risks of IPG

replacement are similar to those at implant, this procedure does not require general anesthesia and therefore some associated risks may not apply.

The lead may need to be replaced or explanted as a result of lead migration, dislodgement, disconnection, fracture, insulation breakage or erosion. While the potential surgical risks of lead revision are similar to those at implant, this procedure is complicated by the presence of scar tissue around the hypoglossal nerve and nerve cuff. Subsequently, the risk of injury or damage to the hypoglossal nerve may be higher in revision or replacement procedures.

The aura6000 System software may change, and it may be desirable or necessary to change the software in the IPG, remote, or aCM to optimize performance. Software changes are non-invasively performed using radio waves.

13.2.2 Risks Associated With the Presence of the aura6000 System

Subjects may also be exposed to risks associated with the presence of the system components. These device risks may be short- or long-term and include, but are not limited to the following:

- Lead migration, dislodgement, disconnection, fracture, insulation breakage or erosion;
- Failure of IPG component, battery, software or telemetry
- IPG migration or flipping
- Ineligible for magnetic resonance imaging (MRI) while implanted with all, or any part, of the system

13.2.3 Risks Associated with the aura6000 System

Most therapy-related side effects are reversible, and corrected by reprogramming or turning OFF the system. Chronic, irreversible stimulation related adverse events are expected to be rare. Potential therapy-related adverse events include, but are not limited to:

- paresthesia or tingling
- pain or discomfort due to stimulation or device malfunction
- paresis
- dysarthria
- excessive stimulation
- pain with stimulation
- reduction in benefit from chronic stimulation
- loss of therapeutic effect
- extrahypoglossal stimulation
- worsening of OSA condition

13.2.4 Risks Associated with the Study Protocol

Subjects also will be exposed to risks associated with the required or optional procedures of the protocol including:

- Exposure to fluoroscopy, x-ray, ultrasound or computed tomography (CT) if needed during the study to troubleshoot device or therapy performance
- Endoscopic imaging as needed to assess subject eligibility, and to characterize, troubleshoot or document device or therapy performance, with possible side effects which include but are not limited to:
    - gagging
    - vomiting
    - nosebleed
    - aspiration
    - esophageal perforation
    - reaction or allergy to sedative, anxiolytic, or anesthetic medications
- Polysomnography (PSG) and associated measurements during sleep
- Suspension of other therapies prior to Endpoint PSG visits

The risks to pregnant women and their unborn child due to the presence of the system and the therapy provided are unknown. Women who are pregnant or breastfeeding or who intend on becoming pregnant are excluded from participating in the study. Women of childbearing potential must maintain adequate contraception during the 12 month course of the study. If a subject is enrolled and implanted with the investigational system and becomes pregnant, the system will be turned OFF with the Therapy Controller or Programmer. The presence of the implanted aura6000 components is not considered to be a risk for pregnancy and delivery. The therapy may be resumed when indicated and as recommended by the subject's primary physician and the investigator.

13.3 Risk Minimization

The following steps are being taken to minimize the likelihood of the above-noted risks:

- All study procedures are conducted by adequately trained and experienced personnel
    - Specific training will be conducted to familiarize the implanting surgeon with surgical technique
    - All sleep studies will be performed by trained sleep laboratory technicians and staff
- Therapy initiation will allow for subjects to accommodate to aura6000 stimulation. Therapy settings and programming changes will be managed by the study site with close communication between ImThera and site personnel.
- Follow up in the first 12 months post implant will identify potential problems as soon as possible and minimize risks and/or discomfort to the subject.
- Inclusion/Exclusion criteria were selected to target subjects who have a high likelihood of benefit while preventing subjects from entering the trial that are at high risk of posing a danger to themselves or society from excessive sleepiness.

- The Control Group will have access to treatment-as-usual (i.e. any non-PAP, non-surgical OSA treatment being used prior to enrollment in the study) throughout the OFF period with the exception of the 14 day washout period prior to Month 4 Endpoint PSG.
- DSMB and CEC study oversight committees will be regularly reviewing safety and effectiveness data.
- Alternative therapy suspension, e.g. PAP, is as short as possible in a non-compliant population

13.4 Risk / Benefit Summary

While the risk for significant injury or death due to the aura6000 System implantation and stimulation of the hypoglossal nerve is low, these risks have yet to be fully quantified in the patient population under study.

Eligibility criteria that exclude subjects who are at higher risk for experiencing an anticipated Adverse Event have been selected in order to reduce the potential risks to subjects that participate in this study.

The study includes efforts to minimize the potential for risk, and is based on a well-defined clinical rationale.

The clinical rationale for potential benefit of the proposed therapy, the results of prior pre-clinical and clinical studies, and the published scientific literature provide evidence for the safety of the proposed use of the aura6000 System. The prior pre-clinical and clinical studies indicate that the potential benefits outweigh the potential risks, and supports the initiation of the proposed pivotal study in support of a premarket application (PMA).

14 Responsibilities, Records and Reports

This study will be conducted according to Good Clinical Practice (GCP) regulations and guidance issued by the Food and Drug Administration (FDA) which are included in the following parts of the FDA Code of Federal Regulations (CFR):

- 21 CFR Part 50: Protection of Human Subjects,
- 21 CFR Part 54: Financial disclosure by clinical investigators
- 21 CFR Part 56: Institutional Review Boards,
- 21 CFR Part 812: Investigational Device Exemptions

The purpose of these regulations is to define the standards and principles for the proper conduct of clinical studies. The ethical standards defined within GCP are intended to ensure that human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not, that the study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings, and that the potential benefits of the research justify the risks.

14.1 Sponsor Responsibilities

The sponsor of a significant-risk medical device study is responsible for obtaining an Investigational Device Exemption (IDE) from the FDA prior to initiating the study. The sponsor is responsible for the following:

- ensuring the study is reviewed and approved by the FDA and that the study is compliant with the IDE regulations (21 CRF parts 50, 54, 56 and 812),
- ensuring the investigative site obtains IRB/EC approval prior to initiating the study,
- selecting qualified investigators,
- obtaining a signed investigator's agreement,
- providing investigators with the information they need to properly conduct the study,
- ensuring patient informed consent is obtained,
- ensuring proper monitoring of the study,
- ensuring that the study is conducted according to the clinical investigational plan,
- ensuring that the investigation treatment is made available only to qualified investigators participating in the study,
- ensuring no changes that effect the scientific soundness of the study or the rights safety and welfare of the subjects are made to the investigational plan without prior approval of FDA or reviewing regulatory agencies, and IRB/EC,
- ensuring that regulatory agencies and all participating investigators are properly informed of significant new information regarding adverse effects or risks associated with the device being studied.

14.1.1 Sponsor Records

The sponsor must maintain accurate, complete and current records relating to the study. These records include:

- Correspondence with sites, study monitors, investigators, an IRB/EC and FDA or other reviewing regulatory agencies.
- Records of investigational device shipment and disposition
- Signed investigator Agreements and financial disclosure if required under CFR 812.43(c)(5)
- Adverse device effects (whether anticipated or unanticipated) and complaints

14.1.2 Sponsor Reports

The sponsor must prepare and submit the following reports:

- Results of evaluation of any reported unanticipated adverse device effects (UADEs) to FDA or other reviewing regulatory agencies, all IRBs/ECs, and investigators within 10 working days after notification by the investigator,
- current investigator list to FDA every six months,
- an annual progress report to FDA and IRBs/ECs,

- any withdrawals of IRB/EC approval to FDA, all IRBs/ECs, and investigators, within five working days after receipt of notice of withdrawal of IRB/EC approval,
- any withdrawal of FDA approval to the IRB/EC, and investigators, within five working days after receipt of notice of withdrawal of FDA approval,
- any device withdrawals or recalls to FDA and IRB/EC within 30 working days after the request is made to an investigator,
- emergency protocol deviations to FDA within five working days after receipt of notice of such emergency use,
- use of the investigational device or treatment without obtaining informed consent to FDA within five working days after sponsor is notified of such use,
- a final report to FDA, IRBs/ECs, and investigators within six months of completion or termination of the study.
- other study-related reports generated upon request by a reviewing IRB/EC, study Clinical Events Committee, and/or FDA

14.2 Investigator Responsibilities

An investigator is responsible for ensuring that the study is conducted according to the signed investigator agreement, the investigational plan, and applicable FDA regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of devices under investigation.

14.2.1 Protection of Human Subjects

The investigator must submit the investigational plan and the patient informed consent form to the governing Institutional Review Board (IRB) or Ethics Committee (EC) and obtain written approval from the IRB/EC before enrolling subjects in the study. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB/EC.

14.2.2 Informed Consent

The investigator (or designee) must explain to each study candidate the nature of the study, its purpose, procedures, expected duration, alternative therapy available and the benefits and risks involved in study participation. Each study candidate will be given the opportunity to ask questions and will be informed of the subject’s right to withdraw from the study at any time without prejudice. After this explanation and before entering the study, the potential subject will voluntarily sign an informed consent statement in the presence of a witness if there is agreement to participate.

14.2.3 Investigator Records

The investigator is responsible for maintaining the following records for a period of two years following the termination or completion of the study. The principal investigator/site must maintain adequate records on all aspects of the study, including the following:

- IRB/EC approvals

- Adverse Event Form and information
- Device disposition
- Protocol Deviations
- Informed Consent Forms
- Correspondence file regarding study
- Case Report Forms
- Subject termination information
- All study-related correspondence with the IRB/EC, sponsor, Study Monitor, and regulatory agencies, including required reports;
- Records of receipt, use, and disposition of devices, including receipt dates, lot numbers, and final device disposition;
- Records of each subject's case history, including information reported on all study-required Case Report Forms (CRFs), evidence of informed consent, all relevant observations of adverse events, the results of diagnostic testing, and the date of each study treatment.
- Copies of the approved clinical investigational plan and any amendments and documentation of any deviations from the clinical investigational plan including documented dates and reasons for each deviation.

14.2.4 Investigator Reports

The investigator is responsible for generating the following documentation:

- Unanticipated adverse device effects (UADEs) (to be reported to the sponsor and the IRB/EC as soon as possible but no later than ten working days after the UADE is known to the investigator),
- Withdrawal of IRB/EC approval (to be reported to the sponsor and FDA within five working days after the withdrawal of IRB/EC approval is known to the investigator),
- Progress reports (provided to the sponsor and IRB/EC at regular intervals (as requested by the governing IRB/EC) but no less than yearly),
- Deviations from the protocol (to be reported to the IRB/EC as soon as possible but no later than five working days after the deviation is known to the investigator). Except in an emergency, prior approval from the sponsor is required).
- Use of the investigational device without informed consent (to be reported by the sponsor to the IRB/EC within five working days after the use occurs).

14.2.5 Investigative Site Inspections

It may be necessary for a regulatory agency to audit the investigational site. The purpose of an audit is to assess the accuracy, adequacy and consistency of the study records and subject data and to assess adherence to the procedures described in this clinical investigational plan. Audits usually take approximately two days. A typical audit visit will include the following:

- upon arrival, an interview with the investigator and study personnel,

- a tour of the facility,
- a review of the study records,
- a review of the case report forms and source documents,
- at the conclusion of the audit, a discussion of any key audit observations.

15 Investigator Information

15.1 Investigators' Curriculum Vitae

Curriculum vitae for each principal investigator and all co-investigators will be submitted to the sponsor and maintained on file with the sponsor.

15.2 Investigator Agreement

Each principal investigator participating in this study will sign an investigator agreement that meets the requirements of CFR 812.43(c). The investigator agreement includes the following:

1) a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience,
2) a statement disclosing if the investigator was involved in an investigation or other research that was terminated, and an explanation of the circumstances that led to termination, if applicable,
3) a statement of the investigator's commitment to:
   a) conduct the investigation in accordance with the agreement, the investigational plan, all applicable FDA regulations, and any conditions of approval imposed by the reviewing IRB/EC or FDA,
   b) supervise all testing of the device involving human subjects; and
   c) ensure that the requirements for obtaining informed consent are met.
   d) provide sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under CRF part 54.

15.3 Financial Disclosure

The sponsor is required to obtain a financial disclosure statement in compliance with CRF part 54 for all investigators. The financial disclosure regulations require the sponsor to obtain a commitment from all investigators to promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study. This information will be maintained by the sponsor, and may be submitted to FDA in the future.

16 Institutional Review Board (IRB/EC) Information

The sponsor will maintain on file, the name, address and chairperson of the IRB/EC at participating centers (or acceptable alternative). This information will be provided to FDA as part of the reporting process in Annual and Semi-annual reports.

17 Informed Consent Materials

Informed consent will be obtained from each study participant. The investigator and/or the study coordinator designee will approach the potential subject, verbally explain the nature of the study, and provide an FDA and IRB/EC approved written informed consent document for his/her review and signature. The investigator and/or study coordinator will be available to answer all questions the subject may have about the study. The informed consent document includes all the required elements as outlined in 21 CRF Part 50.25. A copy of the Informed Consent template is provided in Appendix A – Informed Consent Template.

18 List of Appendices

18.1 Appendix A – Informed Consent Template

18.2 Appendix B – Glossary

19 References

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Appendix A – Informed Consent Template

INFORMED CONSENT

Targeted Hypoglossal Neurostimulation (THN) Study #3

PRINCIPAL INVESTIGATOR:

SPONSOR:

ImThera Medical, Inc.
12555 High Bluff Dr., Suite 310
San Diego, CA 92130 USA
(858) 259-2980

QUESTIONS OR PROBLEMS

For questions about the study or a study-related injury, contact your study doctor.

Study Doctor's name _____

Study Doctor's contact _____

For questions about your rights as a study participant or to address complaints about the study, contact the IRB via:

IRB Chair's name _____

IRB Chair's contact _____

INTRODUCTION

Your doctor has determined that you may be eligible to be in this study of a device called a hypoglossal nerve stimulator for obstructive sleep apnea (OSA).

This consent form, along with discussions you have with the study doctor or staff, will inform you of the benefits and risks of being in this study. There may be some words that you do not understand. Please ask the study doctor or staff to explain any words or information that you do not clearly understand.

You do not have to decide today whether or not you will be in the study. You may take home a copy of this form to think about this or discuss this with anyone you feel comfortable with before making your decision.

This is a research study. Participation in this study is voluntary. If you do not want to be in the study you will still get the same care that you would without being in this study.

If you sign this form you will be screened for the study. Signing this form does not mean that you will automatically be selected to be in the study.

PURPOSE OF THE STUDY

The device used in this study has already been approved outside of the United States. The device is not approved in the United States. For people who join this study in the United States, the device is an "investigational" device. Investigational means that the device being tested has not been approved by the FDA for use outside of this clinical study. The purpose of this study is to generate safety and effectiveness data to support market approval by the FDA for use of the device in patients with OSA.

NUMBER OF PARTICIPANTS

This study will be completed at no more than 20 centers. The study will enroll and implant 141 people.

DEVICE DESCRIPTION

OSA occurs when the muscles in the tongue and the back of the throat relax too much during sleep. When the muscles relax, your airway narrows or closes as you breathe in, and breathing momentarily stops.

The device being used in this study uses pulses of electricity to stimulate the nerves that control the muscles of the tongue. The stimulation is intended to restore tone to the muscles in the tongue and airway during sleep, and thereby reduce apneas and hypopneas.

The device looks and operates much like a heart pacemaker—except that instead of sending pulses to the heart, it sends pulses to a nerve in the neck. The device has the following parts:

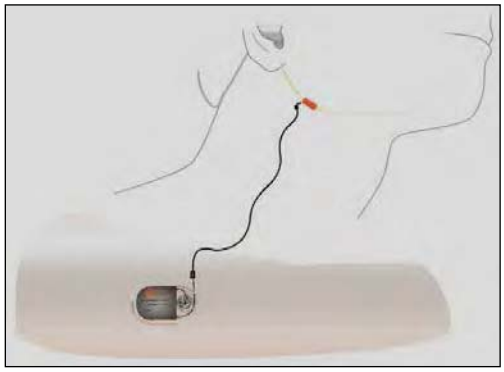
a) IPG—A small metal case with a rechargeable battery and electronics that make pulses which stimulate the nerve

b) Lead with electrode cuff—A cable that carries the pulses from the IPG to the nerve

c) Remote—A remote control device that is used to start, stop or pause stimulation therapy, and to charge the IPG

d) Programmer—A device used by the doctor to adjust the stimulation therapy to the needs of the recipient

Both the IPG and the lead with electrode cuff are implanted. The electrode cuff is put around the hypoglossal nerve in the neck, and the lead wire is routed under the skin to the IPG placed just below the collarbone. Here is a drawing of what this system would look like after it is implanted.



After the system is in place, the programmer is used by a study doctor or his/her staff to adjust the stimulation.

Unlike CPAP, you do not need to be connected to anything at night while you sleep. Each night before going to sleep you will use the remote to turn the IPG on. If you get up in the night, then you can use the remote to pause, and then resume, stimulation. When you get up in the morning you can use the remote to stop stimulation, or you can wait for the IPG to stop itself after an amount of time programmed by your doctor.

The IPG has a rechargeable battery. You will need to charge the IPG approximately every other day. Charging takes typically about 30-90 minutes depending upon how often you charge, and it can be done almost anywhere.

HOW LONG YOU WILL BE IN THE STUDY

You will be in the study for a little over 5 years.

STUDY DESIGN, PROCEDURES, & TESTS

After signing this Informed Consent, the first step will be for you to take some tests to see whether or not you qualify to be included in the study. This phase of the study is called "Screening". The table below shows the procedures performed in the Screening phase. More details about the procedures are provided at the end of this section.

If the Screening tests show that you meet the study requirements, then you will be invited to join the study. If you agree to join, you will be scheduled to have the device surgically implanted.

Visit/Procedure	Enroll	Screening #1	Screening #2	Surgery	Wound Check
Sign Informed Consent	☑				
Doctor's Visit		☑			
Surgeon's Visit		☑			☑
Questionnaires			☑		
Two Sleep Lab / PSG			☑		
Surgery				☑	

Screening Phase Visits and Procedures, and Surgery

After surgery, you will be randomized (assigned by chance, like the flip of a coin) to either the "Treatment Group" or "Control Group". Two out of three people in the study will be assigned to the Treatment Group, and the rest will be assigned to the Control Group. You will be told which group you are randomized when you visit the surgeon a week or two after your surgery.

The two groups have slightly different visit schedules as described in the table below. An important difference is that if you are assigned to the "Treatment Group" then you will begin to use stimulation therapy approximately one month after surgery, whereas if you are assigned to the "Control Group" you will be implanted with the device but not receive any therapy from the device for a period of four months, at which time therapy will start. Please carefully review the risks associated with the device implantation that are described in the informed consent document given to you by your physician. If you are part of the Control Group, you can, during this waiting period, use any other non-PAP and non-surgical sleep apnea treatments that you were using before you enrolled in the study until two weeks before the Month 4 visit, at which time therapy will begin.

Visit Name	Month 1	Month 2	Month 3	Month 4	Month 4 + 1 day	Month 5	Month 10	Month 12	Month 24, 36, 48, 60
Therapy Group	**Yes**	**Yes**	**Yes**	**Yes**			**Yes**	**Yes**	**Yes**
Control Group				**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Follow-up Visit	☑	☑	☑	☑	☑	☑	☑		☑
Doctor's Visit								☑	
Therapy Adjust PSG	☑	☑	☑		☑	☑	☑		
Questionnaires				☑				☑	☑
Endpoint PSG				☑				☑	☑

Study Visits by Randomization Group

The following procedures and tests will be used in this study:

- Doctor's Visit—Your study doctor or staff will do a physical exam, measure your blood pressure, height, weight and other vital signs, and collect information about the drugs that

you currently take. At the first visit (screening visit) he will ask you standard questions about your medical history, lifestyle, occupation, medical insurance history, gender, race, and date of birth, and do a pregnancy test if you are of child-bearing potential. The screening visit could take 1-2 hours; all other doctor visits should be shorter.

- Surgeon's Visit—You will visit the surgeon once before surgery to see if there are any reasons that you should not have the surgery, and then once again after surgery to see how you are healing.
- Upper Airway Exam—The doctor or surgeon will use an endoscope to look at your mouth, nose and throat.
- Follow-up Visit— Your study doctor or staff will measure your blood pressure, weight and other vital signs, and collect information about the drugs that you currently take.
- Questionnaires—The Epworth Sleepiness Scale, Functional Outcomes of Sleep (FOSQ), and EuroQoL Five Dimension (EQ-5D) are questionnaires that are being used to collect data for this study.
    - Epworth Sleepiness Scale (ESS)—You will be asked 8 questions to assess your sleepiness during the day.
    - Functional Outcomes of Sleep (FOSQ)—You will be asked 30 questions to assess the impact of your OSA on your activities of everyday living.
    - EuroQoL Five Dimension (EQ-5D)—You will be asked 6 questions to assess your mobility, self-care, usual activities, pain/discomfort, anxiety and depression and your health. This questionnaire is a generic measure of health for clinical and economic purposes.
    - Snoring Survey—You and your bed partner will be asked a few questions about your snoring.
- Screening PSGs—You will sleep two nights in a sleep center. You will be connected to equipment to record your sleep activity. The second screening PSG screening night must be no more than 14 nights after the first screening PSG, and your surgery must occur no later than 45 days after the last screening PSG.
- Therapy Adjustment Polysomnogram (PSG)—The settings for your device will be adjusted to your specific needs while you sleep overnight polysomnography at a sleep center. It will take multiple programming sessions to find your best settings.
- Endpoint Polysomnogram (PSG)—In addition to the Therapy Adjustment PSGs, you will sleep 2 night at a sleep center during the first year, then one night per year for the next 4 years. You will be connected to equipment to record your sleep activity. This test provides data to

evaluate the effectiveness of the therapy, and if you do not have at least 300 minutes (5 hours) of total sleep time, you will need to complete another PSG exam.

DESCRIPTION OF SURGICAL PROCEDURE

The surgery is done in a hospital operating room under general anesthesia. It takes 60-90 minutes. Two incisions will be made — a five cm incision on the upper neck under the jawbone, and a four cm incision just below the collarbone.

At the neck incision, the surgeon will access the hypoglossal nerve and place an electrode cuff around it. At the incision below the collarbone, the surgeon will create a "pocket" just large enough to hold the IPG. A wire is then passed under the skin between the two incisions and connected to the IPG, and then the incisions are closed with sutures (or "stitches").

Most people will go home either the same day or the day after surgery. When you leave the hospital after your surgery, the device will be turned "off". You will visit the surgeon a week or two later so that he can check on how the incisions are healing. The incisions will take about 1 month to heal, and the IPG and lead will stabilize within your body by the normal healing process. To help your body's healing process, you should not do physical activities that can move the electrode cuff's position around the nerve or the location of the IPG. Accidental movement of the electrode cuff from the nerve or damage to any of the implanted components may require additional surgery to correct or may cause your withdrawal from the study.

RISKS

Risks Associated with Study Drugs

This study does not require you to take any drugs, so there are no increased risks.

Risks related to Polysomnogram (PSG)

There is a chance you may have an allergic reaction to the skin patches used to detect the electrical activity during the PSG. Allergic reactions may include rash at the site of the skin patches.

Risks Associated With the Implantation Procedure

It is anticipated that you will be exposed to operative and postoperative risks similar to related surgical procedures involving the neck, and implantation of an implantable neurostimulator with associated lead. These surgical risks may include, but are not limited to:

- infection
- bleeding
- hematoma
- seroma
- scarring
- dysarthria
- lingual nerve or other surrounding structure injury

- excessive fibrotic tissue growth around the implanted device
- temporary or permanent hypoglossal or other nerve damage resulting in paresis (or weakness), paralysis or other dysfunction including impaired ability to swallow or speak
- temporary or permanent pain or numbness at the implant sites or tunneled path
- complications from intubation, anesthesia or extended procedure time
- heart attack
- allergic or immune system response to the implanted materials
- component migration or erosion through the skin

Risks Related to aura6000 System Revisions, Replacements, Explants

One or more components of the aura6000 System may need to be replaced or explanted in the event of a device failure or serious adverse event such as an infection or another clinical indication for device removal. The potential risks of device explant are the same as the risks associated with the initial procedure, complicated by the presence of the device components and scar tissue which could result in a failure to explant the entire system. Consequently, the risk of injury or damage to the hypoglossal nerve may be higher in revision or replacement procedures.

The IPG may need to be replaced when the battery is no longer able to hold a charge sufficient to deliver adequate therapy. The time to the elective replacement indicator (ERI) is estimated to be eleven (11) years and the time to end of life (EOL) is estimated to be fifteen (15) years or sooner if there is a neurostimulator failure. While the potential surgical risks of IPG replacement are similar to those at implant, this procedure does not require general anesthesia and therefore some associated risks may not apply.

The lead may need to be replaced or explanted as a result of lead migration, dislodgement, disconnection, fracture, insulation breakage or erosion. While the potential surgical risks of lead revision are similar to those at implant, this procedure is complicated by the presence of scar tissue around the hypoglossal nerve and nerve cuff.

The aura6000 System software may change, and it may be desirable or necessary to change the software in your implant or remote (or your doctor's programming system) to optimize performance. Software changes are non-invasively performed using radio waves, so there are no significant risks. Components of the aura6000 System, or their associated documentation may change. All such device changes would be reviewed by the appropriate regulatory bodies before they are released for use.

Risks Associated With the Presence of the aura6000 System

You may also be exposed to risks associated with the presence of the system components. These device risks may be short- or long-term and include, but are not limited to the following:

- lead migration, dislodgement, disconnection, fracture, insulation breakage or erosion;
- failure of IPG component, battery, software or telemetry
- IPG migration or flipping

- Ineligible for magnetic resonance imaging (MRI) while implanted with all, or any part, of the system

Risks Associated with Hypoglossal Nerve Stimulation with the aura6000 System

Most therapy-related side effects are reversible, and corrected by reprogramming or turning OFF the system. Chronic, irreversible stimulation related adverse events are expected to be rare. Potential therapy-related adverse events include, but are not limited to:

- paresthesia or tingling
- pain or discomfort due to stimulation or device malfunction
- paresis
- dysarthria
- excessive stimulation
- pain with stimulation
- reduction in benefit from chronic stimulation
- loss of therapeutic effect
- extrahypoglossal stimulation
- worsening of OSA condition

Risks Associated with the Study Protocol

You also will be exposed to risks associated with the required or optional procedures of the protocol including:

- You will be asked to completely stop the use of all other therapies for your OSA for 14 days prior to some overnight sleep studies.
- Exposure to fluoroscopy, x-ray, ultrasound or computed tomography (CT) if needed during the study to troubleshoot device or therapy performance
- Endoscopic imaging as needed to assess study eligibility, and to characterize, troubleshoot or document device or therapy performance, with possible side effects which include but are not limited to:
    - gagging
    - vomiting
    - nosebleed
    - aspiration
    - esophageal perforation
    - reaction or allergy to sedative, anxiolytic, or anesthetic medications

Polysomnography (PSG) and associated measurements during sleep The risks to pregnant women and their unborn child due to the presence of the system and the therapy provided are unknown. Women who are pregnant or breastfeeding or who intend on becoming pregnant are excluded from participating in the study. Women of childbearing potential must maintain adequate contraception during the 12 month course of the study. If a subject is enrolled and implanted with the investigational

system and becomes pregnant, the system will be turned OFF with the Therapy Controller or Programmer. The presence of the implanted aura6000 components is not considered to be a risk for pregnancy and delivery. The therapy may be resumed when indicated and as recommended by the subject's primary physician and the investigator.

BENEFITS

At this time, the clinical benefit of the aura6000 is unproven. You will receive an aura6000 device at no cost. Your fatigue, excessive sleepiness, and snoring, among other symptoms, may improve as a result of being in this study. You will add to the knowledge about this therapy such that, in the future, other people with OSA may benefit from knowledge gained in this study.

Also, for each overnight PSG visit you successfully complete, you will receive $50 US dollars to partially offset your incidental expenses in travelling to/from the visit. You will also receive an additional $150 US dollar for successfully completing the Month 12 PSG visit.

ALTERNATIVES

There are other options to treat your OSA. Please talk to your study doctor and/or your regular doctor to understand what other options are available to you and the risks and benefits of the alternative therapies. You do not have to be in this study.

COSTS

You will be receiving medical care as a part of this study. You will not be charged for the aura6000 device, or for the costs for the procedures, examinations, or tests required by the study. Your doctor may perform other procedures and tests not required under this study. The costs for these extra non-study procedures and tests, and the costs for your standard medical care, will be charged to you or your insurance. In this case, you will be responsible for the cost of the medical care related to your condition including but not limited to: the hospitalization and procedures, deductibles, co-payments, doctor and clinic fees. Please talk with your doctor and your insurance about these extra non-study costs, and any required pre-approval processes before agreeing to be in this study.

The study center and/or doctor will be paid by the Sponsor for the time, effort, and oversight by your study doctor and staff to accurately collect and submit study data.

CONFIDENTIALITY, USE AND DISCLOSURE OF STUDY INFORMATION

During this study we may collect your medical information, device information and other similar information resulting from study related activities as described herein. The information your doctor gets in this study will be given to the Sponsor and combined with the results of other patients. Your records and information on study participation will be kept as confidential as possible within the law. In order to verify the study data, representatives from the Sponsor or their designees, the IRB, and regulatory bodies may need to inspect and copy your records. Your information may be used to support future studies, publications, training, marketing, regulatory approvals, and for reimbursement purposes.

Patient registration numbers do not contain information that can be traced directly to you. All personnel working on this study are trained on the importance of using patient registration numbers that protect your privacy. The utmost of care is used to make sure that all your information is secure. Study information will be sent to the Sponsor where it will be entered into a secure database. Upon your approval, your personal physician will be informed of your participation in this study.

Some uses and disclosures of your information will be necessary to conduct the study. Therefore, you agree to permit your doctors and other health care providers, their staff, the study center, and its IRB (together known as "Health Care Providers") as well as the Sponsor, and its representatives and agents, to create, obtain, use and disclose certain information that identifies you (known as the "Study Data") as described below:

Your Study Data includes all information:

- About you collected during this study
- In your medical records that is relevant to this study

You agree that the Health Care Providers may:

- Use and disclose your Study Data to conduct this study
- Disclose your Study Data to the Sponsor of the study
- Disclose your Study Data to government agencies, review boards and other persons who oversee the safety and effectiveness of medical products and therapies and the conduct of research; and
- Remove your name and other identifying information from the Study Data for publication and other uses.

You agree that the Sponsor may:

- Use and disclose your Study Data to conduct this study
- Use your data obtained for publishing in peer reviewed journals or scientific forums
- Disclose your Study Data to government agencies, review boards and other persons who oversee the safety and effectiveness of medical products and therapies and the conduct of research
- Keep and use your Study Data as part of an ongoing research database
- Use and disclose your Study Data after the end of this research study for future research and any other business purposes
- Remove your name and other identifying information from the Study Data for publication and other uses.
- Contact you regarding updates to your system during or after the study.

The Sponsor will keep your health information confidential in accordance with all applicable laws and regulations. The Sponsor may use your health information to conduct this research, as well as for additional purposes, such as overseeing and improving its device, new medical research and proposals

for developing new medical products or procedures, health economics analysis, and other business purposes. Your name will not be placed on any mailing lists or sold to anyone for marketing purposes.

There are standard risks of being in a research study which include the loss of confidentiality. Every attempt will be made to ensure that your personal information remains confidential. Once your health information has been disclosed to a third party, federal privacy laws may no longer protect it from further disclosure. No publication about this study will reveal your identity without your specific written permission. These limitations continue even if you take back this consent.

You will not be allowed to see your Study Data while the study is in progress. However, after the study is finished you may see this information upon written request.

This consent does not have an expiration (ending) date as it relates to any Study Data that Sponsor may use to submit to governmental bodies in the future, or keep or use as part of any ongoing research database.

YOUR RIGHTS AS A PARTICIPANT

Taking part in this study is voluntary. You have the following rights.

Confidentiality

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the following groups: domestic or foreign regulatory bodies, the IRB (a group of people who review the study to protect your rights), the US Food and Drug Administration (FDA), and the Sponsor.

Protected Health Information (PHI)

If the study requires the use of your Protected Health Information, it will be obtained from your doctor. It will only be used to support the goals of the study. Your name will not be used and the information will only be used for the duration of the study. The information will be shredded or deleted after the study is completed. You would sign a separate document to grant your permission to use the information.

Right to Withdraw

You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled, and will not affect your access to standard health care with your doctor.

If you decide to withdraw from the study, contact your study doctor in writing and let him/her know that you are withdrawing from the study. The study doctor's contact information is listed on the first page of this consent form.

If you revoke this consent, you will no longer be allowed to be in the study. If for any reason, you quit the study, then your device will be turned off, and you will not be required to return for any follow-up

visits and your doctor will treat you for your OSA as he/she would have treated you if you did not sign this form to be in this study.

In addition, even if you take back this consent, the information already obtained by the Health Care Providers and the Sponsor may be used and disclosed as permitted by this informed consent.

New Findings

If significant new findings develop during the study which may relate to your willingness to continue participating, you and/or your study doctor will be given the information for review and discussion. If new information becomes available that can significantly affect your future health and medical care, this information will be provided to you in written form.

Legal Assistance

This consent form does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Consent Form.

Expense Compensation, Treatment of Injury

Please contact your doctor for essential medical treatment if you believe you have an injury as a result of this study. You will be treated for any injuries. Immediate necessary care is available if you are injured as a result of taking part in this study. In the event that you suffer a physical injury or illness as a result of this study, ImThera Medical will not be responsible to pay for your medical expenses not otherwise covered by a government agency, insurer, or another third party. Neither ImThera Medical nor your doctor has a program in place to provide other compensation in the event of an injury.

OTHER INFORMATION

Commercial Interest

The Sponsor and other researchers and licensees may patent or sell discoveries based on their research. The Sponsor and scientists and licensees may receive money from these activities. There are no plans to pay you or give you a personal economic interest in any products that may be developed from your procedure or information you provide. There are no plans for you to obtain or acquire any financial interest in the research.

Involuntary Withdrawal

Your doctor or by Sponsor may take you out of the study without your consent at any time if you do not follow your doctor's instructions; your safety or wellbeing is in question; or if the Sponsor decides to stop the study. Regulatory bodies may also stop the study. If your participation in the study is stopped, you will be asked to return for a final visit. Arrangements for longer-term follow-up might also be made.

Withdrawal Surgical Procedure

In the event that you withdraw from the study you may be asked to have some or all of the implanted parts of the stimulation system surgically removed. The surgical removal of the implanted electrode and

wires and/or the IPG may carry additional risks that are unknown at this time. Your doctor will discuss the risks and benefits of removal of some or the entire device with you.

Your Obligations as a Participant

As a study participant you will be asked to commit to active and courteous participation in the study. Specifically, you are requested make all efforts to:

1. attend all study-related visits and notify your doctor if your plans change or require alternative arrangements
2. follow instructions in preparing for PSG visits (e.g. abstain from alcohol, other OSA therapies, etc.)
3. provide accurate and timely responses to study questionnaires
4. avoid discussion of your experience with the device, therapy, or your OSA condition in social media, e.g. Facebook, Twitter, blogs, etc.

Device Recovery

In the event of your death, your doctor will seek copies of your medical records regarding your death. This may include emergency room records and hospital records. This information will be used for study purposes and will be kept confidential. Your family may be asked to allow the removal of the device, if necessary, for evaluation. Your family will not be charged for this procedure. If your family objects to the removal and requests that it not be done, your family's wishes will be honored.

Role of the Sponsor's Representative

In this study and at the request of your doctor, a representative of the Sponsor may:

- Provide technical expertise on the device or on the testing that will be conducted
- Be present at the implant, follow up visits, or other study related testing at your doctor's request
- Assist in programming your device or running tests, under the direction of your doctor
- Have some direct contact with you; and
- Be aware of how your device is programmed and your test results.

Your study doctor or their designee will always be present or nearby. Please talk to your study doctor if you have any questions.

Clinicaltrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

STATEMENT OF CONSENT

Your signature below indicates that you have read the above about the THN Study #2 and have had a chance to ask questions to help you carefully consider what your participation will involve. It also indicates that:

- All of your questions have been answered
- You agree that your participation is voluntary and agree to follow your doctor's instructions
- You understand that withdrawing from the study at any time will not incur a penalty for you
- You understand possible consequences of withdrawing from the study
- You agree to allow the use of your relevant personal data for the purpose of this study
- You agree that the Sponsor's representatives, regulatory authorities and Ethics Committee/Institutional Review Board representatives will be granted direct access to your medical records.

You agree to be in the study until you decide otherwise. You are not waiving your legal rights by signing this consent form.

_____	_____
Signature of Participant	Printed Name and Date
_____	_____
Principal Investigator/Designee	Printed Name and Date

Appendix B – Definitions

Apnea–hypopnea index (AHI): Index used to assess the severity of sleep apnea based on the total number of complete cessations (apnea) and partial obstructions (hypopnea) of breathing occurring per hour of sleep.

Anesthesia Severity Assessment (ASA) score: Physical status classification system for assessing the fitness of patients prior to surgery.

Positive Airway Pressure (PAP) Therapy: A device used to treat sleep apnea by positive airway pressure to help keep an open airway.

Oxygen Desaturation Index (ODI): Index used to assess the number of times per hour that oxygen saturation declines by more than 4% for more than 10 seconds.

Polysomnogram (PSG): A comprehensive recording of the biophysiological changes that occur during sleep.

Pain: Physical suffering or discomfort or distressing sensation in a particular part of the body not related to electrical stimulation.

Pain from Stimulation: Physical suffering or discomfort or distressing sensation as a result of electrical stimulation.

Infection: Symptoms assessed, diagnosed and treated with antibiotics by physician.

Bleeding**:** Excessive bleeding treated with medical intervention.

Hematoma: Abnormal buildup of blood in body tissue caused by trauma or surgery observed by clinician.

Paresthesia: Abnormal prickling or tingling or numbness sensation.

No Stimulation: No stimulation detected when IPG is turned on.

Dysphagia: Difficulty in swallowing.

Paresis: Incomplete or slight paralysis of motor functions.

Seroma: The abnormal buildup or pocket of serous fluid in body tissue.

Fibrosis: The production of excessive fibrous tissue, as in reparative or reactive process.

Anesthesia Complication: An unexpected condition or event from anesthesia requiring medical intervention.

Allergic Response: A hypersensitivity to a substance that causes the body to react to any contact with that substance.

Device Migration: Movement of the implanted device within the body.

Worsening of OSA Symptoms: As reported by patient or patient's significant other; excessive sleepiness, morning headaches, increasing choking or gasping while asleep, restless sleep.

Other: Any reported events related to safety or efficacy of the Investigational Protocol or Devices.