Clinical Study Protocol

Radiofrequency Ablation for Multi-level Obstructive Sleep Apnea: A Single-arm, Multicenter study

Short Title: RAMOSA
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INVESTIGATORS

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PROTOCOL SYNOPSIS

Protocol ID number	**990211**
Protocol Title	Radiofrequency Ablation for Multi-level Obstructive Sleep Apnea: A Single-arm, Multicenter study
Version/Date	Revision 4, February 27th, 2014
Sponsor	Olympus Winter & Ibe Kuehnstr. 65 22045 Hamburg Germany
Study Centers	[redacted]
Study Population	Mild to moderate OSAS patients (AHI of 10-30 and BMI ≤ 32)
Investigational Device	CelonProSleep *plus* RF electrode (Olympus Winter & Ibe, Hamburg, Germany)
Investigational Product Description	The CelonProSleep *plus* is a rigid, sterile, single-use, bipolar electrosurgical electrode. It is used in conjunction with the electrosurgical generator CelonLab ENT.
Intended Use	The CelonProSleep *plus* is a FDA-cleared RFA device (K032838) that is indicated for ablation and coagulation of soft tissue in otorhinolaryngology (ENT) surgery including submucosal tissue shrinkage and tissue coagulation in the uvula/soft palate for the treatment of snoring. [redacted]
Study Objectives	The primary effectiveness of the study is to demonstrate a clinically significant reduction of OSAS from Baseline PSG sleep study to the 6-Month follow-up PSG in adults (≥ 22 years) with obstructive sleep apnea (AHI 10-30) and BMI ≤ 32.
Study Planned for	[redacted]
Study Design	Multi center, Open label, single arm, non-randomized study
Scientific	Radiofrequency ablation (RFA) of the upper airway using

background	FDA-cleared devices has demonstrated promise as a treatment alternative for obstructive sleep apnea in multiple published studies. In these studies, repeated RFA of the soft palate and base of tongue region resulted in significant reductions in AHI and daytime sleepiness without significant complications. RFA has several advantages over traditional surgical approaches including its ability to address multiple levels of the airway (nose, palate, tongue); ability to perform in the office under local anesthesia; lower cost; and minimal pain and morbidity. The Celon ProSleep *plus*, the device used in this study, was already used in a few studies to treat soft palate and base of tongue in OSAS patients.
Study Justification	Surgery in OSAS is less commonly used for a number of reasons foremost of which is the inconsistent success and high pain and morbidity of the most commonly performed procedure uvulopalatopharyngoplasty (UPPP; removal of tonsils and uvula and soft palate tissue). RF ablation of the soft palate and base of tongue is considered as a minimal invasive treatment method with relative few post-surgery complications.
Inclusion Criteria	• Adults (≥ 22 years) • Self-report of daytime somnolence • Body mass index (BMI) ≤ 32 • Mild to moderate obstructive sleep apnea (AHI 10-30; lowest O2 sat ≥ 80%) based on a prior PSG conducted within 12 months of enrollment, or based on a 2-night home sleep study using the WatchPAT 200S-3. • Evidence of palate and tongue base collapse on supine fiberoptic examination (Müller's maneuver) • Have failed or have not tolerated CPAP treatment (see Section 5.1 for details) • No prior surgical treatment for OSAS other than nasal surgery or tonsillectomy. • Willing and capable of providing informed consent • Willing and capable to return for all follow-up visits and PSG sleep-studies and filling out the questionnaires.
Exclusion Criteria	• No regular bed partner • Another significant sleep disorder (e.g., insomnia, periodic limb movement) • Tonsillar hypertrophy • Chronic Obstructive Pulmonary Disease (COPD) • Interstitial Lung Disease (ILD) • Cystic Fibrosis • Acute Respiratory Distress Syndrome (ARDS) • Nasal or supraglottic obstruction on fiberoptic

	examination • ASA class III ,IV, V • Latex allergy • Lidocaine allergy • Pregnancy or plans to become pregnant Note: women of childbearing potential must demonstrate a negative pregnancy test upon enrollment; those patients qualified to progress to RFA must also demonstrate a negative pregnancy test within 7 days prior to the date of RFA procedure. • Major depression or non-stabilized psychiatric disorder • Drug or alcohol abuse • Previous palatal or tongue surgery • Stable or unstable angina • CHF • Moderate or severe valvular disease • TIA/CVA • Carotid stenosis or endarterectomy • Anemia • Room air SpO_2 < 95% • Pulmonary hypertension • Dialysis • Central or mixed apnea ≥ 10% of respiratory events • Participation in another clinical study (enrolled in any concurrent study) whose investigational plan is judged to interfere or affect any of the measures of this study
Study Endpoints	Effectiveness of the CelonProSleep *plus* will be assessed by demonstrating adequate reduction in AHI and ODI as defined below: A responder to the CelonProSleep *plus* RFA treatment is defined as a patient with an AHI reduction ≥50% ***and*** a reduction of their ODI ≥25% at the 6-month follow-up PSG, and their AHI at the 6-month follow-up is <20.
# of patients	43 + 10% dropouts (n=48)
Treatment Procedure	Three treatment sessions of RF ablation of the soft palate (7 lesions) and the base of tongue (6 lesions).
Statistical Analysis of Endpoints	The performance endpoints will be assessed by recording the functional parameters and by monitoring the patient clinical status. Safety assessments will consist of recording of any adverse events. Variables will be analyzed by using appropriate statistical techniques for parametric and continuous measurements.
Follow-up	6 months after the last RFA treatment.
Study Duration	24 weeks plus 6 months of follow-up for each patient

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1. BACKGROUND

1.1 Obstructive Sleep Apnea

The United States is currently experiencing an increase in the incidence and prevalence of obstructive sleep apnea (OSA). With prevalence in middle-aged adults of 2 to 4% of the population, untreated OSA increases the risk for cardiovascular disease, including hypertension and heart failure, daytime sleepiness, and increased risk of motor vehicle accidents[1-6].

Despite its prevalence and increased recognition as a cardiovascular risk factor, OSA remains largely under diagnosed. The standard test for diagnosis of OSA is polysomnography (PSG), which produces outputs on a number of physiological variables. The apnea-hypopnea index (AHI), expressed as the number of apneas/hypopneas per hour of sleep, is the most commonly used variable to measure the severity of disease. Generally speaking, an AHI of 5 or greater when associated with daytime sleepiness connotes a diagnosis of sleep apnea. An AHI between 5 and 14 is defined as mild disease, whereas an AHI of 15 to 30 is moderate, and an AHI greater than 30 is severe disease. The goal of treatment of OSA is improvement of AHI and other key variables (such as lowest oxygen saturation, LSAT), and improvement of patient symptoms and reduced cardiovascular and overall mortality.

The first line and most common treatment for OSA is continuous positive airway pressure (CPAP), utilized by an estimated 3 million Americans. CPAP is effective in reducing the AHI if used properly. However, the nasal and/or facial mask required for CPAP during sleep may lead to poor adherence to therapy. Published studies on CPAP have shown that only 58 to 80% of patients accept CPAP therapy[7-10], with 65 to 90% exhibiting long-term adherence to CPAP, therefore 10-40% of patients fail to maintain CPAP use over time[11]. Additionally, many patients treated successfully with CPAP have low treatment satisfaction due to facial discomfort, nasal blockage, abdominal bloating, and loss of intimacy with their bed partner. CPAP variations such as auto-titrating CPAP, heated and humidified air, and bi-PAP (different pressures on inspiration and expiration) have failed to consistently improve patient adherence to therapy, indicating a significant unmet need for CPAP alternatives in patients who are not adherent to therapy[12].

1.2 Diagnosis of Obstructive Sleep Apnea

The gold standard for the diagnosis of OSA remains the attended overnight level I polysomnogram (PSG). PSG's include electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), oronasal airflow, thoracic and abdominal movement, oxygen saturation, snoring level, and body position[13]. However, PSG has many limitations including high cost, long waiting lists, limited availability and the need for technical expertise to perform and interpret. In addition, many patients find the PSG equipment too cumbersome and may be reluctant to spend the night in the laboratory. Thus, it is not possible to perform PSG studies for all individuals suspected of having OSAS and waiting duration for PSG may exceed months to years[18], resulting in patients who are waiting long time for an adequate therapy.

As a result of these factors single and multiple channel monitoring systems have been introduced to screen for OSA. One of these systems is the WatchPAT 200S-3 (Itamar Medical Inc., Franklin, MA,

USA)[1], which is a level III (minimum of 4 physiologic channels) portable diagnostic sleep device that is worn on a patient's wrist along with two self-adhesive finger probes. The device measures several parameters including pulse Oximetry, heart rate, wrist actigraphy (muscle twitches), body position, snoring, and peripheral arterial tonometry (PAT). The WatchPAT 200S-3 uses patented algorithms which interpret the physiologic measurements to detect the presence of sleep-disordered breathing. A major advantage to the system is its ease of use which can be easily applied by the patients in the comfort of their own bedroom, an environment that best reflects the pattern of their sleep habits. Increasingly, the public and third-party payers are requiring home sleep testing devices such as WatchPAT as the initial diagnostic for sleep-disordered breathing due to increased patient acceptance and reduced cost of care.

In 2007, the AASM published its clinical guidelines for the use of unattended portable monitors in the diagnosis of OSA in adult patients[16]. These guidelines state that " the Portable Monitoring Task Force of the American Academy of Sleep Medicine (AASM) makes the following recommendations: unattended portable monitoring (PM) for the diagnosis of obstructive sleep apnea (OSA) should be performed only in conjunction with a comprehensive sleep evaluation. On December 14, 2007 the CMS released its proposed decision for modification of NCD policy 240.41 pertaining to coverage of CPAP therapy for adult obstructive sleep apnea (OSA). The proposed modification allows for an initial 12 week period of CPAP coverage when OSA is diagnosed using both a clinical evaluation and PSG performed in the sleep laboratory or a clinical evaluation and unattended home sleep studies using a Type II, III or IV device[17].

With WatchPAT 200S-3, both RDI and AHI scores are highly reproducible, showing correlation between home and in-laboratory sleep studies[e.g.19-24]. This study will utilize WatchPAT 200S-3 for screening of the qualification of the patient to participate in the study regarding his/her AHI score. In addition, patients will undergo WatchPAT home sleep study at both follow-up visits for determining changes compared to the screening visit. In order to decrease the risk of overestimation of OSA variables with increasing severity of OSA the current study will include only mild to moderate patients.

1.3 Surgical Therapy for OSA

Surgical therapy for OSA is less common than CPAP therapy. Fewer than 100,000 surgical treatments for OSA are performed in the United States annually, despite the fact that up to a third (700,000) of the two million people in the U.S. who start CPAP each year may ultimately fail to adhere to CPAP over the long-term. Surgery is less commonly used for a number of reasons foremost of which is the inconsistent success and high pain and morbidity of the most commonly performed procedure uvulopalatopharyngoplasty (UPPP; removal of tonsils and uvula and soft palate tissue). The most effective surgeries for OSA require multi-level treatment (palate and tongue base levels), are more complex, and are not as widely available since they require specialized surgical training and experience that are not generally available. In the literature, a successful surgical treatment is generally defined as a 50% reduction in AHI and an overall post-treatment AHI of < 20/hour[25].

[1] 510(k) premarket notification numbers K102567, K042916, K010739

Surgical therapy is based in part on an anatomic assessment of the likely sites of obstruction. Anatomic analysis is most commonly performed with fiberoptic examination of the upper airway, with radiographic imaging reserved for cases of suspected craniofacial abnormality. Under the classification of Fujita,[26,27] patients with obstruction in the oropharynx only are considered type I; those with obstruction in the oropharynx and the hypopharynx are considered type II (mixed site of obstruction); while those with hypopharyngeal-only obstruction are considered type III. Most patients (>75%) have a mixed site of obstruction (type II)[28]. Multilevel obstruction is a common denominator for many patients with OSA, whether it is classified as mild, moderate, or severe disease[29-33]. Therefore, surgical treatments must be multi-level by necessity in order to address potential sites of obstruction. Whereas unselected single site surgery of the oropharynx (soft palate) with uvulopalatopharyngoplasty (UPPP) is successful only 40% of the time, surgical success can be improved to greater than 65% when UPPP is combined with procedures to address the base of tongue (hypopharynx). This 65% success rate of multi-level sleep surgery approaches the long-term adherence and success rate of CPAP therapy[25].

Radiofrequency ablation (RFA) of the upper airway using FDA-cleared devices has demonstrated promise as a treatment alternative for obstructive sleep apnea in multiple published studies [29-31, 34]. In these studies, repeated RFA of the soft palate and base of tongue region resulted in significant reductions in AHI and daytime sleepiness without significant complications. RFA has several advantages over traditional surgical approaches including its ability to address multiple levels of the airway (nose, palate, tongue); ability to perform in the office under local anesthesia; lower cost; and minimal pain and morbidity.

RFA enables the surgeon to direct the delivery of a specific amount of radiofrequency energy, measured in joules, to a specific site at a controlled temperature. This radiofrequency energy is delivered at relatively low power and voltage. Application of radiofrequency energy in this manner causes tissue ions to become agitated due to changes in electrical flow inherent in alternating current. These ionic shifts result in resistive heating by the tissue itself, and in comparison to electrocautery, the production of low temperatures (60° to 95°C). Protein, which denatures at temperatures in excess of 47°C, undergoes tissue coagulation along with surrounding stromal and vascular tissue. The lesion created by RFA is consistent with tissue coagulation and results in congestion, edema, and an acute inflammatory response within the first 24 hours. Over a period of 72 hours, the treated area progresses to tissue necrosis which may change to fibrotic tissue over the course of 10 days.

Volumetric reduction occurs in 2 stages. The contracted area of fibrosis occupies a smaller area than normal tissue and retracts the surrounding normal tissue resulting in the first stage of volumetric reduction of tissue. The second stage, resulting in further volumetric reduction, occurs over the course of several months as the body resorbs the area of fibrosis.

The CelonProSleep *plus*, the device used in this study, is a FDA-cleared RFA device (K032838) that is indicated for ablation and coagulation of soft tissue in otorhinolaryngology (ENT) surgery including submucosal tissue shrinkage and tissue coagulation in the uvula/soft palate for the treatment of snoring. The system is intended for use by qualified medical personnel trained in the use of electrosurgical equipment.

1.4 CelonProSleep *plus*

The CelonProSleep *plus* is a rigid, sterile, single-use, bipolar electrosurgical electrode. It is used in conjunction with the electrosurgical generator CelonLab ENT. The device is indicated for the ablation and coagulation of soft tissue in otorhinolaryngology surgery including submucosal tissue shrinkage and tissue coagulation in the uvula/soft palate for the treatment of snoring, and the soft palate (velopharynx) and base of tongue (oropharynx) for the treatment of mild to moderate obstructive sleep apnea syndrome (OSAS).

Two electrodes located coaxially on the distal end of the device allow the generator to deliver a bipolar output to the tissue area, thus a neutral electrode or return conductor is not required. This is an advantage over other approved radiofrequency devices (ex. Somnoplasty) that require placement of a grounding pad on the patient and could interfere with implantable pacemakers. The power output on the device is controlled by the user on the generator unit. During its operation, tissue impedance is measured as coagulation status feedback. An acoustic signal from the generator unit informs the user that the coagulation process is complete and results in the automatic cessation of output power, ensuring safety in operation.

The dimensions of the CelonProSleep *plus* is designed for otorhinolaryngology surgeries—the bend angle and electrode length allow placement of electrode tip on the target tissue areas in the oral cavity and the trocar tip is appropriate for ablation and coagulation of tissues that are difficult to penetrate.

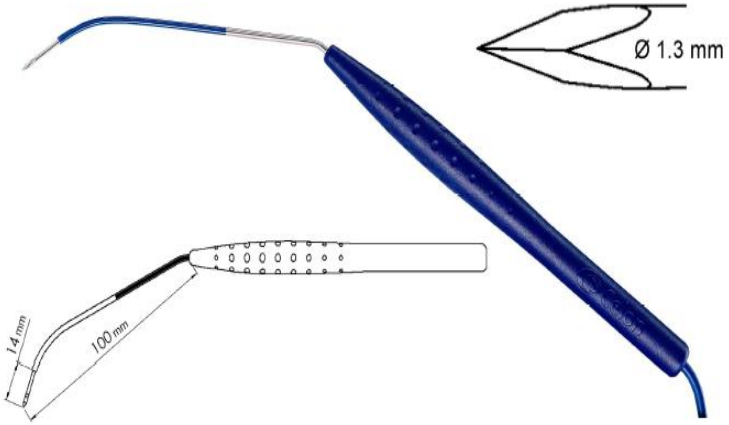

Fig. 1 The CelonProSleep *plus*

Each electrode is supplied with an insulating cover that allowed exposure of only 1 cm of active electrode to avoid mucosal injury during treatment. The application time varied between four to six seconds per puncture (soft palate) and ten to sixteen seconds at the base of tongue, terminated by acoustic ‘end-indication’ and auto-stop facilitated by a thermistor and tissue impedance measurement at the probe tip. Energy delivery can be manually terminated by the operator if any pain or blanching of mucosa occurred.

1.5 Safety of RF ablation of the soft palate and base of tongue

Radiofrequency ablation of the soft palate and base of tongue is considered as a minimally invasive therapy with much less side effects and complications in comparison to other surgical therapies for OSAS[39, 40].

Potential specific complications of radiofrequency ablation include bleeding, infection, ulceration, palatal fistula, tongue weakness, and taste disturbance alongside globus sensation. Long-term complications are unusual but globus sensation may persist in up to 10 % of patients. Most patients recover quickly however and report improvements in snoring although a recent systematic review indicated that further long-term studies are required[41-43].

In a retrospective study, 130 patients underwent one to three sessions of RFA of soft palate (6 lesions) and base of tongue (6 lesions) with either Somnus (Gyros-ENT), or the CelonProSleep *plus* (Caroll et al. [32], with [redacted] the PI in this study). The most common complication of upper airway RFA was mucosal ulceration (11%; mild side effect[45]), which healed with saline gargles within 10 days to 2 weeks. Ten patients (8%) had significant palatal or tongue edema (mild complication), which interfered with speech and/or swallowing but resolved within a few days of starting a taper dose of steroids. One patient had a temporary paresis of the lingual nerve (moderate complication), which resolved a couple of weeks after tongue base RFA. This was attributed to a pressure neuropathy from the laryngoscope because the lingual nerve was not within the field of the RFA application. No patient had a severe or prolonged dysphagia preventing oral diet immediately after the procedure. However, no information is given whether the complications caused by using the Somnus or the CelonProSleep *plus*[32].

Factors that affect RFA complications may be repeated RFA treatment to the same tissue, learning curve of individual surgeons, energy delivered per lesion, temperature selection, anatomical site treated, and perioperative steroid use[45].

Kezirian et al.[45] reported incidence of complications after RF treatment of the soft palate and base of tongue. 22 publications on the soft palate with a total number of patients of 669 and 1406 RF treatment sessions were reviewed. The total number of complications was 119 (0.6%), with 111 minor, 7 moderate, and 1 major complication. Of the reviewed studies only one study used the CelonProSleep *plus*[67] (Tatla et al., 2003: 10 patients, 20 treatment sessions, 120 lesions, 2 mild palatal swelling, mucosal ulceration in one lesion).

The review of 9 studies revealed an incidence of complications for the treatment of the base of tongue of 48 (2.7%). The number of patients in these studies was 614, and the number of treatment sessions was 1392. There were 10 minor, 28 moderate, and 10 major complications. None of these studies used the CelonProSleep *plus* RF device[45].

Farrar et al., (2008, with [redacted] PI)[35] conducted a meta-analysis on published studies to obtain a precise estimate to the effectiveness of RFA in the treatment of OSA. The total number of soft palate complications was 13 (3.9% in 144 patients over 331 treatments sessions), and the total number of base of tongue complications was 38 (3.5% in 252 patients over 1092 treatment sessions). Out of 16 studies

only one study used the CelonProSleep *plus* for RFA treatment of the base of tongue (den Herder[46]: 24 patients, 1-3 treatment sessions, 6 lesions/session, no complications).

A compendium of published studies on RFA of the soft palate and base of tongue is presented in Table 1.

Table 1

Author (yr)	Sample Size	Sites Treated	# of Lesions BOT/SP per session	# RF Sessions	Interval between Treatments	# Complications / n patients	Mean Follow-up	RF Device	Mean Joules	Power
Powel (1999)[47]	18	BOT	3-5	2-9	3-4 wks	One patient pain on swallowing, 1 patient BOT infection	4 mos	Somnus	1543 J/session	10 W
Nelson (2001)[48]	10	BOT	2-6	3	3-6 wks	None	Up to 2 mos	Somnus	1,000 J/lesion 12,000J/ patient	10 W
Woodson (2001)[49]	56	BOT	2-11	3	3-4 wks	25% mild edema, 6.2% moderate (mucosal erosion)	3 mos	Sumnoplasty	2,720 J/session	10 W
Stuck (2002)[50]	18	BOT	4	3.4	4-6 wks	Mild to moderate tongue swelling, One BOT infection	3 mos	Sumnos	2800/session	10 W
Terris (2002)[51]	10	SP	3	3	NA	NA	4 mos	Sumnos	1090/session	10 W
Blumen (2002)[56]	29	SP	3-4 SP	2-3	6-8 wks	3/29	4 mos	Somnus	2067	10 W
Li (2002)[52]	16	BOT	NA	5.5	NA	NA	24 mos	Somnus	1543 J/session	10 W
Fisher (2003)[53]	15	BOT/SP	3 BOT 5 SP	1	1 session	1 SP ulceration	3 mos	Somnus	9750	10 W
Woodson (2003)[29]	26	BOT/SP	3 BOT 3 SP	5 BOT 2 SP	4 wks	Hematomas 2.3% Ulcerations 0.8% Infections 0%	NA	Gyros ENT	3000 BOT/session 1000 SP/session	10 W
Riley (2003)[31]	20	BOT	3	5	4 wks	NONE	3 mos	Gyros ENT		10 W

									7915 Total	
Steward (2004)[30]	26	BOT/SP	3-4 BOT 3 SP	3-5 BOT 1-3 SP	3-4 wks	BOT 2 hematomas, 3 ulceration SP 3 Ulceration	3 mos	Gyros ENT	BOT 1000/session SP 1000/session	10 W
Steward (2004/1)[54]	22	BOT/SP	5 BOT 2 SP	4.8 BOT 1.5 SP	4 wks	3 hematomas, 1 mucosal ulceration, 3.1%	2 to 3 mos	Gyros-ENT	9500 BOT 2350 SP	10 W
Stuck (2004)[55]	18	BOT/SP	4 BOT 3-4 SP	4 BOT 3 SP	4-6 wks	None	Up to 1 mos	Somnus	2800 BOT 1800 SP	10 W
Steward (2005)[34]	29	BOT/SP	1-3 BOT 3 SP	2-3 BOT/ SP	NA	None	23 mos	Gyros-ENT	Up to 3300 BOT/session 1300 SP/session	10 W
Blumen (2006)[68]	10	BOT	3-6	2-3	4 mos	1 pt severe pain, one pt hemilingual hypesthesia, one pt mild swelling	4 mos	Somnus	14,288 J	15 W
Holmlund (2014)[57]	20	SF	3 SP	3	4-6 wks	None	12 mos	Coblator (arthocare)	_____	
Fernandez-Julian (2009)[58]	29	BOT	4	3	4-5 wks	1 patient (mucosal ulceration)	0.75 month	Somnoplasty	3,000 J BOT/session	10 W
Ceylan (2009)[33]	47	BOT/SP	10 BOT 3 SP	1	___	None	12 mos	Gyrus-ENT	3,000 J BOT 1,300 J SP	10 W
Friedman (2007)[59]	122	BOT	10	1	___	1 patient, mucosal ulceration	At least 6 mos	Gyros-ENT	3,000 J BOT	10 W
Hultcrantz (2010)[60]	29	SP	6-8 SP	4	NA	5 patients with small ulcers	40 mos	Elman Surgitrone	NA	
Verse (2006)[39]	60	BOT	4	4	4-6 wks	NA	8 wks	Somnus		10 W
Pazos (2001)[61]	30	BOT/ SP	NA	2 BOT 2SP	6 wks	11 mild 6 moderate 4 severe	1 month	Somnus S2	1,500 J BOT 1,550 J SP	10 W
Den Herder (2006)[46]	73	BOT/ SP	6	1-3	6 wks	2 pts with tongue deviation, resolved within an hour	Up to 1.5 mos	**CelonLab and Celon ProSleep**	84 J X 6 lesions = 504 Joules	
Balsevicius (2013)[62]	32	SP	9 SP	NA	6-8 wks	6 patients mucosal blanching	2-3 mos	**CelonLab and Celon ProSleep**		10 W

						(resolved in 1 month)				
Civelek (2010)[63]	12	BOT	5-7	1	___	None		**CelonLab and Celon ProSleep**	224 J	
Van den Broek (2008)[64]	37	BOT	6	1	___	No major complications, 1 pt edema		**CelonLab and Celon ProSleep**	252 J	7 W
Heywood (2010)[65]	5	BOT/SP	6 BOT SP NA	1	___	None		**CelonLab and Celon ProSleep**	240 J/BOT SP NA	6 W /BOT 10 W/ SP
Olszewska (2012)[66]	79	BOT	8-16	2	NA	None	6 mos	**CelonLab and Celo n ProSleep**	480-960 J/session	6 W
Caroll (& Gillespie, 2012)[32]	130	BOT/SP	6 BOT 6 SP	1-3	6 wks	See description above	5 mos	**CelonLab and Celon ProSleep and Somnus**	Values are given for the Somnus 1800 J BOT/ses 1800 J SP/session	
Tatla (2003)[67]	10	SP	6 SP	2	6 wks	2 mild palatal swelling, one lesion mucosal ulceration	1.5 mos	**CelonLab and Celon ProSleep and Somnus**	360 J SP /session	10 W

Eight studies describe the use of the CelonProSleep *plus* for the RF treatment of the soft palate and base of tongue[32, 46, 62-67]. In seven of these studies there were 199 patients, and the number of lesions varied between 6 and 18 for the base of tongue, and 6 to 9 for the soft palate. The number of lesions among all studies was approximately a minimum of 2,400 (# of patient * # lesions * one session). There were 9 mild complications (0.37%, mucosal blanching), and one moderate complication (0.04%, tongue edema). Details on the eighth study, Caroll et al.[32], and the number of complications are given above.

One of the factors that affect RFA complications is the amount of energy delivered per lesion[45]. A comparison between the studies in the above Table reveals that, the amount of applied energy by using the CelonProSleep *plus* RF device is much less than by using the Gyrus or Somnus devices. For one lesion in the base of tongue Gyrus/Somnus recommend target energy of 750 Joules (J). Celon recommends using a setting power of 7 W that due to the impedance-feedback auto-stop function results in an application time of 7.4 seconds. The applied energy with Celon RF device is E = P * t = 7 W * 7.4 s = 51.8 Joules. Thus, CelonProSleep *plus* applies only 51.8 J/lesion compared to the 750 J/lesion of Gyrus or Somnus.

The Somnus device has a higher energy input and is monopolar, exposing the entire body of the patient, whereas the CelonProSleep *plus* unit has inherent innovative bipolar tip safety. This ensures that only tissue in the immediate vicinity of the probe tip, which has a bipolar arrangement of

electrodes in the needle, is exposed to the radiofrequency current. This removes some of the risks linked to the process and the need for a neutral electrode is lost, eliminating the risk of burns. Further safety is provided by acoustic feedback and an auto-stop power control, whereas the Somnus device relies on the operator visualizing the temperature and impedance signal.

Due to the bipolar electrode the CelonProSleep *plus* device coagulates much faster (although the power setting is less) than the Gyrus or Somnos systems. Therefore, less energy is needed to reach the coagulation threshold of the tissue. In the case of a very slow coagulation process, as happens with the Gyrus or Somnos devices, a big proportion of energy is transported away from the target region by circulating blood before the coagulation threshold is reached.

2 STUDY DESIGN

2.1 Study Type

The RAMOSA Trial is a multi-center, prospective, controlled trial. Sub-studies are not permitted without the prior approval of Sponsor.

2.2 Scale

The study will be conducted at a maximum of 3 centers in which at least one study center will be in the United States. Patients will be enrolled to provide data from up to 48 subjects. Data from 43 subjects is required to demonstrate efficacy and we count 10% for dropouts (Section 3.2 Sample Size Rational). When the treatment limit of 48 subjects is reached, Sponsor may opt to submit for expanded access.

2.3 Duration

The duration of the RAMOSA trial is expected to be approximately 24 weeks, and follow-up data will continue to be collected for 6 months post-treatment. Enrollment in the RAMOSA trial is anticipated to require approximately 1 year from the first regulatory authority approval. Once 48 subjects have been followed for 24 weeks, the clinical data will be reported to regulatory authorities. All subjects enrolled in this study must be followed according to the investigational plan unless Sponsor notifies the Investigator to the contrary, or Sponsor has officially closed the study.

2.4 Rational for patient selection

This study aims to evaluate the CelonProSleep *plus* for multi-level radiofrequency ablation (RFA) of the palate and base of tongue as a treatment for mild to moderate obstructive sleep apnea syndrome (OSAS) in patients with AHI of 10-30 and BMI ≤ 32. The AHI cut-off of 30 is used because patients with AHI > 30 have OSA of such severity that they are unlikely to respond to RFA. Unlike traditional sleep surgery, RFA does not involve radical removal of tissue but works primarily by remodeling and stiffening the tissues of the upper aerodigestive tract. A meta-analysis of RFA studies found a mean AHI reduction of 45% after 24-month follow-up[35]. Since standard measures of surgical success (AHI reduced by 50%) are applied in this study, we anticipate that many patients with severe (AHI >30)

apnea would not be considered a surgical success and should therefore be excluded in favor of other more effective therapy for severe OSA (CPAP or traditional surgery). RFA demonstrates improved sleep outcomes if the procedure is repeated on several occasions in order to deliver enough energy to create the critical mass of scar tissue to offset the increased collapsibility of the upper airway[32, 35]. Therefore, the present trial will repeat upper airway RFA on three occasions in order to maximize treatment effect. The treatment sessions are separated by six weeks since it takes approximately 3-4 weeks for the lesion to convert to scar and therefore all tissues should be healed by week 6[36]. In addition, multiple studies have found that rates of surgical success for OSA decline with increasing patient BMI. This is especially true for patients with morbid obesity (BMI >40) who have a significant level of lingual and parapharyngeal fat which increase the collapsibility of the upper airway. Since most patients with OSA are overweight to obese, too low of a BMI cutoff may be overly restrictive[37]. The BMI cut-off of 32 is a convenient rule-of-thumb frequently used by sleep surgeons which captures a large percentage of the OSA population which are more likely to succeed with sleep surgery while excluding the most obese subset who are less likely to succeed and are at increased risk for surgical complications.

2.5 Determination of last Follow-up visit

Although in-laboratory PSG is the gold standard for diagnosing OSAS, there are a few factors that may lead to biased results when using PSG for determining treatment success in studies that apply long-term follow-up measurements (e.g. one year). Some of these factors are 1) selecting only patients that are willing to participate in a PSG study might lead to a selection bias and thus, excluding patients who are suited for the tested treatment, but are not willing to participate in a PSG study; 2) a long-term follow-up may lead to a high number of dropouts because of various reasons as described below; and 3) PSG records biophysiological changes during sleep, but not the changes occurred in daily life situation from the last treatment till the follow-up visit (e.g. change in personal or professional status, weight changes, or other factors that are not related to the treatment, but contributing to sleep quality). Thus, a longer interval between the treatments to the final follow-up visit will result in an increase in missing data, weaken the association between treatment and effect, and potentially introduce bias into the study.

An analysis of the (prospective) RFA studies that are discussed in section 1.5 (Table 1), reveals correlative relations between the amount of dropouts and the interval between last RFA treatment and the follow-up visit. 12 of these studies had a follow-up visit of up to 4 months[29, 31, 39, 46, 48, 50, 53-55, 58, 62, 67]. The mean dropout in these studies was 9,7%, in compared to 24,7% in studies with follow-up of up to 12 months (7 studies[30, 47, 51, 56, 59, 68, 69]) and 24% in studies in which the follow-up was conducted within 24 months (2 studies[34, 52]).

Out of the 22 reviewed studies only two studies reflect on the problem of keeping a study population for long-term follow-ups (e.g. 12 months,)). Steward et al. (2005)[34], aimed to conduct a long term follow-up with patients treated with RFA (one year, home sleep-study). To this end, all potentially eligible subjects from a parent trial were offered inclusion in the study. Twenty nine of 46 potentially eligible subjects agreed to participate (63%). Of those 17 potentially eligible subjects who did not participate (37%), 5 could not be located (moved or bad phone number), 4 refused, and 8 reported that they were too busy or missed scheduled appointments and didn't follow-up despite multiple phone

calls. In addition, three patients were excluded because of additional treatment after completion of RFA (2 CPAP, 1 surgery).

Discussing the limitations of their study, Friedman et al. (2007)[59] attribute one of the study' limitations to the large number of patients who are lost to follow-up, and declare "Unfortunately, many patients are not willing to return for a follow-up PSG". Based on an "intent-to-treat" analysis the cure rate was 37.2%. The authors estimate, however, that the "true" success rate is closer to 47.5% and state that, "it is possible that most of the patients who have had elimination of symptoms are those who are least likely to participate in the follow-up PSG". In order to increase participation in the long-term follow-up visit, patients were offered free adjunctive treatment such as additional Pillar implants and radiofrequency tongue base reduction based on need as determined by the postoperative PSG. Apparently, most patients who were willing to participate in the follow-up visit, were those who had persistent snoring or symptoms and wanted additional treatment[59].

The problem of a high number of dropouts in long-term follow-ups is not limited to RFA studies. Walker et al. (2007)[70], for example, conducted a study with an extended follow-up (15 months) that was based on an initial study with 90-days follow-up. Out of 53 patients that were enrolled to the initial study, 13 patients were either unable to be contacted or declined further participation; one site with seven patients from the initial study did not participate in the extended follow-up; seven patients did not meet the study inclusion criteria and four patients had other treatments for OSA (e.g., nasal CPAP, uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty) rendered during the extended follow-up period. Thus, the extended follow-up included only 22 patients (41.5%).

Doff et al (2013)[71], conducted a randomized study that compared outcomes of oral appliances(Group I) and CPAP (Group II) after 2 years follow-up. Out of 51 patients in Group I and 52 patients in Group II that started the clinical trial, only 29 and 37 patients (respectively) finished the 2-years follow-up study (64%).

Considering these data the current study will have a follow-up period of 6 months after the last RFA treatment. The period of six months is chosen because 1) this is sufficient time for healing of the treated sites of the upper airways and, 2) it is enough time for following fortification or decline of therapeutic effects, 3) it is not so long that the strength of association of treatment and effect is lost, and 4) it allows the possibility for longer term follow-up data on those patients who can be relied on for a longer follow-up. In addition, a six month follow-up time will allow for earlier identification of non-responders so that these patients can be referred for additional therapy as indicated.

3 HYPOTHESES AND DATA ANALYSIS

3.1 Primary Efficacy Endpoints

The primary effectiveness of the study is to demonstrate a clinically significant reduction of OSAS from Baseline PSG sleep study to the 6-month follow-up PSG in adults (≥ 22 years) with obstructive sleep apnea (AHI 10-30) and BMI ≤ 32.

Effectiveness of the CelonProSleep *plus* will be assessed by demonstrating adequate reduction in AHI and ODI as defined below:

A responder to the CelonProSleep *plus* RFA treatment is defined as a patient with an AHI reduction ≥50% ***and*** a reduction of their ODI ≥25% at the 6-month follow-up PSG, and their AHI at the 6-month follow-up is <20.

The aim of the study is to show that at least 50% of participants met the primary endpoint above. This will be tested with one sided 97.5% confidence interval with ±20% margin of error[73, 74].

In order to record and analyze data for determining the primary endpoints, patients will undergo a PSG sleep study to establish a mean baseline AHI and ODI. Patients will then be treated with a series of three treatments of upper airway radiofrequency ablation with the bipolar electrosurgical electrode CelonProSleep *plus* (Olympus Winter & Ibe, Germany) over 18 weeks. The patient will undergo a second PSG sleep study at the final follow-up examination 6-months later. Mean changes in AHI will be compared for each individual and among all patients. Surgical success is defined if at least 50% of participants experience at least 50% reduction in AHI and 25% reduction in ODI (Performance Goal, PG=50%).

3.1.1 Experimental Design

This is a single-arm assessment of AHI responder rate for treatment of obstructive sleep apnea compared to a performance goal (PG). Patients with 6-month post-treatment AHI measurements will be counted as a responder if they meet the performance goal. A subject will be counted as a non-responder (regardless of AHI measurement at 6 months) under the following circumstances:

a. Death (any cause) between treatment and the 6-month follow-up
b. Unsuccessful radiofrequency treatment attempt
c. Need for an alternative OSA treatment before the 6-month follow-up
d. Subjects who abandon the study
e. Subjects who exit the study after the last treatment, but before the 6-month follow-up

3.1.2 Subjects included in the Primary Efficacy Objective Analysis

The primary efficacy analysis will include all subjects who received all three radiofrequency treatment procedures and the follow-up assessment at 6-months post-treatment.

3.1.3 Hypotheses

Null Hypothesis. Multi-level radiofrequency ablation of the upper airway in adults (age ≥ 22 years) with obstructive sleep apnea (AHI 10-30; Lowest O2 sat ≥ 80%) results in no improvement as defined by the composite endpoint, Section 3.1.

H_0: $\mathbf{TT}_{RAMOSA} \leq PG$
H_A: $\mathbf{TT}_{RAMOSA} > PG$,

where $\mathbf{TT}_{RAMOSA}$ is the proportion of AHI and ODI responders to the multi-level radiofrequency treatment. For this objective, the PG is established at 50%.

3.2 Sample Size Rationale

The sample size proposed for this study is 48 patients. This sample size is comparable to that used in performance and safety studies using radiofrequency ablation for the treatment of upper airways (soft palate and base of tongue, Table 1). In fact, considerable clinical data on the efficacy and safety RFA in OSAS is available from prior studies on this topic.

Recommended sample size is n=48. Sample size is calculated for o the proportion of participants who meet the successes criteria as defined by the performance goal (PG) (Section 3.1).

The following sample size considerations are based on the assumptions that PG=50% with 5% significance level and 80% power.
The sample size of n=43 +10% dropouts, i.e. n=48, is calculated by using the normal approximation for the z-score for testing inference about a single proportion p;

H0: $P_0 < 50\%$
H1: $P_1 \geq 50\%$
and $P1\text{-}P0 \geq 20\%$

Below is the output of PASS12 NCSS program for sample size calculation:

Analysis of One Proportion Tests

Numeric Results for testing H0: P = P0 versus H1: P > P0
Test Statistic: Z Test using S (P0)

Power	N	Proportion Given H0 (P0)	Given H1 (P1)	Difference (P1 - P0)	Target Alpha	Actual Alpha	Beta	Reject H0 If Z ≥ This
	α=0.025							
0.8029	187	0.5000	0.6000	0.1000	0.0250	0.0285	0.1971	1.9600
0.8112	82	0.5000	0.6500	0.1500	0.0250	0.0299	0.1888	1.9600
0.8081	43	0.5000	0.7000	0.2000	0.0250	0.0330	0.1919	1.9600
0.81	26	0.5000	0.7500	0.2500	0.0250	0.0378	0.1805	1.9600

Note that the one the actual exact Alpha of 0.033 will meet the two sided 5% significance.

3.3 Secondary Efficacy Endpoints

To determine whether multi-level radiofrequency ablation of the upper airway in adults with OSAS with the CelonProSleep *plus* bipolar electrode improves daytime sleepiness, snoring, percentage sleep

time at SaO2 < 90%, and sleep-related quality of life without a significant increase in pain, speech or swallowing dysfunction.

The following tools will be applied in order to determine the secondary aims: (1) Epworth Sleepiness Scale (ESS); (2) Functional Outcomes of Sleep Questionnaire (FOSQ), (3) $SaO_{2,}$ and (4) 100 mm VAS scale concerning snoring. ESS, FOSQ, and $VAS_{snoring}$ will be assessed at Baseline, 6 weeks after completion of each upper airway RF ablation treatments, and 6 months post-treatment. The percentage sleep time with SaO2 < 90% will be determined at the final 6-month PSG.

Secondary endpoint statistical analysis includes descriptive statistics of percentages, Means and SD; In cases in which inference will be added to the value, it will be then corrected with Holm's adjustment for testing multiplicity.

3.3.1 Experimental Design

Patients with 6-month post-treatment daytime sleepiness, snoring, and sleep-related quality of life measurements will be counted for statistical analyses as non-responders under the following circumstances:

a. Death (any cause) between treatment and the 6-month follow-up
b. Unsuccessful radiofrequency treatment attempt
c. Need for an alternative OSA treatment before the 6-month follow-up
d Subjects who abandon RAMOSA study
e. Subjects who exit the study after the last treatment, but before the 6-month follow-up

A specific description of analyses of the above secondary endpoints is given below.

3.4 Secondary Endpoints

Secondary endpoints will be examined to provide additional support and details of the primary endpoint findings concerning the RFA treatment. The secondary endpoints assess important patient-based clinical outcomes to compliment the biophysiological primary outcomes. It will be evaluated using mean change at 6-months follow-up from baseline. As supporting evidence, this will be tested with one-sided confidence interval with no corrections for multiple testing.

3.4.1 Functional Outcomes Sleep Questionnaire (FOSQ)

3.4.1.1 Description and Rational

The FOSQ is a validated instrument that assesses the effect of a subject's daytime sleepiness on activities of ordinary living. It is a quality of life measure that is commonly used in clinical evaluation and management of OSA.

3.4.1.2 Objective and Hypotheses

The FOSQ secondary endpoint in this study will be determined by the FOSQ score at the 6-month follow-up compared with the pre-treatment Baseline. The objective is to demonstrate an improvement of daytime sleepiness measured by the FOSQ.

H_0: $\mu_{FOSQ} \leq 0$

H_A: $\mu_{FOSQ} > 0$,

where μ_{FOSQ} is the mean change of FOSQ from pre-treatment baseline to the 6-month post-treatment follow-up. This hypothesis will be tasted using one-sided 95% confidence interval around the mean FOSQ.

3.4.2 Epworth Sleepiness Scale (ESS)

3.4.2.1 Description and Rationale

The ESS is a validated instrument that rates a subject's daytime sleepiness. It is a quality of life measure that is commonly used in clinical evaluation and management of OSA.

3.4.2.2 Objective and Hypotheses

The ESS secondary endpoint in this study will be determined by the ESS score at the 6-month follow-up compared with the pre-treatment Baseline. The objective is to demonstrate an improvement of daytime sleepiness measured by the ESS.

H_0: $\mu_{ESS} \leq 0$

H_A: $\mu_{ESS} > 0$,

where μ_{ESS} is the mean change of ESS from pre-treatment Baseline to the 6-month post-treatment follow-up. This hypothesis will be tested using one-sided 95% confidence interval around the mean ESS.

3.4.3 Visual Analog Scale ($VAS_{snoring}$)

3.4.3.1 Description and Rationale

VAS is a validated instrument that rates different subjective parameters, including snoring. It is a quality of life measure that is commonly used in clinical evaluation and management of OSA. The VAS will be completed by the subject's regular bed partner.

3.4.3.2 Objective and Hypotheses

The $VAS_{snoring}$ secondary endpoint in this study will be determined by the VAS score at the 6-month follow-up compared with the pre-treatment Baseline. The objective is to demonstrate a reduction in snoring.

H_0: $\mu_{VAS} \geq 0$

H_A: $\mu_{VAS} < 0$,

where μ_{VAS} is the mean change of VAS from pre-treatment Baseline to the 6-month post-treatment follow-up. This hypothesis will be tested using one-sided 95% confidence interval around the mean $VAS_{snoring}$.

3.4.4 Percentage Sleep Time at $SaO_2 < 90\%$

3.4.4.1 Description and Rationale

The percentage of time spent with oxygen saturation below 90% has been an increasingly utilized surrogate for morbidity risk in certain sleep apnea populations.

3.4.4.2 Objective and Hypotheses

The SaO_2 secondary endpoint in this study will be determined by the SaO_2 percentage time below 90% during the 6-month PSG sleep study compared with the PSG sleep study at Baseline. The objective is to demonstrate a decrease in SaO_2 percentage time at 6-months.

H_0: $\mu_{SaO2\%time} \leq 0$

H_A: $\mu_{SaO2\%time} > 0$,

where $\mu_{SaO2\%time}$ is the mean change in Percentage time with SaO_2 below 90% from Baseline to the 6-month follow-up. This hypothesis will be tested using one-sided 95% confidence interval around the mean SaO_2.

3.5 Safety and tolerability of RFA Treatment

Safety of radiofrequency treatment will be assessed via the description of all reported adverse events. Adverse events will be summarized by seriousness, severity, relatedness to the procedure and temporal relationship to the procedure. Acute adverse events are those within 14 days of each radiofrequency treatment, long-term adverse events are those events occurring from two weeks following the final treatment until the final 6-month follow-up. No formal statistical hypotheses will be tested.

RFA specific adverse events and complications will be defined as follows (modified after Kezirian et al., 2005)[45]:

- Minor: mucosal ulceration, mucosal crusting, or uvular sloughing,

- Moderate: hemorrhage that is controllable at the office, nerve paresis, or dysphagia to solid food,
- Severe: palatal fistula, hemorrhage requiring hospitalization, nerve paralysis, dysphasia requiring tube feeding, and serious infection or airway compromise requiring hospitalization or surgical intervention.

Tolerability of RFA treatment will be determined with various 100 mm VAS scales concerning pain, speech, and swallowing in order to capture patients' perceived pain, and level of speech and swallowing functions after each RFA treatment. The VAS scales will be scored by the patient immediately following each RFA procedure and 1, 3 and 7 days post-procedure. The use and amount of narcotic pain medication (hydrocodone-acetominophen 5mg/325mg; Maximum 2 tablets every 6 hours, or 8 tablets per day; Narco®) by pill count will be recorded after each treatment. Mean score and the 95% confidence interval for the tolerability VAS scales at each RFA visit will be calculated to capture tolerability profile.

3.6 Ancillary Data Collection

In addition to the primary and secondary endpoint analyses, and to the analyses of RF procedure's tolerability parameters, other supplementary data will be collected as part of the study protocol to ensure patient safety and for further examination of the effect of the therapy.
These assessments will include summaries of all adverse events, information obtained during device interrogation (such as time of active RF treatment in each treated site of the soft palate and base of tongue, power in w, and amount of Joules), blood pressure measurements, and other sleep and cardiopulmonary parameters collected during the PSG sleep study. These assessments include, but are not limited to, the variables that follow:

- Lowest Oxygen Saturation during Sleep (LSAT)
- Mean Oxygen Saturation
- Systolic and Diastolic blood pressure changes

All data will be collected on case report forms at each site. Copies will be scanned and sent via email/fax to the sponsor's data coordinators, who will enter the data and visually check for accuracy. The principal investigator at each treatment site will verify data accuracy. Data will be also checked statistically and inconsistencies will be resolved with the raw data at each site.

4 RESEARCH DESIGN

The study is a prospective, single-arm, multicenter study designed to determine the effectiveness of multi-level radiofrequency ablation (RFA) for mild to moderate obstructive sleep apnea. The study aims to recruit a total of 48 patients at 3 study sites. The Medical University of South Carolina Hospital will serve as the primary site with [redacted] the PI of the study.

4.1.1 Inclusion Criteria (Subjects)

Patients who meet all of the following criteria may be given consideration for inclusion in this study:

- Adults (≥ 22 years)
- Self-report of daytime somnolence
- Body mass index (BMI) ≤ 32
- Mild to moderate obstructive sleep apnea (AHI 10-30; lowest O2 sat ≥ 80%) OSA based on a prior PSG conducted within 12 months of enrollment, or based on a 2-night home sleep study using the WatchPAT 200S-3.
- Evidence of palate and tongue base collapse on supine fiberoptic examination (Müller's maneuver)
- Have failed or have not tolerated CPAP treatment (See Section 5.1for definitions)
- Have been offered and are not interested in oral appliance therapy
- No prior surgical treatment for OSAS other than nasal surgery or tonsillectomy.
- Willing and capable of providing informed consent
- Willing and capable to return for all follow-up visits and PSG sleep-studies and filling out the questionnaires.

4.1.2 Exclusion Criteria

Patients who meet any one of the following criteria will be excluded from this study:

- Another significant sleep disorder (e.g., insomnia, periodic limb movement)
- Absence of regular bed-partner
- Tonsillar hypertrophy (3 or 4 plus)
- Chronic Obstructive Pulmonary Disease (COPD)
- Interstitial Lung Disease (ILD)
- Cystic Fibrosis
- Acute Repiratory Distress Syndrome (ARDS)
- Nasal or supraglottic obstruction on fiberoptic examination
- ASA class III ,IV, V
- Latex allergy
- Lidocaine allergy
- Pregnancy or plans to become pregnant
  Note: women of childbearing potential must demonstrate a negative pregnancy test upon enrollment; those patients qualified to progress to RFA must also demonstrate a negative pregnancy test within 7 days prior to the date of RFA procedure.
- Major depression or non-stabilized psychiatric disorder
- Drug or alcohol abuse
- Previous palatal or tongue surgery
- Stable or unstable angina
- CHF
- moderate or severe valvular disease
- TIA/CVA

- Carotid stenosis or endarterectomy
- Anemia
- Room air $SpO_2 < 95\%$
- Pulmonary hypertension
- Dialysis
- Central or mixed apnea ≥ 10% of respiratory events
- Participation in another clinical study (enrolled in any concurrent study) whose investigational plan is judged to interfere or affect any of the measures of this study

4.2 Sampling Methods

A stratified sample is required to assure patient heterogeneity and representation of the mild and moderate patient in the sample. During recruitment, stratification according to the screening WatchPAT score will take place. Such stratification will be required within all participating medical centers. A list designating number of patients from each stratum will be distributed to the medical centers as part of study set-up. The screening WatchPAT score will serve to estimate AHI results and the patients' stratum prior to recruitment.

For the expected final sample size of n=48 the following stratification

Planed stratified sample scheme:

Strata	AHI level approximated by WatchPAT	Required n (%)
Starta-1	10-15	10 (21%)
Starta-2	15-20	12 (25%)
Starta-3	20-30	26 (54%)

Participating sites are required to meet the specified strata distribution (percentages) as given for the entire sample.

5 PROCEDURES DURING THE STUDY

5.1 Visit 1 - Screening visit and home sleep study

Patient medical records may be initially screened to determine whether an individual meets the general inclusion and exclusion criteria. In addition, the patient must have a history of CPAP failure or intolerance. For the purposes of this study, CPAP failure is identified as an inability to eliminate OSA (AHI remains greater than 10 despite CPAP usage). CPAP intolerance is identified by:

- Inability to use CPAP (device indicates < 5 nights of per week of usage; usage defined as > 4 hours of use per night[76], as verified by 3-month CPAP smart card data, or
- Unwillingness to use CPAP (e.g., patient returns the CPAP system after attempting to use it[77]).

The nature of CPAP intolerance will be specified in the medical records, reflect adequate attempts to pursue CPAP, and be documented by the study physician in the study database according to one or more of the following reasons.

- Non-compliant and specific reasons for non-compliance including details of CPAP attempts
- Experiencing discomfort because CPAP pressure is too high
- Discomfort due to other reason (specify discomfort)
- Causes undesirable clinical effects (specify undesirable clinical effect)
- Patient not using the system enough (< 4 hours of use per night < 5 nights per week; the CPAP counter number will be documented)
- Patient symptoms persist despite CPAP use

If the patient meets this eligibility criterion, the patient will undergo a 2-night home sleep study using the WatchPAT 200S-3 to determine his/her screened AHI. The patient will be instructed in the use of the device and will return it to the office after the 2-night recording for interpretation. Patients who are qualified on the basis of the WatchPAT sleep study to participate in the study will be presented with the risks, benefits and alternatives to the study and will be asked to enroll in the study.

Patients who meet all eligibility criteria and agree to participate in the study must provide written informed consent that has been approved by the center's IRB. For patients who have a limited proficiency of the country's language, the Sponsor will assist the center in obtaining a written translated consent. Translated consent forms must have IRB approval prior to use.

If the patient does not qualify, the patient will be offered advice by the study physician for further management outside of the study.

5.2 Visit 2- Baseline visit and PSG sleep study

This visit will occur within 2 weeks after the Screening Visit. During the Baseline visit, standard medical history and demographics will be obtained from each patient. Patient descriptive information will include height and weight to calculate the body mass index (BMI), gender, blood pressure, heart rate, race, medications, use of alcohol, snoring history, effective CPAP pressure, and the information gained from the study' questionnaires ((Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ)).

In addition, the patient will undergo a Müller's Manoeuvre[37, 38], a technique that looks for collapsed sections of the upper airways such as the oropharynx and hypopharynx. In this maneuver, a fiberoptic scope is passed into the upper airway through the nares while the patient is in supine position. The patient attempts to inhale with mouth closed and nostrils plugged. This leads to a collapse of the airway which can be directly observed with the fiberoptic scope. Müller's maneuver is used to help determine the site of airway obstruction. A positive test result means observation of obstruction at either the retropalatal airway (soft palate; tonsils; lateral pharyngeal walls), retrolingual airway (base of tongue), or a combination of the two sites. Patients will be classified according to the method of Fugita[75] as Class I if only retropalatal collapse is present; class II if both retropalatal and retrolingual collapse is present; and class III if only retrolingual collapse is observed.

Laboratory polysomnography (PSG) will be done no later than 90 days after enrollment and prior to first treatment. PSG will be conducted using standard techniques in the sleep laboratory. The AASM Manual of Scoring Sleep, 2007 will be used as a guideline for rules[78], terminology and technical specifications for the PSG study in all study centers. Briefly, the following list of recordings will be collected:

1. Three channels of electroencephalogram
2. Chin electromyogram
3. Two channels of electrooculogram
4. A single bipolar modified Lead II for electrocardiogram
5. Chest and abdomen belts for respiratory effort measurement
6. One oronasal thermal sensor to detect the absence of airflow for apnea
7. One nasal pressure transducer for detection of airflow for hypopnea
8. One finger oximeter to continuously monitor arterial oxygen saturation
9. One position sensor to electronically determine position (supine, left, right, prone), or a means for documenting position
10. One leg electromyogram to record leg movements

All signals will be recorded on a digital PSG system and stored for off-line analysis by the PSG core lab.
Prior to the PSG, the patients will fill out, or respond to, a Pre-PSG Interview that contains questions about recent behavior that may affect sleep during the PSG.

During the PSG, the coordinator or PSG technician will fill out a PSG Log indicating technical aspects of the PSG recording that the Core Lab needs to score the PSG file, such as signal montage filtering and user events including body positions. The user events and body positions may be recorded directly onto the PSG recording system rather than on the PSG log if the recording system can create a readable file of the user notes that a core lab can use to assist with scoring.

Subjects who fail to show mild-to-moderate OSA (AHI 10-30; Lowest O2 sat. > 80%) on the baseline PSG will not proceed to treatment and will be considered a screening failure. These subjects will be offered alternative therapy by their study doctor as indicated.

5.3 Visit 3- Stage I: First Radiofrequency Treatment (within 4 weeks of baseline PSG)

The research team will greet the patient and will escort him to triage for vitals. The patient will then be escorted to the procedure room, and will be given oral antibiotics prior to the treatment. The patient will be asked to complete the specified questionnaires and VAS scales concerning, snoring (bed partner), speech and swallowing in order to capture patient's baseline perceived pain and level of speech and swallowing function. VAS for pain will be conducted at the end of this session. The patient will be sitting upright in an examination chair. A crash cart is available in all units where the procedure is performed. Surgeons have both BLS and/or ACLS training. The patient will then undergo the first of three radiofrequency treatments to the upper airway. Radiofrequency ablation procedures will take

place in an outpatient setting under local anesthesia. The RFA procedure will be performed using standard surgical techniques and a new RFA applicator will be used for each of the 3 treatment visits.
To perform RFA of the soft palate, a tongue blade will be inserted, bringing the palate into view. The soft palate will be anesthetized with three sprays of topical anesthetic using a typical spray applicator (benzocaine 14%, butamben 2.0%, tetracaine hydrochloride 2.0%; Cetacaine®) followed by an injection of 8 to 10 cc of 1% lidocaine with 1:100,000 epinephrine. The physician will then insert the surgical handpiece needle electrode into the submucosal tissue of the soft palate. The radiofrequency generator delivers energy beneath the surface tissue while monitoring temperature. Tissue is heated in a limited area around the needle electrode, creating a coagulative lesion beneath the surface. The energy application is immediately aborted if there are signs of tissue blanching on the mucosal surface. Discomfort is minimal during the procedure and the surface tissue is protected from thermal damage by the submucosal lidocaine infiltrate which expands the thickness of the soft palate tissue. A single-prong RFA applicator (CelonProSleep *plus*, Olympus, Germany) is used to create 7 lesions of 54 joules (J) each (Celon Power Setting 12W, as indicated in the Instruction for Use): two laterally above the anterior tonsillar pillar; two paramedian to the uvula; and three at the hard and soft palate junction (Fig. 1).

Following the procedure, the patient rinses his/her mouth with cool tap water. The throat is checked in 5 minutes by the surgeon to make sure there is no ongoing oozing. In the event of ongoing ooze, the spot will be treated with a stick of silver nitrate cautery.

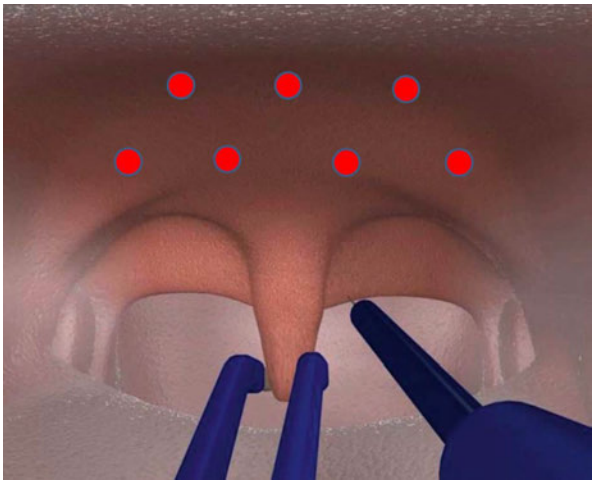

Fig. 1 Points of RF treatment – soft palate

The 7 lesions in the documented positions provide sufficient energy application to the soft palate without concern of extensive energy overlap. A 54 J lesion creates an average lesion size of 0.40 cubic centimeters, and each lesion is a centimeter or more removed from the adjacent lesion. The probe is placed in the submucosal tissues so that the probe cannot be seen through the overlying mucosa. The physician will perform a gentle tug on the probe once inserted to make sure that it is in the proper position within the palatal muscles and not within the submucosal tissues. The natural contour of the probe prevents penetration through the soft palate, and the generator will fail to activate if the tip of the probe is not within tissue.

To perform RFA of the tongue base, the anterior tongue is grasped by the surgeon with clean gauze. The tongue is sprayed with 3 sprays of topical anesthetic (benzocaine 14%, butamben 2.0%, tetracaine hydrochloride 2.0%; Cetacaine®) followed by an injection of 6 cc of 1% lidocaine with 1:100,000 epinephrine in the middle third of the tongue posterior to the circumvallate papillae. The patient then undergoes 6 lesions of RFA each placed 1cm from the midline for a total of three lesions on either side of the tongue. The tongue base is the posterior 1/3 of tongue posterior to the anterior tonsillar pillars and circumvallate papilla. The area to be treated corresponds to the middle third of the tongue base which includes the highest dorsum of the tongue and 1 centimeter to either side of the midline (Fig. 2). The CelonProSleep *plus* single prong applicator will then be used to create the 6 lesions spaced approximately 1 cm apart of 80-84 J each (Celon Power Setting 7W, as indicated in the Instruction for Use). As higher power settings lead to smaller lesion sizes, the recommended power settings for soft palate and base of tongue were chosen to fit into the body structure without endangering the mucosa if the lesion becomes too big.

After the RF treatment, the patient then rinses his/her mouth with cool tap water. The throat is checked in 5 minutes by the surgeon to make sure there is no ongoing oozing. In the event of ongoing ooze, the spot will be treated with a stick of silver nitrate cautery.

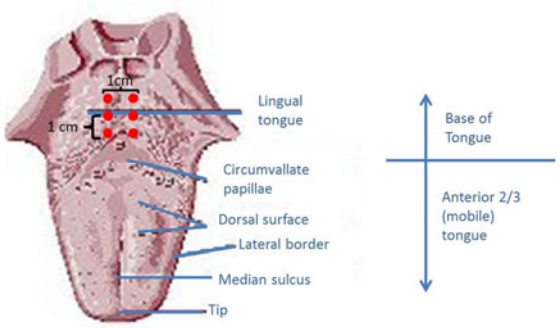

Fig 2 Points of RF treatment – Base of tongue

After completion of both RFA procedures, the research team will monitor the patient for up to 3 hours post-procedure. Patients must demonstrate adequate pain control, breathing, swallowing and speech prior to discharge. The patient's vitals will be taken prior to the patient being released from the clinic. The research team will ask the patient to walk around the clinic for five minutes to assess the patient's post-operative status. The patient will be provided prescriptions for an antibiotic (amoxicillin or clindamycin), an oral steroid (7-day methylprednisolone taper pack), and an oral pain medication to take if needed (Acetaminophen/Hydrocodone). In addition, the patients will be asked to have a soft diet for at least 2 days after the RFA treatment. The patient will then repeat the questionnaires specified above. Patients will be asked in advance to have their bed partner present to drive them home. The research team will escort the patient and bed partner out to the car. Each patient will be provided an emergency contact number to allow them to contact study personnel or their designees 24-hours a day.
The patients will repeat the pain, speech, and swallowing VAS scales at 1, 3, and 7 days post RFA treatment via telephone in order to document persistent ongoing pain, and post-treatment discomfort. The number of pills of narcotic pain medication (hydrocodone-acetominophen 5mg/325mg; Maximum 2 tablets every 6 hours, or 8 tablets per day; Narco®) used in the first 7 days following the procedure will be recorded.

Clinical examination and assessment of the palate and base of tongue will be performed at days three and 10 following each RF procedure to observe effects on speech and swallowing, as well as other complications as described in the Table below.

Following medical actions will be taken in case of development of side effects and/or complications due to the RFA treatment: Minor and moderate complications such as mucosal ulceration, mucosal crusting, uvular sloughing, hemorrhage controllable in clinic, palatal edema, mild dysphagia, and local infection can be managed with antibiotics, topical medicated gargles, and regular follow-up until the events resolved. Severe complications such as tongue abscess or airway distress due to edema may require hospitalization for medical care (IV fluids; steroid; antibiotics) and/or surgical intervention (airway support; abscess drainage). In a case of an emergency situation arise in the office each treatment center should be fully equipped with crash cart and should have access to a full array of endoscopic and surgical instruments. Rapid transport to an Emergency Department should be available should the need arise.

5.4 Visit 4 – Stage II: Second Radiofrequency Treatment (6 weeks later)

The study physician will perform a brief history and examination to make sure the patient tolerated the first treatment well and that the patient's tissues are fully healed with no visible ulceration or granulation. If there is a complication such as abscess and ulceration, the second treatment will be delayed until patient's tissues are fully healed. The patient will be given oral antibiotics and will then undergo a second treatment as outlined above. Treatment will be done in the same region and location since there is no concern about RFA lesion overlap once the tissues have healed. The patient will be prescribed pain medication if needed, along with a short course of oral antibiotics and steroids as outlined above.

After completion of both RFA procedures, the research team will monitor the patient for up to 3 hours post-procedure. Patients must demonstrate adequate pain control, breathing, swallowing and speech prior to discharge. The patient's vitals will be taken prior to the patient being released from the clinic. The research team will ask the patient to walk around the clinic for five minutes to assess the patient's post-operative status. The patient will be provided prescriptions for an antibiotic (amoxicillin or clindamycin), an oral steroid (7-day methylprednisolone taper pack), and an oral pain medication to take if needed (Acetaminophen/Hydrocodone). In addition, the patients will be asked to have a soft diet for at least 2 days after the treatment. The patient will then repeat the questionnaires specified above. Patients will be asked in advance to have their bed partner to drive them home. The research team will escort the patient and the bed partner out to the car as outlined above.

The patients will repeat the pain, speech, and swallowing VAS scales at 1, 3, and 7 days post RFA treatment via telephone in order to document persistent ongoing pain, and post-treatment discomfort. The amount of narcotic pain medication used in the first 7 days following the procedure will be recorded using pill count.

Medical examinations and medical actions needed due to development of side effects and/or complications will be the same as described in Section 5.3 above.

5.5 Visit 5 - Stage III: Third Radiofrequency Treatment (6 weeks later)

The doctor will perform a brief history and examination to make sure the patient tolerated the second treatment well and that the patient's tissues are fully healed. If there is a complication such as abscess and ulceration, the third treatment will be delayed until patient's tissues are fully healed. The patient will be given oral antibiotics and will then undergo a third treatment as outlined above. Treatment will be done in the same region and location. The patient will be prescribed pain medication if needed, along with a short course of oral antibiotics and steroids as outlined above.

After completion of both RFA procedures, the research team will monitor the patient for up to 3 hours post-procedure. Patients must demonstrate adequate pain control, breathing, swallowing and speech prior to discharge. The patient's vitals will be taken prior to the patient being released from the clinic. The research team will ask the patient to walk around the clinic for five minutes to assess the patient's post-operative status. The patient will be provided prescriptions for an antibiotic (amoxicillin or clindamycin), an oral steroid (7-day methylprednisolone taper pack), and an oral pain medication to take if needed (Acetaminophen/Hydrocodone). In addition, the patients will be asked to have a soft diet for at least 2 days after the treatment. The patient will then repeat the questionnaires specified above. Patients will be asked in advance to have their bed partner drive them home. The research team will escort the patient and bed partner out to the car as outlined above.

The patients will repeat the pain, speech, and swallowing VAS scales at 1, 3, and 7 days post RFA treatment via telephone in order to document persistent ongoing pain, and post-treatment discomfort. The amount of narcotic pain medication used in the first 7 days following the procedure will be recorded.

Medical examinations and medical actions needed due to development of side effects and/or complications will be the same as described in Section 5.3 above.

5.6 Visit 6 - Follow-Up Visit (6 weeks later)

The patient will undergo complete post-treatment evaluations including sleep history and physical examination (including height, weight, and blood pressure) as done in Baseline Visit. The patient will be asked to complete questionnaires including Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ) and 10 cm VAS concerning pain, snoring (bed partner), speech, and swallowing. The study physician will inform the patient on his/her study results and medical condition and will give recommendations for ongoing management as needed.

5.7 Visit 7- Final Follow-up Visit (6-Months later after last RF treatment)

The patient will undergo complete post-treatment evaluations including sleep history and physical examination (including height, weight, and blood pressure) as done in Baseline Visit. The patient will be asked to complete questionnaires including Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ) and 10 cm VAS concerning pain, snoring (bed partner), speech, and

swallowing. In addition, each patient will undergo a second PSG sleep study not later than 30 days after the Final Study Visit. The PSG sleep study will be conducted using standard techniques in the sleep laboratory as defined in section 5.2 above.

5.8 Visit 8 – Final Study Visit (after the PSG sleep study)

Shortly after the 2nd PSG study, the study physician will inform the patient on his/her study results and medical condition and will give recommendations for ongoing management as needed.

6 DURATION

This study has a minimum of eight visits. The first visit, the Screening Visit, is planned for determining whether patient qualifies for the study. This visit will take up to 1 hour. In the second visit, the Baseline Visit, which occurs up to 2 weeks later, standard medical history, demographics and various questionnaires will be obtained from the patient. In addition, the patient will undergo a Müller's Maneuver and will be sent to the sleep lab for a PSG study (one night). This visit will last about 60 minutes.
The third visit is the first RF treatment session and will last about 1 hour. The fourth and fifth visits involve additional RF treatments and will last about one hour each. The first follow-up visit will occur 6 weeks after the third treatment visit and will last as well about 1 hour. The 7th visit, the 6-month follow-up visit, will occur 6 months later and will be no more than 1 hour. At the end of this visit the patient will be admitted to a sleep labor for undergoing the 2nd PSG study. Finally, the 8th and final Visit will last about 30 minutes. The patients may require additional visits in case of complications that are needed to be treated in the hospital or if they have a question or concern. The entire duration of the study for an individual patient is no longer than 24 weeks plus 6 months of follow-up.

7 INSTRUMENTS

The following outcome measures will be utilized to represent meaningful measurements of therapy success:

1. Apnea-hypopnea index (AHI) - is an index of sleep apnea severity that combines the frequency of apnea and hypopnea events. The severity of obstructive sleep apnea is determined by the measurement of apneas and hypopneas. An obstructive apnea is defined as a cessation (> 90% decrease) of airflow for at least 10 seconds with breathing effort; and a hypopnea is defined as an event with at least a 30% reduction in airflow lasting at least 10 seconds, and with ≥ 4% oxygen desaturation. The frequency of apneas and hypopneas per hour of sleep is termed the apnea-hypopnea index (AHI). AHI values are typically categorized as 5–15/hr = mild; 15–30/hr = moderate; and > 30/h = severe. AHI will be determined at baseline and at the 6-months follow-up visit.

2. Oxygen Desaturation Index (ODI) – ODI is defined as the number oxygen desaturation events, where there is a ≥ 4% desaturation from pre-event baseline, that occur per hour of sleep. ODI generally correlates well with AHI [15], and it is reasonable to conclude that a 25% reduction in ODI represents a

clinically meaningful improvement. ODI will be determined at baseline and at the 6 months follow-up visit.

3. 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 ESS Scale has been validated primarily in OSA. It is used to measure excessive daytime sleepiness, and is often utilized before and after the administration of treatment (e.g. CPAP) to document improvement of symptoms. The patient will complete this questionnaire at the Baseline, at Visit 3 (prior to the 1st RFA treatment), Visit 4 (prior to the 2nd RFA treatment), at Visit 5 (prior to the 3rd RFA treatment), at Visit 6 (6 weeks follow-up post 3rd RFA treatment), and at Visit 7 (6 months follow-up).

4. Functional Outcomes of Sleep Questionnaire (FOSQ) - The FOSQ is a quality-of-life questionnaire designed specifically to evaluate the impact of disorders of excessive sleepiness on activities of daily living. This is a self-report measure that assesses the effect of excessive sleepiness on activities of ordinary living, including activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcomes. The patient will complete a FOSQ at the Baseline, at Visit 3 (prior to the 1st RFA treatment), Visit 4 (prior to the 2nd RFA treatment), at Visit 5 (prior to the 3rd RFA treatment), at Visit 6 (6-Weeks follow-up post 3rd RFA treatment), and at Visit 7 (6-months follow-up).

5. Pain will be measured on a 10-point Visual analog Scale (VAS_{PAIN}, 0 = "no pain" and 10 = "severe pain"). Measurements will be done on day 1, 3, and 7 post (each) RFA treatment.

6. Snoring will be measured on a 10-point Visual analog Scale ($VAS_{SNORING}$) and filled out by the bed partner. This scale will be used to asses by the patient and his/her bed partner snoring levels. The scale will range from 0 (no snoring noise) to 10 (extreme noise - bed partner leaves the room). Measurements will be done on day 1, 3, and 7 after the first RFA treatment, on the 2nd and 3rd RF treatments, prior to the treatment and on both follow-up visits.

7. Functional parameters such as speech and swallowing will be measured on a 10-point Visual analog Scale (VAS_{SPEECH} / $VAS_{SWALLOWING}$) ranging from zero (no problems/not affected) to 10 (severe problems/severely affected). Measurements will be done on day 1, 3, and 7 post each RFA treatment.

8 STATISTICAL ANALYSES

All analyses and graphs will be performed with common statistical packages. In general, summary statistics will consist of the following:

Continuous variables will be summarized by the number of observations (n), the mean, the standard deviation (SD), the standard error (SE), the median, the minimum, maximum and 95% confidence limits about the mean.

Categorical variables will be summarized by frequency and percentage in the corresponding categories and associated 95% confidence limits.

8.1 Primary Efficacy Endpoint

The primary endpoint of AHI and ODI obtained at the 6-month follow-up will be compared to the Baseline measurement. The subject is a responder if the reduction in AHI is ≥ 50%, and ODI reduction is ≥ 25%. The proportion of subjects meeting the responder criteria among all included subjects will be evaluated using a one-sided 95% confidence interval. In addition one sample test of the proportion of patients meeting the PG at 6month is significantly different than 50%. The study is designed to demonstrate success rate of 20% beyond the PG of 50%. Proportion with 95% CI will be given using normal approximation to the Binomial. P-Value will be derived based on the exact binomial distribution of the null hypothesis, that is assuming p=0.5.

8.2 Additional Analysis

Demographic, medical history and operative characteristics will be summarized for the study cohort, by clinical site, and by groupings of all sites. At a minimum, this will include age, gender, race, weight, and BMI.

Supporting analyses will be conducted to provide additional information on the safety and efficacy of multi-level radiofrequency treatment. Descriptive statistics will be utilized to summarize all adverse events. Regression models evaluating the change of continuous outcomes of AHI and ODI as well as logistic regression for the categorical outcome of response to treatment as defined in the primary objective will be used. A description of the relationship between BMI change and effectiveness outcomes will be performed by a cross-tabulation of BMI change versus responder and non-responder groups.

Data collected on all enrolled study subjects will be analyzed on an intend-to-treat and as-treated basis. Disease information and demographic variables, such as age, ethnic group, and sex, will be summarized by means of summary statistics. A normality distribution test (Kolmogorov-Smirnov) will be performed for all variables. Simple descriptive statistics such as frequency, mean, standard deviation, minimum, and maximum will be calculated for all outcome variables. If these variables are not normally distributed, other descriptive measurements such as median and the interquartile range will be calculated. For comparison between pre- and post-treatment variables, McNemar's-will be used with categorical variables. For continuous variables, a paired t-Test (normal distribution) or a Wilcoxon signed rank Test (not normal distribution) will be used to compare data at visit 2 (Baseline) and at visit 6 (six weeks after final RFA treatment). In addition, for long longitudinal analysis a One-Way ANOVA with Repeated Measures (or mixed models) will be used to model the outcome and cofactors over the multiple time-points. Significant interactions will be followed up using post-hoc analysis with Holms' adjusted P-values.

Site homogeneity will be evaluating by testing the interaction term in the analysis of covariance (ANCOVA) at a significance level of 0.15.

8.3 Statistical Power Considerations

According to the sample size calculation (section 3.2) the actual expected power is 80.8%.

8.4 Analysis Sets

The following defines the analytic sample for the relevant endpoint used in a particular analysis.

Safety Analysis Set (SAS): The safety analysis set will include all subjects who receive radiofrequency treatment.

Full Analysis Set (FAS): The full analysis set will include all subjects who receive radiofrequency treatment and completed all 8 visits of the study.

8.5 Handling of Missing Data, Subject Withdrawals, and Treatment Failures

Subjects that are lost-to-follow-up will be categorized as treatment failures from the time point of dropout forward. Sensitivity analyses will also be conducted excluding lost-to-follow-up subjects to see what impact, if any, they might have on the overall results of clinical activity. Time-to-event analyses will consider these subjects as censored at the lost-to-follow-up time point. All data will be recorded on a CRF forms and will be subjected to regular monitoring.

Every effort will be made to follow subjects for study observation and encourage compliance with study measurements to minimize the amount of missing data.

8.6 Interim Analyses

There are formal interim analyses planned for the first 15 patients and then every 15 completed patients. Review of safety data will be evaluated on a continual basis throughout the study. Review of safety data by a Clinical Research Office (CRO) for the purpose of general safety review will be done; however, the review of such data is not intended to impact the study conduct unless there are safety concerns. As such, it is expected that the trial will continue to its scheduled completion barring any unexpected safety issues.

9 RISK ANALYSIS

9.1 Risks of Confidentiality

(1) Each patient at the time of enrollment will be assigned a subject number. The codebook linking the patient identifiers to the subject number will be keep in a locked cabinet in the locked office of each Principal Investigator. The subject number is the number that will appear on all study related documents.

(2) Study staff will be trained on the importance of confidentiality. All medical information recorded as part of the study will be captured using pre-printed standardized forms (Case Report Forms) specific to the study. The only identifier on the forms will be the subject study number. The forms for a given subject will be kept in individual study folders and stored in a locked cabinet in the locked office of the study coordinator.

(3) All adverse events and serious adverse events will be documented in the subject study folder. Serious adverse events will be immediately communicated to the institutional IRB per standard protocol.

9.2 Risks and Discomforts

The direct risks of radiofrequency ablation of upper airway tissues include the following:
(1) Risk of bleeding - The use of a probe inserted into upper airway tissues will result in minor bleeding. The amount of bleeding is minimal due to the use of epinephrine and the superficial nature of the procedure. Bleeding, if present, can be controlled with pressure, silver nitrate cautery, and/or suture ligature. All surgeons will have many years of experience with radiofrequency ablation.

(2) Risk of pain or discomfort - Needle and probe insertion into the tissue will cause mild pain and discomfort that is typically well tolerated in an awake patient. The patient will be given topical anesthetic and a local anesthetic of lidocaine prior to the procedure, and is therefore expected to have minimal discomfort.

(3) Risk of hematoma - The use of a needle and probe will result in some bleeding and the possibility of hematoma (swelling of blood or clot) formation. The risk of this uncommon complication is expected to be minimal, and the use of epinephrine in the lidocaine additionally reduces the risk of hematoma formation. Observed hematomas will be drained under local anesthesia in order to prevent breathing or swallowing issues.

(4) Risk of infection or abscess - The procedure involves penetrating tissue with the probe which has the potential risk of infection. This risk is minimized by the use of antibiotics and steroids after each treatment. Patients will be followed closely after the procedure to assess for signs and symptoms of infection and/or abscess.

(5) Nerve Trauma - This is a theoretical risk since the application of the RFA energy will be applied far from the natural landmarks of the lingual and hypoglossal nerves.

(6) Dysphagia - Slight difficulty in swallowing is common but all patients are expected to resume at least a diet of soft foods immediately following the procedure. It is anticipated that all patients will resume a normal diet by post-procedure day 3.

(7) Procedure Duration- This is a theoretical risk. However, the CelonProSleep *plus* has a built-in automatic turn-off system shuts off after delivering certain amount of energy.

(8) Other risks may include airway problems, nasopharyngeal stenosis, ulceration of the treated site, paresthesias, edema of tongue, change in speech, and other possible unexpected symptoms.

9.3 Minimization of Risk to the Patient

Risks can be minimized through the use of proper surgical procedures, compliance with this protocol and device specifications, adherence to the guidelines for patient selection, close monitoring of the

subjects' physiologic status during treatment and follow-up procedures, and by promptly supplying the Sponsor with all pertinent information required by this protocol.

The surgical risks are minimized in this study by including OSA subjects who do not have significant co-morbidities, utilizing surgeons who have previous clinical experience and thorough protocol related training prior to initiation of the clinical trial. RAMOSA study surgeons must be familiar with neck surgery, the tongue and pharyngeal muscle movements, and have previously used RFA in the treatment of snoring.

Additional measures will be taken to minimize risk to subjects as part of this investigational plan:
• Reported adverse events will be reviewed regularly and reported to the sponsor throughout the study. Any severe adverse event will be reported to the institutional IRB and sponsor in a timely fashion. Appropriate medical measures will be immediately taken to resolve all adverse events.

9.4 Potential Benefits

Although no assurances or guarantees can be made, there is a reasonable expectation that the use of radiofrequency ablation may be beneficial. Radiofrequency ablation (RFA) of the upper airway using FDA-cleared devices has demonstrated promise as a treatment alternative for obstructive sleep apnea in multiple published studies [29-31, 34]. In these studies, repeated RFA of the soft palate and base of tongue region resulted in significant reductions in AHI and daytime sleepiness without significant complications. RFA has several advantages over traditional surgical approaches including its ability to address multiple levels of the airway (nose, palate, tongue); ability to perform in the office under local anesthesia; lower cost; and minimal pain and morbidity. The CelonProSleep *plus*, the study device used in this study, is similar to other FDA-cleared RFA devices (e.g. Gyros or Somnos) but delivers the RF energy more rapidly thereby adding to patient comfort during the procedure. In addition, due to the bipolar electrode the CelonProSleep *plus* device coagulates much faster (although the power setting is less) than the Gyrus or Somnos systems. Therefore, less energy is needed to reach the coagulation threshold of the tissue.

10 ADVERSE EVENT MANAGEMENT

Timely, accurate, and complete reporting and analysis of safety information for clinical studies is crucial for the protection of subjects, Investigators, and Sponsor. Data collected in this study may be used in support of global regulatory approvals. Sponsor has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations. All adverse events and adverse device effects will be reported to all Institutional Review Boards (IRB's). At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. Detailed information regarding such adverse events will be recorded on a specific case report form (CRF) for adverse events. Investigators will be asked to make a judgment as to the relationship of the event to the study device. Follow-up data to ascertain the existence of residual effects from the event will be obtained.

10.1 Definitions

For the purpose of this protocol, the following definitions shall apply:

10.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject (without taking into account the relationship with the device under investigation). The AE can be any unfavorable or unintended sign, symptom, or disease temporally associated with the use of the device (ICH E2A). All new and/or worsening adverse events (AE) will be collected throughout the study duration, starting when the subject is enrolled into the study (when the Subject Informed Consent is signed) and reported to the Sponsor on an Adverse Event Case Report Form. In addition, all deaths must be reported. Documented pre-existing conditions are not considered adverse events unless there is a change in the nature or severity of the condition and required additional medical or pharmacological treatment.
All adverse events should be followed until the adverse event has been resolved, is ongoing with no further actions to be taken, the subject exits the study or until study closure, whichever occurs first. Investigators will categorize AE's according to their severity and relatedness (e.g., to the surgical procedure, to the CelonProSleep plus, etc.). The Sponsor will then review all reported adverse events for completeness, and ask for clarification or additional information if necessary.

AE Definitions for Investigator Classification
Investigators are responsible to categorize adverse events according to their seriousness and relatedness. The definitions for classifications are included below. Those events that do not meet the criteria for Serious Adverse Event are considered non-serious.

10.1.2 Adverse Device Effect (ADE)

Any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error:

10.1.3 Serious Adverse Event (SAE)

A serious adverse event is an adverse event that:
(1) Led to death
(2) Led to a serious deterioration in the health of the subject that:

-Resulted in life-threatening illness or injury (the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death);

-Resulted in permanent impairment of a body function or permanent damage to body structure; or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure;

-Required in-patient hospitalization or prolongation of existing hospitalization;

-Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

10.1.4 Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is and Adverse Device Effect that has resulted in any of the consequences characteristic of a SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

10.1.5 Relatedness

Investigators are also responsible to categorize adverse events according to their relatedness. The definitions for relatedness classifications are included below.

10.1.5.1 Surgical Procedure Related

Surgical procedure related adverse events are those that are related or possibly related to the procedures involved in the CelonProSleep plus or those normally associated with a surgical procedure. These events typically occur within 10 days of treatment.

10.1.5.2 Other Surgical Procedure Related

Other surgical procedure related adverse events are those that are normally associated with a surgical procedure, but the surgical procedure was not associated with the CelonProSleep plus.

10.1.5.3 Pre-existing or Independent Condition Related

Any event, although temporally associated, that was attributable to a preexisting or independent condition. .

10.1.5.4 Other

Any event that cannot be classified in any of the above categories.

10.2 AE Definitions for Sponsor Classification

10.2.1 Unanticipated Adverse Device Effect (UADE)

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 CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects..

10.2.2 System component-relatedness

Adverse events that are System-related will be further assessed by the Sponsor according to whether the event resulted from the presence or performance of the surgeon.

10.3 Adverse Event Adjudication

Upon receipt, adverse event CRFs are reviewed for completeness by the Sponsor and Sponsor will request clarification and/or additional information from the Investigator, when necessary. The Sponsor, with the assistance of the Investigator, will also determine whether an event is reportable to regulatory agencies / competent authorities. A Clinical Events Committee (consisting of independent physicians) will review serious adverse events at regular intervals. The CEC is responsible for reviewing the Investigator's assessment and classification of each event.

10.4 Adverse Event Outcome Status

Adverse Events when reported are assigned an "open" or "closed" outcome status by centers depending on the nature of the event or the corrective action involved. When clinically appropriate, centers should work to close events that may not be resolvable during the term of the investigation. Centers may move outcome status to "closed" or alternatively, add text to the adverse event description at follow-up visit addressing that the adverse event is ongoing but for study purposes and outcome data, the event is considered closed.
An Event is "closed" if the subject/event is fully recovered or partially recovered and no further recovery is expected.
An Event is "open" if the subject/event is partially resolved, unchanged, or worsened, or further recovery is otherwise expected. In the case the Event remains open, continue to follow this Event on an adverse event form at each follow-up visit until the event is closed.

10.5 Notification of Serious Adverse Events

The Investigator will report any SAE to the Sponsor as soon as possible, but not later than 24 hours after the investigator learns of the event. All SAEs should be documented on the Adverse Event Case Report Form and an explanation of any medical treatment administered or surgical intervention should be provided. The form must be completed, signed and sent by fax to the Sponsor within 24-hours of learning of the adverse event.

The SAE report must be followed by a full written report

10.6 Subject Deaths

A subject death during the study must be reported to Sponsor as soon as possible. IRB regulations and/or Ethics Committee requirements may require notification of the study Sponsor within 24 hours of learning about the event. The center's IRB/MEC must be notified of any deaths in accordance with that center's IRB/MEC policies and procedures.
Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed by the principal Investigator or authorized co-Investigator. The death letter must include all of the following:

a) Date and time of death
b) Place death occurred

c) Immediate cause of death
d) The relatedness of the death to the CelonProSleep *plus*, surgical procedure, clinical investigation, or subject condition.
e) Whether or not the death was witnessed
f) Device status and/or activity at the time of death
g) Any other circumstances surrounding the death
h) Approximate time interval from the initiating event to death (temporal course)
i) Investigator or co-Investigator signature and date
j) Any information listed above that is unavailable or unknown must be specified in the death letter. Also submit the following documentation:

- If the subject expired in the hospital, A copy of the medical records for that admission (e.g. H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)
- A copy of the most recent clinic visit (if not already submitted to Sponsor)
- Death certificate (if available)
- Obituary (if able to obtain)

Data collected from the subject up to the point of death will remain documented on CRFs and/or worksheets. In addition to the Patient Status Change CRF, these may include the adverse event forms (if applicable), and Device Status Change CRF.
CelonProSleep *plus* and related Sponsor system components (e.g., probe) should be removed intact and returned promptly to Sponsor for analysis.

11.0 PROTOCOL DEVIATIONS/MODIFICATION

An Investigator is required to conduct this study in accordance with the signed Investigator's Agreement, this investigational protocol, applicable laws and regulations, and any conditions of approval imposed by the reviewing IRB/MEC.

The Investigator shall notify the Sponsor and the reviewing IRB/MEC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred. Except in such an emergency, prior approval by the Sponsor is required for a change in or deviations from this plan and, if these changes or deviations could affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, IRB/MEC and national authority approval is also required.

All deviations from the investigational plan must be reported to Sponsor, together with the reason for the deviation. In some circumstances, the center may be required to notify the center's IRB/MEC and Sponsor will notify the national authorities and/or suspend the center's participation in this clinical trial. In these circumstances, Sponsor will perform a compliance visit to evaluate adherence to the investigational plan, compliance with applicable regulations, and any additional specific issues related to the event. Additional training on the protocol and related procedures may also be necessary. At this time Sponsor will ask the Investigator to review the Investigator Agreement and applicable regulations regarding medical device clinical studies, specifically Investigator responsibilities.

12.0 DATA QUALITY ASSURANCE

12.1 Required Data

All required data for this trial will be collected on standardized case report forms (CRFs) designed specifically for the study. In general, the CRFs will be completed by a trained clinical research coordinator at the investigational site. Worksheets may be used to collect information that is not commonly recorded in medical records. Otherwise, all data should be corroborated by clinic or hospital records. Source documents must be available for review during monitoring visits. In the case of patient questionnaires, the CRF may be completed by the subject or the subject may complete a worksheet with the data then being transferred to a CRF by the clinical research coordinator, depending on the accepted practice at the site.

12.2 Monitoring Procedures

The study will be administered by the Department of Otolaryngology at the Medical University of South Carolina, and two other sites to be determined, and will require approval and monitoring by the sponsor.

Each site will allow Olympus Winter & Ibe, the Sponsor of the study and an independent CRO, to monitor the study activities and records to ensure that all investigators are in compliance with 1) appropriate regulatory requirements, 2) recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions, 3) the protocol, and 4) the investigator's agreement.

Study sites will be monitored to ensure completed case report forms match the Sponsors records and to resolve any differences. Original source-documents will be kept in patient charts at the investigator's site and will be available for verification during monitoring or regulatory agency audit.
The monitor's responsibilities include: maintaining regular contact with each investigational site, through telephone contact and on-site visits, to ensure that the investigational plan is followed; that complete, timely and accurate data are submitted; that problems with inconsistent and incomplete data are addressed; and that the site facilities continue to be adequate.
The Sponsor will review significant new information, including unanticipated adverse events, and ensure that such information is provided to the investigators, and IRB's, as appropriate.

The Investigator(s) will ensure that an informed consent form is signed by each patient prior to study enrollment. Informed consents will be obtained according to individual institutional guidelines. These documents will be audited to ensure they have been signed prior to the RFA procedure and that the correct version was used.

Standardized case report forms must be completed for all patients enrolled into the study. Completion of standard case report forms will be required by all participating centers. The case report form should be a complete and accurate record of the patient's data collected during the study according to GCP recommendations. It is the responsibility of the investigator to ensure the quality of the data collected and recorded.

The case report forms will be reviewed for errors, omissions, internal consistency, and to ensure that the investigator has signed and dated the appropriate sections. Data entry will be done in a manner to ensure accuracy and the entered data will be audited for verification and validation purposes.

12.3 Patient Data Protection

All information and data concerning patients or their participation in this trial will be considered confidential. Only authorized personnel will have access to these confidential files. All data used in the analysis and reporting of this study will be without identifiable reference to the patients.

12.4 Ethical and Regulatory Considerations

The study will be performed in accordance with Good Clinical Practices and recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

The protocol and informed consent will be reviewed and approved before enrollment of patients by the appropriate Institutional Review Board where the study will be conducted.

13 ROLES AND RESPONSIBILITIES

13.1 Role of the Sponsor Representatives

Olympus Winter & Ibe will serve as the Sponsor of this study. A Sponsor is defined as a person or organization that initiates, but does not actually conduct, the investigation (FDA regulation 21 CFR 812.3(n)).

Olympus Winter & Ibe personnel may provide technical support to the investigator and other health care personnel (collectively HCP) as needed during surgical procedures. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of Olympus equipment.

At the request of the Investigator and while under their supervision, Olympus personnel may assist with operation of the equipment during treatment of study subjects. Typical tasks may include:

- Clarifying device setup and operation as requested by the Investigator or other health care personnel
- Observing testing or medical procedures to obtain information relevant to prptocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Olympus Winter & Ibe personnel will not:

- Practice medicine
- Provide medical diagnosis
- Independently collect critical study data (defined as primary or secondary endpoint data)

13.2 Investigator's Role and Responsibilities

13.2.1 Clinical Investigators

The Investigator is responsible for conducting the study in accordance with the signed agreement, the investigational plan, applicable laws, the latest version of the "Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Patients" and any conditions of approval imposed by the reviewing regulatory body.

The clinical investigator shall be responsible for the day to day conduct of the clinical investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

The clinical investigator shall have the resources to conduct the clinical investigation properly and obtain from the sponsor the information which he judges essential about the device and be familiar with this information.

The clinical investigator shall ensure that adequate information is given to the subject both in oral and written form, on the nature of the clinical investigation. This information shall be easily understandable by the subject. This information shall include the aims, expected benefits for him and/or others, risks and inconveniences and an explanation of any alternative methods, and of possible consequences of any withdrawal from the clinical investigation. Subjects shall be allowed sufficient time to decide whether or not they wish to participate. The subjects shall be informed that his/her participation in the clinical investigation is completely voluntary and confidential. The subject shall be made aware that the data relating to the study may be made available to third parties while maintaining anonymity.

The investigators must obtain a written IRB approval prior to including any patients into the study.

13.2.2 Investigator Selection

This study will be conducted by qualified Investigators who have experience with obstructive sleep apnea diagnosis and treatment, including knowledge of alternative therapy efficacy. The Investigator may have direct experience with the use of CelonProSleep *plus*. A principal Investigator and his/her sub-Investigator must be experienced in and responsible for: selection and evaluation of patients, strict adherence to this investigational protocol, which includes all testing requirements to provide for optimal safe and efficacious use of the CelonProSleep *plus*, collection of patient consent and study data, and submission of death letters, notes, etc.; if applicable.

It is acceptable for the Principal Investigator to delegate one or more of the above functions to an associate or sub-Investigator who is a trained healthcare professional, and who is trained on the study

protocol according to their role in the study. However, the principal Investigator remains responsible for proper conduct of the study. The study is not transferable to other centers attended by the Investigator unless prior approval is obtained from the Sponsor and the appropriate reviewing institutional oversight committee and regulatory body as required.

13.3. Study Initiation

Before participating in the clinical trial, each Investigator and sub-Investigator is required to submit to Sponsor a signed Investigator's Agreement. Prior to the Investigator's participation, the Investigator must forward written approval from the appropriate reviewing IRB to Sponsor.

13.4 Clinical Events Committee (CEC)

A Clinical Events Committee, consisting of independent physicians, will review all adverse events at regular intervals. The CEC is responsible for reviewing the Investigator's assessment and classification of each event. The CEC will also adjudicate subject withdrawals to determine whether therapy efficacy constituted a reason for their withdrawal. Study withdrawal due to therapy failure will be included in primary secondary analysis.

13.5 Patient Informed Consent

All patients will receive full and adequate verbal and written information and sign the informed consent form prior to their inclusion in the study. A copy of the approved informed consent form along with a copy of each patient's signed consent form will be maintained by each investigator in a designated clinical study administrative file. A copy of the signed consent form must be given to each patient.

13.6 Study Termination

The sponsor reserves the right to discontinue the study or a study site at any time. The reason(s) for termination shall be discussed with each investigator. Discontinuation shall be effected by fax or registered mail. If discontinuation occurs, the appropriate regulatory authorities and the Institutional Review Board involved shall be informed in writing within 72 hours after the discontinuation has been notified to the Investigators. Reasons for such action taken by the sponsor include, but are not limited to:

- Successful completion of the trial at the center
- The required number of subjects for the trial has been recruited
- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the investigator

13.7 Withdrawal

The only reason for patient withdrawal from this study is patient request.

13.8 Protocol Deviations

An Investigator is required to conduct this study in accordance with the signed Investigator's Agreement, this investigational protocol, applicable laws and regulations, and any conditions of approval imposed by the reviewing IRB.

An Investigator shall notify the Sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred. Except in such an emergency, prior approval by the Sponsor is required for a change in or deviations from this plan and, if these changes or deviations could affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, IRB and national authority approval is also required.

All deviations from the investigational plan must be reported to Sponsor, together with the reason for the deviation. In some circumstances, the center may be required to notify the center's IRB and Sponsor will notify the national authorities and/or suspend the center's participation in this clinical trial. In these circumstances, Sponsor will perform a compliance visit to evaluate adherence to the investigational plan, compliance with applicable regulations, and any additional specific issues related to the event. Additional training on the protocol and related procedures may also be necessary. Prior to continuing involvement in this clinical trial, the results of Sponsor compliance visit and concurrence from the center's IRB and/or national authorities may also be required. At this time Sponsor will ask the Investigator to review the Investigator Agreement and applicable regulations regarding medical device clinical studies, specifically Investigator responsibilities.

13.9 Stopping Rules

If Sponsor makes a decision to discontinue the study (e.g., because of slow enrollment, unanticipated adverse event, or other scenario), Sponsor will promptly inform all Investigators, IRB, and relevant regulatory authorities; along with detailed information on how enrolled subjects should be managed thereafter. All subjects enrolled in this trial will continue to be followed according to the protocol unless Sponsor advises otherwise.

14.0 REFERENCES

1. Fletcher EC, et al. Undiagnosed sleep apnea in patients with essential hypertension. Ann Intern Med 1985;103:190-195.
2. Millman RP, et al. Daytime hypertension in obstructive sleep apnea: prevalence and contributing risk factors. Chest 1991;99:861-866.
3. Partinen M. and Palomaki H. Snoring and cerebral infarction. Lancet 1985;2:1325-1326.
4. Koskenvuo M, et al. S. Snoring as a risk factor for ischaemic heart disease and stroke in men. BMJ 1987;294:16-19.
5. Hung J, et al. Association of sleep apnoea with myocardial infarction in men. Lancet 1990;336:261-264.
6. Malone S, et al. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 1991;338:1480-1484.
7. Malone S, et al. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 1991;338:1480-1484.
8. Waldhorn RE, et al. Long-term compliance with nasal continuous positive airway pressure therapy of obstructive sleep apnea. Chest. 1990;97:33-38.
9. Meurice JC, et al. Predictive factors of long term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. Chest. 1994;105:429-433.
10. Rauscher H, et al. Nasal CPAP and weight loss in hypertensive patients with obstructive sleep apnea. Thorax. 1993;48:529-533.
11. Grunstein RR. Sleep-related breathing disorders, 5: nasal continuous positive airway pressure treatment for obstructive sleep apnoea. Thorax. 1995;5;0:1106-1113.
12. Meurice JC, et al. Predictive factors of long term compliance with nasal continuous positive airway pressure treatment in sleep apnea syndrome. Chest. 1994;105:429-433.
13. Kenny P, et al. Terris. A comparison of polysomnography and the WatchPAT 200S-3 in the diagnosis of obstructive sleep apnea. Otolaryngology–Head and Neck Surgery (2007) 137, 665-668.
14. American Academy of Sleep Medicine. Portable monitoring in the diagnosis of obstructive sleep apnea. J Clin Sleep Med 2006;2:274.
15. Decision Memo for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) (CAG-00093R). 2005. (Accessed at http://www.cms.hhs.gov/mcd/viewdecisionmemo. asp?id=110.)
16. Portable Monitoring Task Force of the American Academy of Sleep Medicine: Collop NA, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. J Clin Sleep Med. 2007 Dec 15;3(7):737-47.
17. Decision Memo for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) (CAG-00093R2). http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=204&fromdb=true.
18. Ceylan T. et al. Quick Diagnosis in Obstructive Sleep Apnea Syndrome: WatchPAT-200. Iran Red Crescent Med J. 2012;**14**(8): 475-478
19. Pillar G, et al. Autonomic Arousal Index (AAI): An Automated Detection based on Peripheral Arterial Tonometry. Sleep 2002; 25(5):543-5
20. Pillar G, et al. An automatic ambulatory device for detection of AASM defined arousals from sleep: the WP100. Sleep Med 2003; 4(3):207-212.
21. Bar A, et al. Evaluation of a Portable Device Based on Peripheral Arterial Tone for Unattended Home Sleep Studies. Chest 2003; 123(3): 695-703.
22. Zou D, et al. Validation a Portable Monitoring Device for Sleep Apnea Diagnosis in a Population Based Cohort Using Synchronized Home Polysomnography. Sleep 2006; 29(3):367-374.
23. Ayas N, et al. Assessment of a Wrist-worn Device in the Detection of Obstructive Sleep Apnea. Sleep Med 2003; 4(5):435-442.

24. Pittman SD, et al. Using a Wrist-Worn Device Based on Peripheral Arterial Tonometry to Diagnose Obstructive Sleep Apnea: In-Laboratory and Ambulatory Validation. Sleep 2004; 27(5):923-933.
25. Sher AE, et al. The efficacy of surgical modification of the upper airway in adults with obstructive sleep apnea syndrome. Sleep 1996; 19: 156-177).
26. Fujita S. Pharyngeal surgery for obstructive sleep apnea and snoring. In: Fairbanks D, Fujita S, Ikematsu T, et al. Snoring and Obstructive Sleep Apnea. New York, NY; Raven Press; 1987:101-128.
27. Fujita S, et al. Evaluation of the effectiveness of uvulopalatopharyngoplasty. Laryngoscope 1985;95:70-74.
28. Ravesloot MJL and de Vries N. One hundred consecutive patients undergoing drug-induced sleep endoscopy: results and evaluation. Laryngoscope 2011; 121: 2710-2716.
29. Woodson BT, et al. A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg. 2003 Jun; 128(6):848-61.
30. Steward DL, et al. A comparison of radiofrequency treatment schemes for obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg. 2004 May;130(5):579-85.
31. Riley RW, et al. An adjunctive method of radiofrequency volumetric tissue reduction of the tongue for OSAS. Otolaryngol Head Neck Surg. 2003 Jul;129(1):37-42.
32. Carroll W, et al. Snoring management with nasal surgery and upper airway radiofrequency ablation. Otolaryngol Head Neck Surg. 2012 Jun;146(6):1023-7. Epub 2012 Feb 8.
33. Ceylan K, et al. First-choice treatment in mild to moderate obstructive sleep apnea: single-stage, multilevel, temperature-controlled radiofrequency tissue volume reduction or nasal continuous positive airway pressure. Arch Otolaryngol Head Neck Surg. 2009 Sep;135(9):915-9.
34. Steward DL, et al. Multilevel temperature-controlled radiofrequency for obstructive sleep apnea: extended follow-up. Otolaryngol Head Neck Surg. 2005; 132: 630-5.
35. Farrar J, et al. Radiofrequency ablation for the treatment of obstructive sleep apnea: a meta-analysis. Laryngoscope 2008; 118: 1878-83.
36. Powell NB, et al. Radiofrequency volumetric reduction of the tongue: a porcine pilot study for the treatment of obstructive sleep apnea syndrome. Chest 1997; 111: 1348-55.
37. Friedman M, et al. Staging of obstructive sleep apnea/hypopnea syndrome: a guide to appropriate treatment. Laryngoscope 2004; 114: 354-359.
38. M Friedman. Sleep apnea and snoring: Surgical and non-surgical therapy. Sounders (Elsvier) 2009. (Muller's maneuver).
39. Verse T, et al. Multilevel surgery for obstructive sleep apnea: short-term results. Otolaryngol Head Neck Surg. 2006; 134:571–7.
40. Stuck BA, et al. Complications of temperature-controlled radiofrequency volumetric tissue reduction for sleep-disordered breathing. Acta Otolaryngol 2003; 123:532–535.
41. Stuck BA. Radiofrequency-assisted uvulopalatoplasty for snoring: long-term follow-up. Laryngoscope 2009; 119:1617–1620.
42. Back LJ, et al. Radiofrequency ablation treatment of soft palate for patients with snoring: a systematic review of effectiveness and adverse effects. Laryngoscope 2009; 119:1241–1250.
43. Baisch A, et al. Combined radiofrequency assisted uvulopalatoplasty in the treatment of snoring. Eur Arch Otorhinolaryngol 2009; 266:125–130.
44.
45. Kezirian EJ, Powell NB, Riley RW, et al. Incidence of complications in radiofrequency treatment of the upper airway. Laryngoscope 2005; 115: 1298–1304.
46. den Herder C, et al. Bipolar radiofrequency induced thermotherapy of the tongue base: Its complications, acceptance and effectiveness under local anesthesia. Eur Arch Otorhinolaryngol. 2006; 263: 1031–40.

47. Powell NB, et al. Radiofrequency tongue base reduction in sleep-disordered breathing: a pilot study. Otolaryngol Head Neck Surg 1999; 120: 656–664.
48. Nelson LM. Combined temperature-controlled radiofrequency tongue reduction and UPPP in apnea surgery. Ear Nose Throat J. 2001; 80:640–4.
49. Woodson BT, et al. A multi-institutional study of radiofrequency volumetric tissue reduction for OSAS. Otolaryngol Head Neck Surg 2001; 125: 303–311.
50. Stuck BA, et al. Tongue base reduction with temperature-controlled radiofrequency volumetric tissue reduction for treatment of obstructive sleep apnea syndrome. Acta Otolaryngol 2002; 122: 531–536.
51. Terris DJ, et al. Minimally invasive tongue base surgery for obstructive sleep apnoea. J Laryngol Otol 2002; 116: 716–721.
52. Li KK, et al. Temperature-controlled radiofrequency tongue base reduction for sleep-disordered breathing: Long-term outcomes. Otolaryngol Head Neck Surg. 2002; 127(3):230-4.
53. Fischer Y, et al. Multilevel temperature-controlled radiofrequency therapy of soft palate, base of tongue, and tonsils in adults with obstructive sleep apnea. Laryngoscope. 2003;113:1786–91.
54. Steward DL. Effectiveness of multilevel (tongue and palate) radiofrequency tissue ablation for patients with obstructive sleep apnea syndrome. Laryngoscope 2004; 114: 2073–2084.
55. Stuck BA, et al. Combined radiofrequency surgery of the tongue base and soft palate in obstructive sleep apnoea. Acta Otolaryngol. 2004;124:827–32.
56. Blumen M, et al. Radiofrequency ablation for the treatment of mild to moderate obstructive sleep apnea. Laryngoscope 2002; 112:2086–2092.
57. Holmlund T, et al. Effects of Radiofrequency versus Sham Surgery of the Soft Palate on Daytime Sleepiness. Laryngoscope. 2014 Jan 4. doi: 10.1002/lary.24580.
58. Fernández-Julián E, et al. Randomized study comparing two tongue base surgeries for moderate to severe obstructive sleep apnea syndrome. Otolaryngology–Head and Neck Surgery 2009; 140, 917-923.
59. Friedman M, et al. Minimally invasive single-stage multilevel treatment for obstructive sleep apnea/ hypopnea syndrome. Laryngoscope 2007; 117: 1859–1863.
60. Hultcranz E, et al. Long-term effects of radiofrequency ablation of the soft palate on snoring. Eur Arch Otorhinolaryngol. 2010; 267(1):137-42.
61. Pazos G, Mair EA. Complications of radiofrequency ablation in the treatment of sleep-disordered breathing. Otolaryngol Head Neck Surg 2001; 125: 462–466.
62. Balsevičius T, et al. Controlled trial of combined radiofrequency-assisted uvulopalatoplasty in the treatment of snoring and mild to moderate OSAS (pilot study). Sleep Breath. 2013; 17(2):695-703.
63. Civelek S, et al. GlideScope Video Laryngoscope–Assisted Tongue Base Radiofrequency for the Treatment of Obstructive Sleep Apnea: Pilot Study. Journal of Otolaryngology-Head & Neck Surgery 2010;39(4),329–334.
64. Aavan den Broek E, et al. UPPP combined w06ith radiofrequency thermotherapy of the tongue base for the treatment of obstructive sleep apnea syndrome. Eur Arch Otorhinolaryngol. 2008; 265(11):1361-5.
65. Heywood Rl, et al. Radiological airway changes following bipolar radiofrequency volumetric tissue reduction. The Journal of Laryngology & Otology (2010), 124, 1078–1084.
66. Olszewska E, et al. Selected surgical managements in snoring and obstructive sleep apnea patients. Med Sci Monit, 2012: 18(1): CR13-18.
67. Tatla T, et al. Celon (R) radiofrequency thermo-ablative palatoplasty for snoring—a pilot study. J Laryngol Otol 2003; 117:801–806.
68. Blumen M, et al. Radiofrequency tongue reduction through a cervical approach: a pilot study. Laryngoscope 2006; 116:1887–1893.
69. Jacobowitz O. Palatal and tongue base surgery for surgical treatment of obstructive sleep apnea: a prospective study. Otolaryngol Head Neck Surg. 2006; 135(2):258-264.
70. Walker et al. Extended follow-up of palatal implants for OSA treatment. Otolaryngol Head Neck Surg. 2007; 137(5):822-7.

71. Doff et al. Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. Sleep. 2013 Sep 1;36(9):1289-96.
72. ZAR, Jerrold H. Biostatistical analysis (1999).
73. Joseph L. Fleiss, Bruce Levin, Myunghee Cho Paik. Statistical Methods for Rates & Proportions. 2003.
74. Newcombe, R.G. Interval estimations for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine 1998; 17, 873-890
75. Fugita S. Surgical treatment of obstructive sleep apnea: UPPP and lingualplasty (laser midline glossectomy). In: Guilleminault C, Partinen M, eds. Ostructive sleep apnea syndrome: clinical research and treatment. New York: Raven Press, 1990: 129-151.
76. Weaver TE et al. An instrument to measure functional status outcomes of excessive sleepiness. Sleep 1997; 20:835-843.
77. Grote L, et al. Therapy with nCPAP: incomplete elimination of sleep related breathing disorder. Eur Resp J 2000; 16:921-927.
78. Iber C, Ancoli-Israel S, Chesson A, Quan SF 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, Illinois: American Academy of Sleep Medicine, 2007.

APPENDIX I

TIME TABLE (STUDY FLOW CHART)

	Visit 1 **Screening**	**Visit 2** **Baseline Intake**	**Visit 3** **1st RFA**	**Visit 4** **2nd RFA**	**Visit 5** **3rd RFA**	**Visit 6** **Follow-up** (6 weeks post-treatment)	**Visit 7** **Final Follow-up** (6 months post-treatment)	**Visit 8** **Final Study Visit**
Time	Week 0	Week 2	(up to) Week 6	(up to) Week 12	(up to) Week 18	(up to) Week 24	6 months later	shortly after last PSG
Intake and consent form	X							
Inclusion criteria	X							
Medical history	X							
Physical examination	X		X (on the day of the RF treatment, 3 and 10 days later)	X (on the day of the RF treatment, 3 and 10 days later)	X (on the day of the RF treatment, 3 and 10 days later)	X	X	X
VAS snoring		X	X	X	X	X	X	
WatchPat (patients screening before PSG)	X							

PSG sleep study (AHI)		X No longer than 90 days after enroll-ment					X Within 4 weeks	
oxygen desaturation index (ODI)		X					X	
Müller's Manoeuvre		X						
Epworth Sleepiness Scale (ESS)		X		X	X	X	X	
Functional Outcomes of Sleep Questionnaire (FOSQ)		X		X	X	X	X	
VAS pain, speech, and swallowing			X (1, 3 and 7 days after RF treatment)	X (1, 3 and 7 days after RF treatment)	X (1, 3 and 7 days after RF treatment)	X	X	
Adverse Event Form		X	X	X	X	X	X	X
RFA Treatment			X	X	X			
End of Study Form								X
Study results and medical consultation								X