SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implanted Phrenic Nerve Stimulator for Central Sleep Apnea

Device Trade Name: **rem**edē® System

Device Procode: PSR

Applicant's Name and Address: Respicardia Inc.
12400 Whitewater Drive, Suite 150
Minnetonka, MN 55343

Date(s) of Panel Recommendation: N/A

Premarket Approval Application (PMA) Number: P160039

Date of FDA Notice of Approval: October 6, 2017

II. INDICATIONS FOR USE

The **rem**edē® System is an implantable phrenic nerve stimulator indicated for the treatment of moderate to severe central sleep apnea (CSA) in adult patients.

III. CONTRAINDICATIONS

The **rem**edē System is contraindicated for the following:

- Patients with an active infection
- Patients known to require magnetic resonance imaging (MRI)

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the **rem**edē System Implant and Clinician Use Manual.

V. DEVICE DESCRIPTION

The **rem**edē System is an implantable device designed to treat moderate to severe CSA. The system includes an implantable pulse generator (IPG) and transvenous leads for unilateral stimulation of the phrenic nerve and sensing respiration via transthoracic impedance. The **rem**edē IPG is programmed via telemetry using the **rem**edē System Programmer. See Figure 1 below illustrating the relative position of the implantable system IPG and leads in relationship to the phrenic nerves.

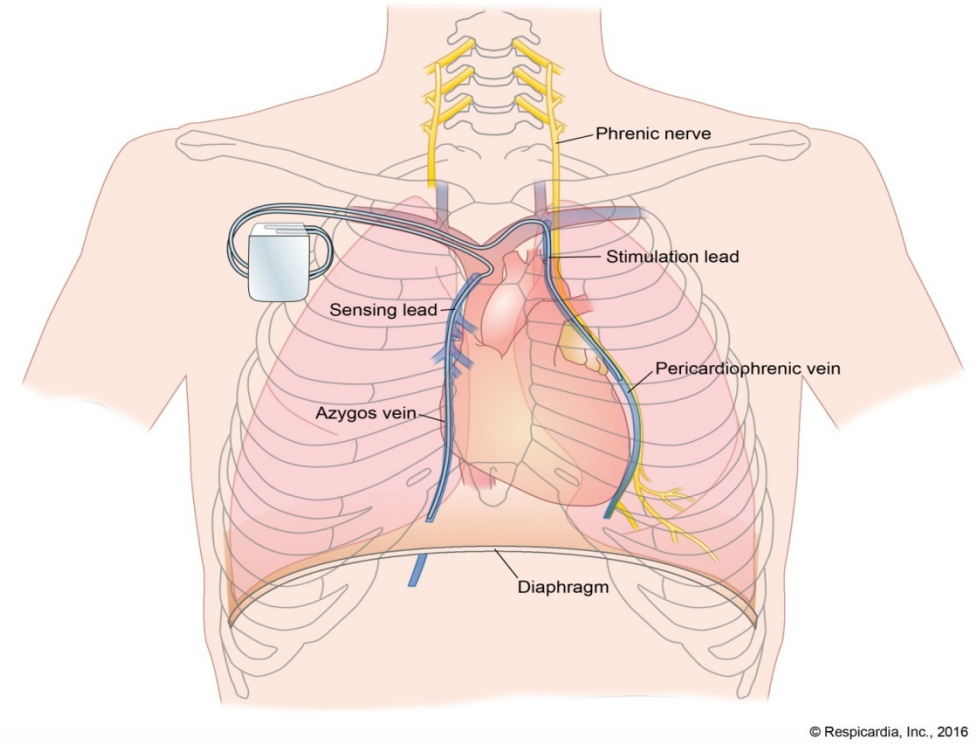

Figure 1 The remedē System and Implant Location

The **rem**edē System includes:

- Model 1001, **rem**edē Implantable Pulse Generator (IPG)
- Model 1006, **rem**edē External IPG (eIPG)
- Models 2001, 2002, 2003, 2004 respi**stim**™ L Left Stimulation Lead
- Models 5045, 5055, 5065 and 5085 respi**stim**™ LQ Left Stimulation Lead
- Models 4045, 4055, 4065 and 4085 respi**stim**™ LQS Left Stimulation Lead
- Models 3101, 3102, 3103, 3104, 3105, 3106, 3201, 3202, 3203, 3204, 3205 and 3206 respi**stim**™ R Right Stimulation Lead
- Model 1002A, **rem**edē System Programmer and accessories
    - **rem**edē Programming Software
    - Model 1004A, **rem**edē Programming Wand or Model 1004A-F, **rem**edē Flexible Programming Wand

remedē Implantable Pulse Generator (IPG)
The **rem**edē IPG, Model 1001, is an implantable, programmable stimulator designed for transvenous phrenic nerve stimulation. The system can monitor the patient's respiratory signals and provides electrical stimulation to the left or right phrenic nerve to restore patients to normal breathing during sleep. The **rem**edē IPG is comprised of electronic circuitry components and a battery, which are hermetically sealed in a titanium case. The operation of the **rem**edē IPG is supported via telemetry using a **rem**edē System programmer that allows for configuration of programmable parameters, initiation of system tests, and review of diagnostic data. The **rem**edē IPG is compatible with transvenous leads with IS-1 terminals.

remedē External IPG (eIPG)
The Model 1006 **rem**edē eIPG device is a fully functional pulse generator encased in a plastic enclosure used only to conduct electrical testing during the implant procedure. The use of this device allows stimulation lead placement to be assessed prior to removing the IPG device from its sterile packaging.

Stimulation Lead
The Applicant has developed the respistim family of leads for phrenic nerve stimulation to treat CSA. The respistim family of transvenous stimulation leads is designed for chronic stimulation and sensing.

Sensing Lead
The **rem**edē System measures transthoracic impedance to detect respiration through a commercially available transvenous lead or a respistim lead. The sensing lead is an optional component recommended to improve monitoring capabilities. However, this may depend on the implant procedure if time and circumstance do not allow. In the event that a sensing lead is not placed, respiratory sensing signals will be obtained by measuring impedance from the stimulation lead to the IPG. In this case, the functionality of the system is not impacted, but diagnostic software tools may display information with lower respiratory signal quality.

remedē System Programmer and Ancillary Components
The **rem**edē System Programmer Model 1002A is a tablet computer that provides a user interface and connects to the Model 1004A or Model 1004A-F Programming Wand to communicate with the **rem**edē IPG via magnetic inductive telemetry. The **rem**edē System Programming Software is provided with the **rem**edē System Programmer. The **rem**edē System Programmer is supplied with a medical grade power supply and power cable.

The Programmer communicates with the **rem**edē IPG when the **rem**edē Programming Wand is placed over the subject's device. The **rem**edē Flexible Programming Wand, which can be used in place of the more rigid **rem**edē Programming Wand, is designed to allow the option of extended communication with the system to enable real-time monitoring of the subject and system in marker mode, such as during overnight sleep studies.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of moderate to severe central sleep apnea. Each treatment has advantages and disadvantages. A patient should fully discuss these treatment options with their physician to select the therapy that best meets expectations and lifestyle.

Treatment alternatives include:

- Positive Airway Pressure (PAP) Therapies
    - Continuous Positive Airway Pressure (CPAP)
    - Bi-Level Positive Airway Pressure (BPAP)
    - Adaptive Servo Ventilation (ASV)
- Nocturnal Oxygen Therapy
- Medications:
    - Acetazolamide
    - Theophylline

VII. MARKETING HISTORY

The **rem**edē System received CE Mark approval on August 13, 2010. Although two (2) implants were placed under CE Mark during Q2-Q3, 2013, the product was not officially launched for commercial use in the European Union until December 2014. The **rem**edē System has not been withdrawn from the market in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Implant Procedure-Related

- Adverse contrast dye reaction such as allergic reaction, pulmonary edema, or worsening renal function
- Adverse reaction to radiation exposure
- Thromboembolism
- Air embolism
- Bleeding
- Cardiac perforation including tamponade
- Hematoma, seroma, local bruising or swelling
- Hypotension

- Local wound healing issues at device implant site including wound dehiscence, pocket erosion, extrusion, movement of implanted device, keloid formation
- Pneumothorax
- Hemothorax
- Vascular damage, e.g., venous dissection, perforation

Lead and System-Related

- Adverse biocompatibility reaction to the implanted system
- Infection
- Lead breakage
- Lead dislodgement
- Lead not connected or secured appropriately in device header
- Implantable device malfunction
- Requirement for more energy to stimulate the nerve or ineffective stimulation
- Venous occlusion

Therapy-Related

- Crosstalk with another implanted device
- Disrupted sleep
- Muscle fatigue or discomfort in diaphragm, chest or abdomen from appropriate stimulation
- Nerve dysfunction
- Perturbation of blood gases causing hypoxia, hypercapnea and/or hypocapnea
- Inappropriate sensations
- Worsening heart failure, respiratory status or overall health

Other Procedure, System or Therapy-Related

- Anxiety
- Arrhythmia, including ventricular fibrillation
- Death
- Depression
- Hypotension
- Pain
- Skin irritation or local allergic reaction
- Thrombus or embolism, potentially leading to pulmonary embolism or stroke

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The **rem**edē System has been tested in non-clinical environments to ensure compliance to specifications and regulations, and to verify and validate functionality. Bench testing demonstrated the **rem**edē System met all requirements.

remedē System Testing

Testing was performed to demonstrate **rem**edē System compliance with the System Specification, and it included an evaluation of System functional performance including electrical, mechanical, and software performance; electromagnetic compatibility (EMC); environmental and mechanical robustness; electrical safety; and compliance with applicable international standards:

- ISO 14708-1:2014 Implants for Surgery- Active Implantable Medical Devices Part 1: General requirements for safety, marking, and for information to be provided by the manufacturer
- ISO 14798-3:2008 Implants for Surgery- Active Implantable Medical Devices Part 3: Implantable Neurostimulators
- IEC 60601-1-2:2007, *Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic compatibility – Requirements and tests*
- IEC 60601-1:2005 (3rd Ed), Medical electrical equipment – Part 1: General requirements for basic safety and essential performance

The remedē System Verification and Validation testing shown in Table 1 demonstrated compliance with specification requirements and essential performance. Evaluations of functional performance, EMC, environmental and mechanical robustness, electrical safety, and international standards compliance confirmed that the **rem**edē System is acceptable for human use.

Table 1 remedē System Test

Test	Purpose	Result
Electromagnetic Compatibility - Immunity	To assure the **rem**edē System meets essential performance and functions as designed when exposed to electromagnetic energy per IEC 60601-1-2:2007 in a clinic or ambulatory setting, including testing for vulnerability to emissions from RFID.	PASS
Electromagnetic Compatibility - Emissions	To assure the **rem**edē System electromagnetic emissions meets requirements of IEC 60601-1-2:2007 and are low enough that they do not interfere with other equipment that also may be in use in a clinical setting.	PASS
Electrical Safety	To assure the **rem**edē System meets basic safety and essential performance requirements of IEC 60601-1:2005 +A2012.	PASS
Thermal Cycling	To assure the **rem**edē System meets the requirements of ISO 14708-1 and is	PASS

Test	Purpose	Result
	sufficiently robust to survive exposure to temperature variations that may occur during shipment and storage.	
Mechanical Shock and Vibration	To assure the **rem**edē System meets the requirements of ISO 14708-1 and verify device is not damaged by mechanical loads (shock, vibration, atmospheric pressure change)so it can be expected to survive during shipment and handling, as well as during the life of a patient implant.	PASS
Diagnostic Ultrasound Compatibility	To assure exposure to diagnostic ultrasound meets the requirements of ISO 14708-1 and does not damage the **rem**edē IPG.	PASS
Defibrillation Compatibility	To assure exposure to defibrillation energy meets the requirements of ISO 14708-1 and does not damage the **rem**edē IPG.	PASS
Concomitant Device Compatibility	To establish conditions which may impact concomitant device interaction. Testing was not done to any performance criteria but results were found to be informative and acceptable.	PASS
Protection against Pressure	To assure the **rem**edē IPG meets the requirements of ISO 14708-1 and will not be damaged by exposure to elevated or low pressure environments.	PASS
Temperature rise limit during single fault condition	Temperature rise should meet meets the requirements of ISO 14708-1 and should not cause burns during single fault conditions	PASS
Battery Testing	To verify battery capacity, longevity, and safety requirements are met.	PASS
Firmware (FW) /Software (SW) Verification Testing	To verify FW and SW requirements are implemented as specified in the system requirements and design specifications.	PASS

respi**stim Left and Right Lead Testing Summary**

Test leads were subjected to the testing shown in Table 2 after exposure to three (3) cycles of Ethylene Oxide (EtO) sterilization (the maximum allowed in production), three (3) cycles of thermal shock, packaging, and shipping following normal distribution practices.

Table 2 respi**stim Left and Right Lead Test Summary**

Test	Purpose	Result
Thermal Shock	To assure that the various shipping and storage temperatures will not affect the function of respi**stim** leads. After testing, there shall be no discolorations, separated glue joints, broken tubing, fractured coils, or any other constructional defects or signs of degradation.	PASS
Connector Insertion/Withdrawal	To assure that respi**stim** leads will fit into the proper header cavity without excessive force. The maximum compressive force (insertion force) and tensile force (withdrawal force) shall not exceed 3 lbf (13.3 Newtons) compressive and 2.5 lbf (11.1 Newtons) tensile for the terminal connector.	PASS
Guide wire /stylet Compatibility	To assure the respi**stim** leads can be used with the appropriate guide wire or stylet without damaging the lead or guide wire. Lead and guidewire/stylet must be undamaged, with no kinking, after fully inserted and removed.	PASS
Ligature Sleeve	To assure that the respi**stim** leads ligature sleeve can properly secure the lead and protect the lead body from a suture tie during implantation. The ligature sleeve shall be capable of securely anchoring the lead and also protecting the lead when sutured. When tied the sleeve shall not move more than 1-cm when 0.2-lbf in a wet test environment is applied. Also, after being tied, no visual deformation of the underlying insulation or conductors is allowed.	PASS
Pacing Impedance	To assure that the respi**stim** leads pacing impedance values (Zp) meet specification requirements. Sensing impedance for groups of two (2) electrodes shall be 200-2500 ohms.	PASS
Sensing Impedance	To assure that the respi**stim** leads sensing impedance values (Zs) meet specification requirements. Sensing impedance for groups of two (2) electrodes shall be 100-2500 ohms.	PASS
Durability and Insulation Integrity	To assure that respi**stim** leads can meet the insulation integrity requirements. The leads were preconditioned by exposure to the tensile forces that might occur during handling and after implantation prior to performing the insulation integrity test. Testing shall result in no permanent functional damage to include: fracture welds, breakage of conductors, slippage of crimped joints, tearing of insulation or moldings, or formation of pinholes in tubing. Permanent elongation must be <5%. DC resistance from terminal pin to	PASS

	electrode must be less than 50Ω ± 5% for DFT (75% MP35N, 25% Silver) conductors and less than 200Ω ± 5% for 100% MP35N conductors. The lead must withstand a dielectric test voltage with less than 1.5mA leakage current between any two (2) conductors that have contact with the body and less than 320uA leakage current between any conductor and a reference electrode.	
Electrical Impedance	To assure that the minimum electrical impedances measured between conductive elements intended to be electrically separated by the sealing rings of respi**stim** leads are at least 50 kΩ.	PASS
Conductor Flexibility/Fatigue	To assure that the body of the respi**stim** Left Stimulation Lead can withstand the flexural stresses that might occur after implantation without fracture of any conductor. Test articles shall withstand at least 47,000 flexing cycles of both directions at a rate of 2 HZ without fracture of any conductor or breach of insulation. Continuity measurements (DC resistance) shall be less than 50 Ω ± 5%, with no significant differences observed before and after the conductor flex testing.	PASS
Connector Flexibility/Fatigue	To assure that the respi**stim** lead connectors can withstand the flexural stresses that might occur after implantation without fracture of any conductor. Test articles shall withstand at least 82,000 flexing cycles of 45° ± 2° in both directions at a rate of 2 HZ without fracture of any conductor or junction/termination/bond or breach of insulation. Continuity measurements (DC resistance) shall be less than 50 Ω ± 5%, with no significant differences observed before and after the connector flex testing.	PASS

B. Animal Studies

Respicardia conducted a series of pre-clinical laboratory studies involving 34 animals to evaluate the **rem**edē System and the feasibility of transvenous unilateral phrenic nerve stimulation as shown in Table 3. Studies included five (5) acute and two (2) chronic animal studies. The animal studies provided initial evidence that transvenous stimulation of the phrenic nerve could safely contract the diaphragm both in an acute and chronic environment. The studies also demonstrated that the **rem**edē System met its functional requirements and was safe for chronic human implant.

Table 3 Animal Studies

Device(s)	Number of Animals	Species/ Survival	Study Objective	Results
Eupnea System (Prototype-used to demonstrate proof of concept)	3	Porcine/Acute-1 day	To establish that stimulation of right phrenic nerve from the superior vena cava safely contracts the hemi-diaphragm	Transvenous stimulation of the right phrenic nerve from the superior vena cava resulted in synchronized contractions of the right hemi-diaphragm (confirmed by airflow and fluoroscopy) without simultaneous cardiac and skeletal muscle stimulation.
Eupnea System (Prototype-used to determine effective stimulation range)	4	Porcine/Acute-1 day	To establish right phrenic nerve stimulation parameters for the control of respiration from a site located in the SVC	Demonstrated transvenous, bipolar stimulation provided in a range from 0 – 30mA could evoke a diaphragmatic response as evidence by abdominal motion and esophageal pressure measurements.
Eupnea System (Prototype-used to determine maximum stimulation range)	6	Porcine/Acute-1 day	To establish maximum stimulation parameters of the right phrenic nerve from the SVC and under various fault conditions	The system was shown to be safe under maximum stimulation parameters and various fault conditions. Under fault conditions, no premature atrial or ventricular contractions, hemodynamic changes or unintended skeletal muscle stimulation were observed.
remedē System	1	Porcine/Acute-1 day	To demonstrate implantable and external defibrillators safely detect and treat a fibrillation event while **rem**edē System therapy is active	Demonstrated no increase in the required time, defibrillation energy, or sensitivity of either an implantable or external defibrillator to detect, convert via shock, and confirm conversion of a cardiac event while **rem**edē System stimulation therapy was active.

Table 3 Animal Studies

Device(s)	Number of Animals	Species/ Survival	Study Objective	Results
Eupnea System (Prototype-used to demonstrate proof of concept)	1	Porcine/Acute-1 day	To demonstrate that the Research Breadboard (Prototype electronic circuit) and the Eupnea System complete a closed loop system	The system provided impedance data to the controlling interface and the interface provided stimulation commands. These two functions demonstrate that the system is a working closed loop system. The study also demonstrated that thoracic impedance sensing was not impacted during a pulse train.
remedē System	7	Canine/Chronic (9 – 18 weeks)	To assess chronic lead and IPG biocompatibility, safety and performance	Biocompatibility and electrical performance data obtained from eighteen (18) weeks of canine implant identified no safety issues for both the respi**stim** Right Stimulation Lead and respi**stim** Left Stimulation Lead. Additionally, no safety issues were identified with the **rem**edē IPG during the nine (9) weeks of IPG implant.

Table 3 Animal Studies

Device(s)	Number of Animals	Species/ Survival	Study Objective	Results
remedē System	12	Canine/Chronic (6 months)	Perform chronic animal study in accordance with Good Laboratory Practices (GLP) per 21CFR Part 58. Evaluate the **rem**edē System for biocompatibility, biostability, impact on animal health during the post-operative period, and general system function, handling, and integration.	Histopathology (biocompatibility) evaluation demonstrated some erosion of endothelial cells and formation of thrombi. These are common of transvenous implants and often have no significant sequelae. Histopathology included specific neural complex evaluations at the stimulation site with anatomically appropriate non-stimulation control sites, as well as general large organ pathology. Biostability was demonstrated through satisfactory integrity of the conductor and insulation material after 6 months follow-up. Animal health was determined to be acceptable through the post-operative period including animal behavior and habits, diet, and electrophysiological parameters such as capture thresholds and sensing signal parameters. The **rem**edē System, when integrated into the canine implant and chronic follow-up evaluations, functioned and handled as intended.

C. Additional Studies

Biocompatibility Testing

Biocompatibility of the **rem**edē System was evaluated in accordance with ISO10993-1 Biological evaluation of medical devices – Part I: Evaluation and testing within a risk

management process. The **rem**edē IPG is characterized as a permanent tissue/bone contacting implant device. As a permanent tissue/bone contacting implant, the **rem**edē IPG biocompatibility evaluation addressed cytotoxicity, sensitization, irritation, acute systemic toxicity, subacute/subchronic toxicity, genotoxicity, implantation, and material mediated pyrogenicity.

The respi**stim** leads are characterized as permanent blood contacting implant devices. As permanent blood contacting implant devices, the respi**stim** lead biocompatibility evaluation addressed cytotoxicity, sensitization, irritation, acute systemic toxicity, subacute/subchronic toxicity, genotoxicity, implantation, haemocompatibility, and material mediated pyrogenicity.

The biocompatibility evaluation of the **rem**edē IPG and respi**stim** leads were supported by a combination of biocompatibility testing on finished, sterilized product as well as information from comparable products produced by the OEM suppliers. The comparable products used to support biocompatibility were manufactured utilizing the identical manufacturing processes and sterilization, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.). The **rem**edē System is considered biocompatible for its intended use.

Sterilization, Shelf Life, and Packaging

The **rem**edē IPG and torque wrench are contained in the IPG packaging and provided sterile using ethylene oxide (EtO) sterilization processes that have been validated to produce a sterility assurance level (SAL) of 10^{-6}.

The **rem**edē IPG was evaluated for equivalency to existing devices currently manufactured and sterilized at Centro de Construcción de Cardioestimuladores del Uruguay (CCC Medical). The equivalence evaluation of the **rem**edē IPG, including torque wrench, to these existing device configurations was performed according to Association for the Advancement of Medical Instrumentation, Technical Information Report (AAMI TIR 28:2009 "Product Adoption and Process Equivalency for Ethylene Oxide (EtO) Sterilization", specifically Annex A "Guide for evaluation of a product for adoption into an EtO product family or EtO processing group"). The assessment evaluated equivalency from the product design characteristics inclusive of hardest-to-sterilize product, materials, manufacturing assembly characteristics, sterilization process parameters, sterile barrier system, and sterile load characteristics. The products used identical packaging materials (inner and outer trays, Tyvek lids) and packaging configuration and did not present a greater sterilization challenge from the perspective of device design or manufacturing process. Bacteriostasis/fungistasis testing was incorporated into the sterilization (dose verification) testing by including control samples to verify that nothing in/on the IPG packaging configuration inhibits growth of microorganisms. The sterilization process is revalidated by CCC Medical on an annual basis; the revalidation activity includes an annual monitoring of EtO/ECH (ethylene chlorohydrin) residuals, and endotoxin testing.

The respi**stim** lead is provided sterile using EtO sterilization processes that have been validated to produce a SAL of 10^{-6}. The respi**stim** lead was adopted into the existing sterilization cycle at Oscor, Inc. based on demonstrated similarities between the respi**stim** lead to Oscor, Inc. leads in terms of design and manufacturing processes. The respi**stim** lead is packaged using the same packaging materials and configuration as Oscor, Inc. permanent pacing leads. The respi**stim** lead also uses the same label materials, device packaging, and shipping packaging as Oscor, Inc. permanent pacing leads. Bacteriostasis/fungistasis testing was incorporated into the sterilization (dose verification) testing by including control samples to verify that nothing in/on the lead packaging configuration inhibits growth of microorganisms.

As part of the respi**stim** lead inclusion qualification, additional testing was performed to demonstrate that gas residuals (EtO and ECH) would continue to meet the limits as stated in ISO 10993-7. Ten (10) respi**stim** leads were subjected to full cycle sterilization and were tested for EtO and ECH. The respi**stim** lead test samples met the ANSI\AAMI\ ISO 10993-7:2008/Cor 1:2009 EtO/ECH residual acceptance criteria for Permanent Contact devices. The sterilization process is revalidated by Oscor, Inc. on an annual basis; the revalidation activity includes an annual monitoring of gas residuals (EtO and ECH). Bacterial endotoxin monitoring is performed quarterly on three (3) representative samples.

Shelf Life and Packaging

Shelf life of the packaged Model 1001 IPG has been established as two (2) years based on testing including 2-year Accelerated and Real-time Aging IPG Sterile Barrier Integrity and Seal Strength tests. This testing was performed upon an equivalent CCC Medical IPG with the same blister packaging materials, design and sealing methods as the **rem**edē IPG.

The packaging meets the standards in ISO11607-1, Packaging for Terminally Sterilized Medical Device Part I: Requirements for Materials, Sterile Barrier Systems and Packaging Systems. Distribution simulation testing of the Model 1001 IPG in its shelf box was shown to meet ASTM standard D4169-05: Standard Practice for Performance Testing of Shipping Containers and Systems, distribution cycle 13, Assurance Level 1– Truck/Air spectrum.

Shelf-life for the respi**stim** leads has been established as three (3) years based on testing including 3-year Accelerated and Real-time Aging performed upon an equivalent Oscor, Inc. lead with the same blister packaging materials, design, and sealing methods as the respi**stim** leads. The packaging meets the standards in ISO11607-1, Packaging for Terminally Sterilized Medical Device Part I: Requirements for Materials, Sterile Barrier Systems and Packaging Systems.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Feasibility and Pilot Studies

Six (6) human clinical studies were completed prior to the start of the **rem**edē System Pivotal Trial to assess the safety and effectiveness of phrenic nerve stimulation therapy to treat central sleep apnea. These studies began with a cadaver survey followed by a venography study, two (2) acute feasibility studies and two (2) chronic studies. A summary of these six (6) human clinical studies is provided below in Table 4.

Table 4 Summary of Human Clinical Studies

Clinical Study/IDE Number, if applicable	Study Design	Objective	Number of Sites	Number of Subjects	Conclusion
Cadaver Survey	Proof of Concept	To characterize potential stimulation sites for providing phrenic nerve stimulation via a transvenous lead	1	48	The phrenic nerve was located in close proximity to veins on both the left via the left pericardiophrenic vein or the right via the right brachiocephalic vein.
Venography Study	Nonrandomized, multicenter, open label feasibility study	To determine if a vein adjacent to the right or left phrenic nerve could be identified and transvenous stimulation delivered within that vein could produce a diaphragmatic movement.	11	80	The phrenic nerve was able to be stimulated via the left pericardiophrenic vein. The right phrenic vein was found not to be a suitable candidate for phrenic nerve stimulation. In addition, the study helped identify the techniques, catheters and wires needed to identify the left pericardiophrenic vein.

Table 4 Summary of Human Clinical Studies

Clinical Study/IDE Number, if applicable	Study Design	Objective	Number of Sites	Number of Subjects	Conclusion
Effects of Acute Phrenic Nerve Stimulation in Patients with Periodic Breathing Study	Nonrandomized, single center, open label, acute feasibility study	To evaluate: 1) transvenous stimulation of the phrenic nerve was possible 2) the ability of the Eupnea System to disrupt periodic breathing, and 3) evaluate subject tolerance to stimulation.	1	26	Acute unilateral transvenous stimulation of the phrenic nerve was able to cause diaphragmatic contraction. When stimulation was applied following a series of central sleep apneic events, a trend toward stabilization of breathing and heart rate as well as improvement in oxygen saturation was seen. This stimulation improved indices of periodic breathing and was not associated with adverse events.
Eupnea System Acute Feasibility Study/ G070146	Nonrandomized, single center, open label, acute feasibility study	To determine whether periodic breathing could be interrupted safely by transvenous stimulation of the phrenic nerve.	6	53	Stimulation of the phrenic nerve was well tolerated. This study confirmed the clinically and statistically significant improvement in respiratory and sleep parameters with stimulation of the phrenic nerve. Apnea Hypopnea Index,(AHI), central apnea index (CAI), oxygenation, and arousal index all improved when comparing the overnight control sleep study results to the overnight therapy sleep study results.

Table 4 Summary of Human Clinical Studies

Clinical Study/IDE Number, if applicable	Study Design	Objective	Number of Sites	Number of Subjects	Conclusion
remedē System (chronic) Feasibility Study	Nonrandomized, single center, open label, chronic feasibility study	To evaluate the initial experience with chronic unilateral transvenous phrenic nerve stimulation.	1	8	The **rem**edē System chronic stimulation energy levels are consistent once implant healing has occurred and can be effectively and safely used for the chronic delivery of stimulation to the phrenic nerve via adjacent venous electrode. Compared to baseline, there were significant improvements in each subject in AHI, CAI, left ventricular ejection fraction, and 6-minute walk distance at 6 months of therapy.
Chronic Evaluation of the **rem**edē System (Pilot Study)/G070146	Nonrandomized, multicenter, pilot study	To evaluate chronic, transvenous, unilateral phrenic nerve stimulation to treat central sleep apnea	14	57	The findings indicated that **rem**edē System therapy demonstrated improvement in endpoints for AHI, CAI, ArI, and REM sleep in CSA patients in a non-randomized cohort of subjects. The most common SAE reported was for lead dislodgement. No significant safety signals were identified. The findings provided evidence to support additional study in a larger prospective, randomized, controlled trial.

remedē System Pivotal Trial

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for transvenous phrenic nerve stimulation with the **rem**edē System for treatment of moderate to severe central sleep apnea (CSA) in adult patients in the US, Germany, and Poland under IDE # G120196. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were implanted between April 17, 2013 and May 28, 2015. The database for this PMA reflected data collected through October 15, 2016 and included 151 patients that were enrolled and randomized. There were 31 investigational sites.

The **rem**edē System Pivotal Trial was a prospective, randomized, controlled, multicenter trial. The primary objectives of the trial were to determine the safety and effectiveness of therapy delivered by the **rem**edē System in the treatment of central sleep apnea. The primary effectiveness endpoint (analyzed in the modified intention-to-treat (ITT) primary effectiveness analysis population (discussed below)) was defined as a comparison of the proportions of subjects who achieved a 50% or greater reduction in apnea-hypopnea index (AHI) from baseline to 6 months post-therapy initiation between the Treatment group and the Control group.

The Treatment group received optimal medical management in addition to **rem**edē System therapy. The Control group also received optimal medical management, but the remedē System therapy was inactive. Although the Control group received the remedē System implant, the therapy was not activated for the first 6 months. Following the 6-month post-therapy initiation visit endpoint assessments, **rem**edē System therapy was activated for the Control subjects for the remainder of the trial in addition to continuing to receive optimal medical therapy.

Optimal medical therapy was determined by the individual treating clinician based on standard clinical practice and guidelines. Subjects with Central Sleep Apnea often have multiple co-morbidities whichwere adequately treated and stable prior to study enrollment. In addition, prior to collection of the primary effectiveness endpoint data 6 months post therapy initiation, changes to medications were discouraged and remained as stable as subject condition allowed.

AHI was measured via polysomnography (PSG). All PSG data, including the assessment of the primary endpoint, was evaluated by a PSG core laboratory that was blinded to subject randomization assignments. Randomization assignments were based on computer-generated random numbers prepared by an independent, third-party statistician. The randomization was stratified by investigational site using random blocks of size 2 and 4 within each site. Block sizes were not revealed to investigational sites or subjects. The randomization schedule was loaded into the electronic data capture (EDC) system. The PSG core laboratory remained blinded to treatment assignment throughout all PSG evaluations. Clinical Events Committee

(CEC) physicians and Data Safety Monitoring Board (DSMB) were blinded to the subject treatment assignment where possible. The interim analysis was performed by an unblinded independent third-party statistician.

The primary safety endpoint (analyzed in the ITT population) was defined as the freedom from Serious Adverse Events (SAEs) associated with the implant procedure, the **rem**edē System, or the delivered therapy through the 12-month post-therapy initiation visit. SAEs were defined as any event leading to death, serious deterioration of health, life-threatening illness or injury, permanent impairment, inpatient hospitalization or prolongation of existing hospitalization, or surgical intervention to prevent permanent impairment. Since all randomized subjects were scheduled to receive the **rem**edē System, there was no formal test of hypotheses comparing freedom from related SAEs between randomized groups. Adverse events were adjudicated by an independent Clinical Events Committee.

If the primary effectiveness endpoint was met, changes in pre-specified secondary endpoints from baseline to 6 months were hierarchically tested between the Treatment and Control groups in the following order in the per protocol population: mean reduction in central apnea index (CAI), AHI, and arousal index (ArI); mean increase in percent of time spent in rapid eye movement (REM) sleep; the proportion of patients with "moderate" or "marked" improvement in the Patient Global Assessment (PGA) health related quality of life instrument; and mean reduction in oxygen desaturation index 4% (ODI4) and Epworth Sleepiness Scale (ESS).

All subjects who met study inclusion/exclusion criteria underwent an implant attempt of the **rem**edē System and were randomized in a 1:1 fashion to Treatment (**rem**edē System with active therapy) or Control (**rem**edē System with inactive therapy). Control subjects remained without **rem**edē System therapy until after completion of all 6 month assessments at which time **rem**edē System therapy was initiated. See Figure 2 below.

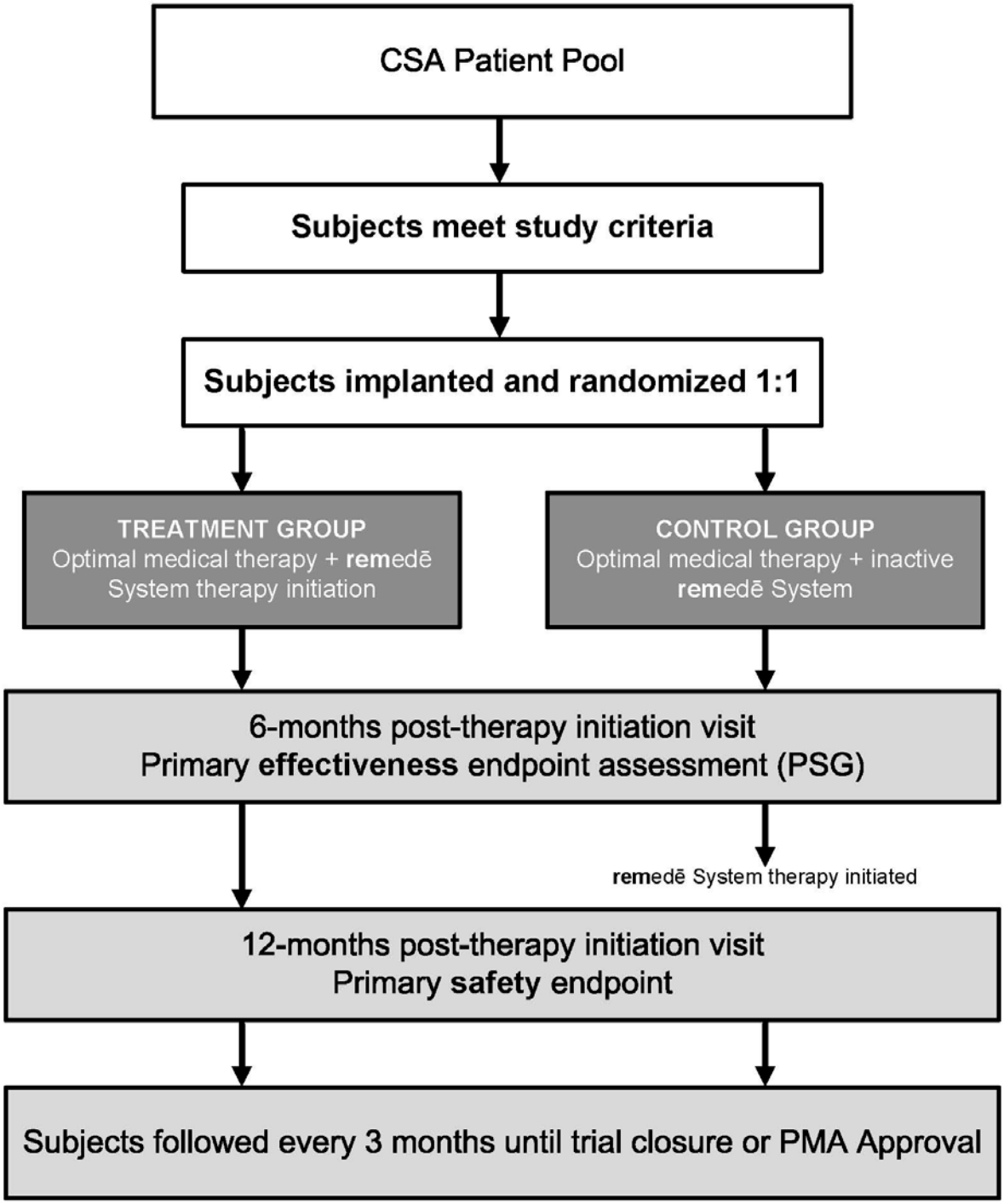

Figure 2 Subject Flow Diagram

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the **rem**edē System Clinical Investigational Plan was limited to patients who met the following inclusion criteria:

- At least 18 years of age
- Central Sleep Apnea confirmed by core laboratory analysis of PSG with electroencephalogram (EEG) within 40 days of scheduled implant:
    - AHI greater than or equal to 20 events/hour
    - CAI at least 50% of all apneas, with at least 30 central apnea events during the qualifying PSG
    - Obstructive Apnea Index (OAI) less than or equal to 20% of the total AHI
- Medically stable for 30 days prior to all baseline testing (including PSG), i.e., no hospitalizations for illness, no breathing mask-based therapy, and on stable medications and therapies:
    - Stable medications were defined as no changes during this period except for those within a pre-specified sliding scale medication regimen
    - If the subject had heart failure, the baseline testing (including PSG) should occur at least 6 months after initial diagnosis
    - If the subject had systolic heart failure, the baseline testing (including PSG) should occur after maximally titrating beta blockers, angiotensin converting enzyme-inhibitors (ACE-I) and other medications indicated in the current guidelines (unless contraindicated or not considered medically necessary) and after receiving any indicated device therapy including devices for cardiac resynchronization therapy and/or primary prevention of sudden cardiac death
    - If subject had a hospitalization or physician visit requiring intravenous (IV) medication between the screening PSG and implant, the subject must be re-screened when stable
- Expected to tolerate study procedures in the opinion of the investigator, in particular:
    - Ability to lie down long enough to insert the **rem**edē System without shortness of breath and able to tolerate instrumentation for the PSG/PG testing
    - Expected to tolerate therapy titration and the sensation of therapy, and communicate therapy experience

- In the investigator's opinion, willing and able to comply with all study requirements
- Signed Institutional Review Board/Medical Executive Committee approved informed consent (including Health Insurance Portability and Accountability Act [HIPAA] authorization in the US)

Patients were not permitted to enroll in the **rem**edē System Clinical Investigational Plan study if they met any of the following exclusion criteria:

- Pacemaker dependent subjects without any physiologic escape rhythm
- Suspected inability to place catheter for delivery of stimulation lead (e.g. previously known coagulopathy, distorted anatomy, prior failed pectoral implant, etc.)
- Evidence of phrenic nerve palsy
- More than 2 previous open chest surgical procedures (e.g., coronary artery bypass graft [CABG])
- Etiology of CSA known to be caused primarily by pain medication
- Documented history of psychosis or severe bipolar disorder
- Cerebrovascular accident (CVA) within 12 months of baseline testing
- History of idiopathic pulmonary hypertension, World Health Organization Class 1
- Limited pulmonary function with either forced expiratory volume (FEV1)/ forced vital capacity (FVC) less than 65% of predicted value or FVC less than 60% of predicted value
- Baseline oxygen saturation less than 92% while awake and on room air after 5 minutes of quiet rest
- Anticipated need for chronic oxygen therapy or breathing mask-based therapy for 6 months post-therapy initiation visit
- Active infection or sepsis within 30 days of enrollment
- Currently on renal dialysis or creatinine level greater than 2.5 mg/dL or calculated creatinine clearance equal to or less than 30 ml/min using the Cockcroft-Gault equation
- Poor liver function with baseline aspartate transaminase (AST), alanine transaminase (ALT), and/or total bilirubin greater than three (3) times the upper limit of normal (per laboratory normal at each site)

- Hemoglobin less than 8 gm/dL
- In subjects with heart failure, American College of Cardiology (ACC)/American Heart Association (AHA) Heart Stage D
- Within the 3 months prior to baseline testing, any of the following: uncorrected severe valvular stenosis, valve replacement or repair (percutaneous or surgical), myocardial infarction (MI), CABG surgery, percutaneous coronary intervention (PCI), cardiac ablation, new cardiac resynchronization device or new pacemaker implant
- New implantable cardioverter defibrillator or any implantable device generator change-out within 30 days prior to baseline testing or anticipated within the first 6 months of enrollment
- Other anticipated surgery or invasive procedure expected to affect ability to perform testing at 6-month post-therapy initiation visit
- Unstable angina
- Allergy to or intolerant of contrast dye
- Pregnancy or of child bearing potential without a negative pregnancy test within ten days prior to **rem**edē System implant
- Life expectancy or expected time to transplant or left ventricular assist device of less than 12 months
- Currently enrolled or planning to enroll in another trial that may conflict with protocol requirements or confound subject results in this trial

2. Follow-up Schedule

Subjects underwent baseline PSG followed by an implantation attempt of the **rem**edē System. Subjects were randomized 1:1 to either the Treatment group or Control group at the implant procedure, with random block sizes of assignment within investigational site. Subjects were evaluated at the therapy initiation visit, one month after the **rem**edē System implant. The therapy initiation visit included an overnight PSG for all subjects. Treatment subjects had therapy initiated during this overnight; whereas, Control subjects had therapy initiated following the primary effectiveness endpoint assessment at the 6-month post-therapy initiation visit.

Visits occurred at implant, therapy initiation (1 month post-implant), 3, 6, 9, and 12 months post-therapy initiation, and are ongoing every 3 months until trial closure.

In addition to the PSG, subjects were assessed at visits by physical exams, laboratory results, echocardiograms, six-minute walk test, Holter monitor, and quality of life questionnaires (including Epworth Sleepiness Scale, SF-12, EQ-5D,

Patient Global Assessment, Fatigue Severity Scale, Minnesota Living with Heart Failure, and patient experience). Not all assessments were required at each visit. PSGs were conducted at baseline, 1 month therepay initiation (treatment arm), 6 months, 9 months (treatment arm), 12 months, 15 months (control arm), and every 3 months until trial closure.

Following the initiation of therapy, subjects underwent titration of therapy under physician direction based on individual subject needs. Subject evaluation and system setting adjustments occurred during one or more follow-up visits with optional overnight monitoring via in-home pulse oximetry, in–home or in–laboratory polygram (PG), or in–laboratory PSG. Visit timing was per physician discretion. Programming changes to optimize therapy were made as needed.

Primary evaluations for primary effectiveness results and hierarchically tested secondary endpoints occurred at the 6-month follow-up visit and for primary safety at the 12-month follow-up visit.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Primary Safety Objective

The primary safety objective of the trial was demonstration of the safety of the **rem**edē System and therapy for central sleep apnea as defined by freedom from SAEs associated with the implant procedure, the **rem**edē System, or the delivered therapy through the 12-month post-therapy initiation visit, as determined by the CEC.

Since all randomized subjects were scheduled to receive the **rem**edē System, there was no formal test of hypotheses comparing freedom from related SAEs between Treatment and Control.

Primary Effectiveness Endpoint

The primary effectiveness endpoint (analyzed in the modified ITT effectiveness analysis population) was defined as a comparison of the proportions of subjects who achieved a 50% or greater reduction in AHI from Baseline to 6 months post-therapy initiation between the Treatment group and the Control group in the ITT primary effectiveness analysis population. Subject success on the primary AHI endpoint was defined as a subject achieving a 50% or greater reduction in AHI using standard attended PSG with EEG equipment from Baseline to 6-month post-therapy initiation visit.

Secondary Hierarchically Tested Endpoints

The secondary objectives included demonstration of effectiveness on the following hierarchically tested secondary endpoints. The secondary endpoints were evaluated using the per protocol population.

1. Mean reduction in the Central Apnea Index (CAI) from Baseline to 6 months post-therapy initiation visit in the Treatment group compared to the Control group.
2. Mean reduction in the Apnea-Hypopnea Index (AHI) from Baseline to 6 months post-therapy initiation visit in the Treatment group compared to the Control group.
3. Mean reduction in the Arousal Index (ArI) from Baseline to 6 months post-therapy initiation visit in the Treatment group compared to the Control group.
4. Mean increase in Rapid Eye Movement (REM) sleep from Baseline to 6 months post-therapy initiation visit in the Treatment group compared to the Control group.
5. Overall quality of life measured via Patient Global Assessment (PGA) at 6 months post-therapy initiation visit in the Treatment group compared to the Control group. Subjects responded to the question "Specifically in reference to your general health, how do you feel today as compared to how you felt before having your device implanted?" on a seven point scale ranging from markedly worse to markedly improved. The endpoint was defined as the comparison of the proportions of subjects in the Treatment group with a "moderate" or "marked" improvement in the PGA at 6 months post-therapy initiation visit compared to the Control group.
6. Mean reduction in the Oxygen Desaturation Index 4% (ODI4) from Baseline to 6 months post-therapy initiation visit in the Treatment group compared to the Control group.
7. Mean reduction in the Epworth Sleepiness Scale (ESS) from Baseline to 6 months post-therapy initiation visit in the Treatment group compared to the Control group.

Primary Effectiveness Endpoint Statistical Hypothesis

The following hypotheses were evaluated for the primary effectiveness endpoint:

H_0: The proportion of subjects who have achieved a 50% or greater reduction in AHI from Baseline to 6 months post-therapy initiation visit in the Treatment group ($P_{Treatment}$) is less than or equal to that in the Control group ($P_{Control}$).

$$P_{Treatment} \leq P_{Control}$$

H_1: The proportion of subjects who have achieved a 50% or greater reduction in AHI from Baseline to 6 months post-therapy initiation visit in the Treatment group ($P_{Treatment}$) is greater than that in the Control group ($P_{Control}$).

$$P_{Treatment} > P_{Control}$$

The hypotheses for the primary effectiveness endpoint were tested using a Fisher's Exact test for two proportions.

Secondary Hierarchically Tested Endpoints

The hypotheses associated with the secondary hierarchically tested endpoints were tested if significance was demonstrated for the primary effectiveness endpoint. Endpoints were tested using two-group Student's t-tests and Fisher's Exact tests as appropriate, using a hierarchical closed-test procedure for maintaining overall Type I error level across the multiple endpoints. Statistical significance of an endpoint could be claimed if all tests of prior endpoints were statistically significant. If normality assumptions for both groups were not met for parametric tests then the hypotheses were tested using a nonparametric exact Mann-Whitney or Wilcoxon Signed-Rank test, as appropriate.

If the one-sided p-value is ≤ 0.025 for an endpoint, the null hypothesis was rejected in favor of the alternative and it was determined that the **rem**edē System was superior compared to Control. The hypotheses for the seven (7) hierarchical endpoints were:

1. Central Apnea Index at 6 months

   H_0: The mean reduction in central apnea index (CAI) from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta CAI_{Treatment}$) is less than or equal to that in the Control group ($\Delta CAI_{Control}$).

   $$\Delta CAI_{Treatment} \leq \Delta CAI_{Control}$$

   H_1: The mean reduction in CAI from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta CAI_{Treatment}$) is greater than that in the Control group ($\Delta CAI_{Control}$).

   $$\Delta CAI_{Treatment} > \Delta CAI_{Control}$$

2. Apnea-Hypopnea Index at 6 months

   H_0: The mean reduction in Apnea-Hypopnea Index (AHI) from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta AHI_{Treatment}$) is less than or equal to that in the Control group ($\Delta AHI_{Control}$).

   $$\Delta AHI_{Treatment} \leq \Delta AHI_{Control}$$

H_1: The mean reduction in AHI from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta AHI_{Treatment}$) is greater than that in the Control group ($\Delta AHI_{Control}$).

$$\Delta AHI_{Treatment} > \Delta AHI_{Control}$$

3. Arousal Index at 6 months

H_0: The mean reduction in arousal index (ArI) from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta ArI_{Treatment}$) is less than or equal to that in the Control group ($\Delta ArI_{Control}$).

$$\Delta ArI_{Treatment} \leq \Delta ArI_{Control}$$

H_1: The mean reduction in AI from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta ArI_{Treatment}$) is greater than that in the Control group ($\Delta ArI_{Control}$).

$$\Delta ArI_{Treatment} > \Delta ArI_{Control}$$

4. Rapid eye movement sleep at 6 months

H_0: The mean increase in the percent of sleep time spent in rapid eye movement (REM) from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta REM_{Treatment}$) is less than or equal to that in the Control group ($\Delta REM_{Control}$).

$$\Delta REM_{Treatment} \leq \Delta REM_{Control}$$

H_1: The mean increase in the percent of sleep time spent in REM from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta REM_{Treatment}$) is greater than that in the Control group ($\Delta REM_{Control}$).

$$\Delta REM_{Treatment} > \Delta REM_{Control}$$

5. Overall quality of life measured via Patient Global Assessment at 6 months

Subjects responded to the question “Specifically in reference to your general health, how do you feel today as compared to how you felt before having your device implanted?” on a seven point scale ranging from markedly worse to markedly improved.

H_0: The proportion of subjects with a “moderate” or “marked” improvement in the Patient Global Assessment (PGA) from Baseline to 6 months post-therapy initiation visit in the Treatment group ($P_{Treatment}$) is less than or equal to that in the Control group ($P_{Control}$).

$$P_{Treatment} \leq P_{Control}$$

H_1: The proportion of subjects with a "moderate" or "marked" improvement in the Patient Global Assessment from Baseline to 6 months post-therapy initiation visit in the Treatment group ($P_{Treatment}$) is greater than that in the Control group ($P_{Control}$).

$$P_{Treatment} > P_{Control}$$

6. Oxygen Desaturation Index 4% at 6 months

H_0: The mean reduction in the hourly rate of events of oxygen desaturation $\geq$4% (ODI4) from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta ODI4_{Treatment}$) is less than or equal to that in the Control group ($\Delta ODI4_{Control}$).

$$\Delta ODI4_{Treatment} \leq \Delta ODI4_{Control}$$

H_1: The mean reduction in the hourly rate of events of oxygen desaturation $\geq$4% (ODI4) from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta ODI4_{Treatment}$) is greater than that in the Control group ($\Delta ODI4_{Control}$).

$$\Delta ODI4_{Treatment} > \Delta ODI4_{Control}$$

7. Epworth Sleepiness Scale at 6 months

H_0: The mean reduction in the ESS from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta ESS_{Treatment}$) is less than or equal to that in the Control group ($\Delta ESS_{Control}$).

$$\Delta ESS_{Treatment} \leq \Delta ESS_{Control}$$

H_1: The mean reduction in ESS from Baseline to 6 months post-therapy initiation visit in the Treatment group ($\Delta ESS_{Treatment}$) is greater than that in the Control group ($\Delta ESS_{Control}$).

$$\Delta ESS_{Treatment} > \Delta ESS_{Control}$$

B. Accountability of PMA Cohort

At the time of database lock, of 151 patients enrolled in the PMA study, 90% (136) patients were available for analysis at the 6 month post-operative primary effectiveness endpoint and 83% (126) patients were available for analysis at the 12 month post-operative primary safety analysis.

Subject accountability at the time of the data snapshot through the 30-month visit is shown in Table 5.

Table 5 Summary of Randomized Subject Accountability (ITT)

			Months Post-therapy Initiation Visit				
Subjects	**Implant**	**Therapy Initiation[3]**	**6**	**12**	**18**	**24**	**30**
TREATMENT							
Expected at visit[1]	73	72	65	60	42	23	6
Visit at interval [n (%)][2]	73 (100%)	67[4] (93%)	63 (97%)	59 (98%)	41 (98%)	22 (96%)	6 (100%)
Missed Visit	0	5[5]	2	1	1	1	0
CONTROL							
Expected at visit[1]	78	76	73	71	52	31	7
Visit at interval [n (%)][2]	78 (100%)	76 (100%)	73 (100%)	67 (94%)	49 (94%)	30 (97%)	7 (100%)
Missed Visit	0	0	0	4	3	1	0

[1] Expected at visit=Randomized – (died + withdrawn + not yet overdue)
[2] Number and percentage of expected visits completed
[3] Treatment subjects have therapy turned on at this visit; control subjects were turned on at 6-month visit
[4] One subject who attended the therapy initiation visit did not have therapy turned on
[5] These subjects exited after missing the visit window and did not have therapy turned on

The analysis populations for the study are identified as follows:

- **Intention-to-Treat (ITT) Population (151 subjects):** Subjects who were consented, randomized, and underwent an implant attempt. All safety evaluations were based on the ITT population.
- **Modified ITT Primary Effectiveness Analysis Population (141 subjects):** Treatment group subjects who did not have a 6-month PSG result for reasons unrelated to the implant procedure, the **rem**edē System, or delivered therapy were excluded from the ITT primary effectiveness analysis population and subjects who did not have 6-month PSG results for reasons related to the procedure, system or therapy were imputed as not achieving ≥50% reduction in AHI for analysis of the primary effectiveness endpoint. Control group subjects who did not have the 6-month PSG result were excluded from the population, regardless of reason.
- **Per Protocol (PP) Population (131 Subjects):** Subjects were excluded from the per protocol population if they met any of the following pre-specified criteria:

ii. Did not meet one or more of the major inclusion/exclusion criteria, defined as:

Major inclusion criteria:

1. CSA criteria: AHI≥20, CAI≥50% of apneas with at least 30 central apnea events, OAI≤20% of AHI

Major exclusion criteria:

1. Pulmonary function: FEV1/FVC<65% of predicted value or FVC<60% of predicted value
2. Oxygen saturation<92% awake and on room air at rest
3. Etiology of CSA known to be caused primarily by pain medication
4. Hemoglobin less than 8 gm/dL
5. In subjects with heart failure, ACC/AHA Heart Stage D

iii. Did not successfully receive an implant

iv. Did not have analyzable core laboratory AHI results from a PSG at the 6-month post-therapy initiation visit

v. Subject was randomized to the Treatment group and had the system programmed off for ≥48 consecutive hours in the 30 days preceding the 6-month post-therapy initiation PSG assessment.

The per protocol population was used to evaluate all secondary endpoints and to evaluate the primary effectiveness endpoint as an exploratory analysis, unless otherwise specified.

Forty-three (43) subjects had exited the trial as of the data snapshot on October 15, 2016 (24 subjects in the Treatment group, 19 subjects in the Control group). Table 6 displays the reasons for trial discontinuation for the ITT population.

Table 6 Summary of Reasons for Trial Discontinuation through the Database Snapshot (ITT)

	Treatment (N=73)	**Control (N=78)**	**Pooled (N=151)**
Exit reason	**% (n) Subjects**	**% (n) Subjects**	**% (n) Subjects**
Physician-initiated withdrawal[1]	1% (1)	3% (2)	2% (3)
Subject Death	15% (11)	14% (11)	15% (22)
Subject Lost to Follow-Up[2]	1% (1)	1% (1)	1% (2)
Subject-initiated withdrawal[3]	8% (6)	5% (4)	7% (10)
System explanted[4]	7% (5)	1% (1)	4% (6)
Total	33% (24)	24% (19)	28% (43)

[1] Two (2) intervening medical condition, one (1) subsequent to failed implant attempt.
[2] One (1) subsequent to failed implant attempt, one (1) after multiple attempts unable to contact.

[3] Four (5) due to intervening medical condition, two (2) subsequent to failed implant attempt, three (3) due to relocating away from the study site.
[4] Two (2) IPG pocket infection, one (1) concomitant ICD infection, two (2) failed stimulation leads, one (1) opted for system explant after battery depletion, two (2) subject-initiated withdrawals also underwent system explant.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study evaluating central sleep apnea in the US.

The baseline characteristics of the randomized subjects demonstrated an average age of 65 years. Subjects were primarily male (89%) and white (95%).

The majority of subjects had at least one co-morbidity, with cardiovascular conditions being the most prevalent: hypertension (75%), hyperlipidemia (74%), heart failure (64%), and coronary artery disease (56%). Concomitant implantable cardiovascular stimulation devices were present in 42% (64/151) of the subjects at baseline. The randomization was successful, resulting in balanced baseline characteristics between the Treatment and Control groups.

Baseline PSG indicated that the randomized population had moderate to severe CSA with subjects having an average AHI of 46 events/hour at Baseline (scored by a core laboratory). The average AHI was higher in the Treatment group than in the Control group at Baseline (mean ± standard deviation [SD]), 48.8±19.3 vs. 43.7±16.8 events/hour, respectively, but this difference did not reach statistical significance (p=0.126) and has no clinically significant impact. The majority of the contributing events were central apneas, with averages of 30.0±18.0 events/hour in the Treatment group and 26.6±16.1 events/hour in the Control group. AHI associated respiratory indices are summarized in Table 7.

Table7 Summary of Baseline Polysomnogram AHI and Associated Respiratory Indices (ITT)

Variable	Treatment	Control	P-value[1]	Pooled
AHI (events/hour)	48.8 ± 19.3 (73) 48.3 [20.0, 98.1] 32.1, 60.2	43.7 ± 16.8 (78) 40.1 [20.1, 81.3] 31.5, 52.7	0.126	46.2 ± 18.2 (151) 43.0 [20.0, 98.1] 31.8, 58.3
CAI (events/hour)	30.0 ± 18.0 (73) 26.0 [5.6, 83.2] 15.6, 41.6	26.6 ± 16.1 (78) 21.2 [6.9, 72.1] 13.9, 36.4	0.275	28.2 ± 17.1 (151) 23.5 [5.6, 83.2] 14.2, 40.0
OAI (events/hour)	2.6 ± 3.2 (73) 1.8 [0.0, 16.2] 0.5, 3.1	2.3 ± 2.7 (78) 1.0 [0.0, 10.5] 0.2, 3.7	0.239	2.4 ± 3.0 (151) 1.6 [0.0, 16.2] 0.4, 3.4
MAI (events/hour) [Mixed Apnea Index]	3.1 ± 4.1 (73) 1.3 [0.0, 18.7] 0.4, 4.1	2.2 ± 3.3 (78) 0.7 [0.0, 14.4] 0.1, 2.5	0.029	2.6 ± 3.7 (151) 0.9 [0.0, 18.7] 0.2, 3.4
HI (events/hour)	13.1 ± 11.2 (73) 14.0 [0.0, 62.9] 2.8, 19.8	12.7 ± 11.6 (78) 9.9 [0.0, 55.2] 3.7, 19.2	0.711	12.9 ± 11.4 (151) 11.6 [0.0, 62.9] 3.5, 19.8

Mean ± SD (n)/median [min, max]/Q1,Q3 for continuous variables.
[1] Nominal 2-sided p-value from Kruskal-Wallis test.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the pooled ITT cohort of 151 patients available for the 12 month evaluation. The key safety outcomes for this study are presented below in Table 8. Adverse effects are reported in Tables 9 to 10.

Adverse effects that occurred in the PMA clinical study:

There were no unanticipated adverse device effects (UADEs). There were no deaths related to the implant procedure, the **rem**edē System, or the delivered therapy.

The percentage of pooled subjects (Treatment and Control) in the ITT population free from related serious adverse events associated with the implant procedure, the **rem**edē System, or the delivered therapy through the 12-month visit was 91% (138/151) (95% exact CI [86%, 95%]). No statistical hypothesis testing was performed on this endpoint (Table 8).

Table 8 Summary of Freedom from Related SAEs through 12-Month Visit (ITT)

Variable	Pooled[1] (N=151)
Freedom from related SAEs	91% (138) (86%, 95%)
[1] Percent (n) and 95% exact confidence interval.	

Thirteen (13) subjects (9%) each reported a single implant procedure, **rem**edē System, and/or delivered therapy related SAE. Table 9 displays the number of each type of event reported, along with the number and percentage of subjects who experienced the event. Interventions for SAEs included antibiotics, hospitalization, device reprogramming, surgical revision and/or explantation.

Table 9 Summary of Serious Adverse Events by Relation to Implant Procedure, remedē System, or Delivered Therapy through 12 Months

Pooled (N=151)								
	Implant, System and/or Therapy Related[1,2]		Implant Procedure Related		System Related		Delivered Therapy Related	
Event	n Events	% (n) Subject	n Events	% (n) Subject	n Event	% (n) Subject	n Events	% (n) Subject
Any Event	13	9% (13)	9	6% (9)	6	4% (6)	2	1% (2)
Impending Pocket Erosion	2	1% (2)	1	1% (1)	1	1% (1)	0	0% (0)
Implant Site Infection	2	1% (2)	2	1% (2)	0	0% (0)	0	0% (0)
Lead Dislodgement	2	1% (2)	2	1% (2)	2	1% (2)	0	0% (0)
Concomitant Device Interaction	1	1% (1)	0	0% (0)	1	1% (1)	1	1% (1)
Elevated Transaminase	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Extra-Respiratory Stimulation	1	1% (1)	0	0% (0)	0	0% (0)	1	1% (1)
Implant Site Hematoma	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Lead Component Failure	1	1% (1)	0	0% (0)	1	1% (1)	0	0% (0)
Lead Displacement	1	1% (1)	1	1% (1)	1	1% (1)	0	0% (0)
Non-Cardiac Chest Pain	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)

[1]Relationship defined as probably or definitely related.
[2]Events and subjects with events may be counted as implant procedure, system and therapy related so may not add up to the combined events or subjects.

Forty-eight percent (48%) of subjects experienced a non-serious event related to the implant procedure, the **rem**edē System and/or delivered therapy. Table 10 displays the number of each type of event reported, the number and percentage of subjects who experienced the events, and the relationship of the event to the implant procedure, the **rem**edē System or delivered therapy.

Table 10 Summary of Related non-Serious Adverse Events and Observations through 12 Months

Pooled (N=151)								
	Implant, System and/or Therapy Related[1,2]		Implant Procedure Related		System Related		Delivered Therapy Related	
Event	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects	n Events	% (n) Subjects
Any Event	105	48% (73)	30	17% (25)	11	7% (11)	67	35% (53)
Diaphragmatic Stimulation	48	25% (38)	0	0% (0)	1	1% (1)	48	25% (38)
Extra-Respiratory Stimulation	15	9% (14)	0	0% (0)	0	0% (0)	15	9% (14)
Implant Site Pain	7	5% (7)	7	5% (7)	0	0% (0)	0	0% (0)
Implant Site Hematoma	5	3% (4)	5	3% (4)	0	0% (0)	0	0% (0)
Implant Site Bruising	4	3% (4)	4	3% (4)	0	0% (0)	0	0% (0)
Elevated Lead Impedance	3	2% (3)	1	1% (1)	3	2% (3)	0	0% (0)
Elevated Thresholds	2	1% (2)	0	0% (0)	2	1% (2)	0	0% (0)
Implant Site Inflammation	2	1% (2)	2	1% (2)	0	0% (0)	0	0% (0)
Insomia	2	1% (2)	0	0% (0)	0	0% (0)	2	1% (2)
Programming Error	2	1% (2)	0	0% (0)	1	1% (1)	1	1% (1)
Venous Thrombosis	2	1% (2)	0	0% (0)	2	1% (2)	0	0% (0)
Back Pain	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Concomitant Device Interaction	1	1% (1)	0	0% (0)	0	0% (0)	1	1% (1)
Diarrhea	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Dissection of Subclavian Vein	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Hypoxia	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)

Implant Site Erythema	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Implant Site Infection	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Implant Site Swelling	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Inadequate Lead Position	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Lead Dislodgement	1	1% (1)	1	1% (1)	1	1% (1)	0	0% (0)
Lead Displacement	1	1% (1)	0	0% (0)	1	1% (1)	0	0% (0)
Suture Irritation	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)
Urticaria	1	1% (1)	1	1% (1)	0	0% (0)	0	0% (0)

[1]Relationship defined as probably or definitely related.
[2]Events and subjects with events may be counted as implant procedure, system and therapy related so may not add up to the combined events or subjects.

The implant success rate was high (97%). The reasons for unsuccessful implant attempts in five (5) subjects who were unable to receive the device were due to inability to access the target vein, inability to find suitable electrode placement or inability to capture nerve within acceptable current values. Serious implant procedure related complications, including lead dislodgements, were low and comparable to those of implantable transvenous systems for other indications. Most of the adverse events related to delivered therapy were resolved with reprogramming of treatment parameters of the **rem**edē System.

Explants of the **rem**edē System occurred in 5.3% (8/151) of subjects. Explants occurred for the following reasons:

- Two (2) subjects had devices explanted due to implant site infection of the remedē System.
- One (1) subject had device explanted due to ICD pocket infection (ICD and remedē System shared a common venous entry point requiring explant of both systems).
- One (1) subject had device explanted due to lead component failure.
- One (1) subject had device explanted due to failed stimulation lead modification procedure.
- One (1) subject had the device explanted due to device battery depletion
- Two (2) subjects chose to have an elective explant (one due to intervening medical condition (depression) and one withdrew consent and requested system explant).

Although the sample size was small, the Kaplan-Meier curves showing the time to death for both the Treatment and Control groups showed no evidence of increased risk of death.

2. Effectiveness Results

The analysis of effectiveness was based on 141 subjects in the Modified ITT Primary Effectiveness Analysis Population (68 Treatment and 73 Control) at the 6-month time point. Key effectiveness outcomes are presented in Tables 11 through 14.

The primary effectiveness endpoint was met with a statistically significant higher percentage of subjects in the Treatment group achieving a 50% or greater reduction in AHI from baseline to 6 months post-therapy initiation than the Control group ($p<0.0001$). The Treatment group had 51% (35/68) success compared to Control with 11% (8/73), resulting in a difference of 41% with 95% confidence interval for the difference of (25%, 54%) (Table 11). This difference is considered clinically meaningful.

Table 11 Summary of Primary Effectiveness Endpoint at 6 Months (modified ITT)

Variable	Treatment[1]	Control	Difference	P-value[2]
Proportion of subjects with AHI reduced ≥50%	51% (35/68) (39%, 64%)	11% (8/73) (5%, 20%)	41% (25%, 54%)	<0.0001

Percent (n/N) and 95% Exact Confidence Interval (Wilson method).

[1] Includes seven (7) subjects imputed as not achieving ≥50% reduction in AHI.

[2] P-value from 1-sided Fisher's Exact Test.

All of the hierarchically tested secondary endpoints had statistically significant differences between groups that favored the Treatment group in the per protocol population, shown in Table 12 below as mean change ± SD for continuous variables. Beyond the improvements in respiratory and sleep metrics, improvements in the patient-centered quality of life and sleepiness hierarchically tested secondary endpoints were demonstrated. In the Patient Global Assessment, Treatment group subjects reported improved quality of life as evidenced by 60% of subjects recording a "moderate" or "marked" improvement. Subjects were less sleepy as evidenced by the magnitude of the difference in improvement in the Epworth Sleepiness Scale between Treatment and Control groups.

Table 12 Secondary Hierarchically Tested Endpoints Change from Baseline at 6 Months (Per Protocol)

Endpoint	Treatment (N=58)	Control (N=73)	Between Group Difference	1-Sided P-value
Central Apnea Index (events/hour)	-25.7 ±18.0	-2.9 ± 17.7	-22.8 ± 17.8	<0.0001†
Apnea-hypopnea Index (events/hour)	-23.9 + 18. 6	1.1 ± 17.6	-25.0 ± 18.1	<0.0001‡
Arousal Index (events/hour)	-20.2 ± 18.9	-5.0 ± 18.1	-15.2 ± 18.5	<0.0001‡
% of REM Sleep (%)	1.8 ± 8.2	-0.6 ± 7.8	2.4 ± 7.9	0.0244†
Patient Global Assessment (Proportion of subjects with "moderate" or "marked" improvement)	60% (35/58)	6% (4/72)	55%	<0.0001Δ
Oxygen Desaturation ≥4% Index (events/hour)	-19.1 ± 18.4	3.6 ± 17.3	-22.7 ± 17.8	<0.0001‡
Epworth Sleepiness Scale (points)	-3.6 ± 5.6	0.1 ± 4.5	-3.7 ± 5.0	<0.0001†

Mean ± SD for continuous variables and percent (n/N) for categorical variables.

† From Mann-Whitney test for difference in change from Baseline between groups.

‡ From t-test for difference in change from Baseline between groups.

Δ From Fisher's Exact Test.

CAI, AHI, ArI, % REM Sleep, ODI, and ESS all show sustained improvement at 18 months.

3. Subgroup and Additional Analyses

An effectiveness exploratory endpoint that assessed the proportion of Treatment subjects who achieved a ≥50% reduction in AHI in the per protocol group at 6 and 12 months (Table 13), demonstrating durability of effect beyond 6 months. Preliminary results using available 18-month data show continued durability of effect. No statistical testing was performed for this endpoint.

Table 13 Summary of AHI Reduction ≥50% in the Treatment Group (Per Protocol)

Proportion of Subjects Achieving ≥50% reduction in AHI	
Visit	**Treatment**
6-Month	60% (35/58) (47%, 72%)
12-Month	67% (36/54) (53%, 78%)
18-Month	64% (21/33) (47%, 78%)
Percent (n/N) and 95% Wilson Score Confidence Interval.	

As pre-specified, Control subjects had **rem**edē System therapy turned on after all 6-month assessments were performed. The effectiveness of **rem**edē System therapy was evaluated in this group looking at the proportion of subjects in the Control group achieving ≥50% reduction in AHI after receiving 6 months of **active** therapy. The results were consistent with that of the Treatment group at 6 months with 55% (36/65) achieving a ≥50% reduction in AHI (Table 14).

Table 14 Summary of AHI Reduction ≥50% in the Control Group after 6 Months of Active Therapy (Per Protocol)

Proportion of subjects achieving ≥50% reduction in AHI			
Months of active therapy	**Treatment**	**Control**	**Pooled**
6 Months	60% (35/58) (47%, 72%)	55% (36/65) (43%, 67%)	58% (71/123) (49%, 66%)
Percent (n/N) and 95% Wilson Score Confidence Interval.			

Site Pooling:
The poolability of data across investigational sites and geography (US versus EU) was assessed by Zelen's test for the homogeneity of odds ratio across these strata and Cochran Mantel-Haenszel statistics for testing a common odds ratio after adjusting for strata.

Investigational sites enrolling nine (9) or fewer subjects were combined into pooled sites based on country for the site-based analysis. Investigational sites with more than nine (9) subjects were analyzed individually. The Cochran-Mantel-Haenszel test ($p<0.001$) indicated randomized group remains a significant predictor of ≥50% reduction in AHI when controlling for pooled investigational

site in the ITT primary effectiveness endpoint population. The Zelen's test p=0.836 indicated no statistically significant departure from homogeneity of odds ratio for subjects achieving ≥50% AHI reduction among pooled investigational sites. This demonstrated pooling sites for the primary effectiveness analysis is acceptable.

The responder rates for the primary endpoint were further analyzed by geography (US versus EU). The Cochran-Mantel-Haenszel test (p<0.001) indicates randomization assignment remained a significant predictor of ≥50% reduction in AHI when controlling for geography. The Zelen's test (p=0.181) indicated no statistically significant departure from homogeneity of odds ratio for ≥50% reduction in AHI between US and EU. Thus, there is no statistical evidence against pooling of the geographies for the primary effectiveness endpoint.

Subgroup analyses:
A gender subgroup analysis for the primary effectiveness endpoint was performed in the modified ITT population. For males, there was a difference in the proportion of subjects achieving a ≥50% reduction in AHI between Treatment and Control groups (52% [31/60] vs. 9% [6/68], nominal p<0.001). While the observed proportion of subjects achieving a ≥50% reduction in AHI for females was higher in the Treatment than in the Control group, the same magnitude of difference was not observed (50% [4/8] vs. 40% [2/5], nominal p = 0.587). The study was not adequately powered for evaluation in women.

In the subset of white subjects in the modified ITT population, the proportions of subjects achieving ≥50 reduction in AHI were 52% (34/66) and 12% (8/69) for Treatment and Control, respectively. Similarly, the proportions of subjects achieving ≥50 reduction in AHI in the Black or African American subset were 50% (1/2) for Treatment and 0% (0/3) for Control. The study was not adequately powered for evalutation in African American subset population.

A subset of baseline factors (demographics, characteristics, medical history, and implant metrics) were assessed for association with an outcome of AHI reduction ≥50% using a logistic regression model. Eight (8) identified factors were included in a backward selection multivariate logistic regression analysis to determine a final model containing the most influential baseline factors. Randomized group remained significant (p<0.001), with an odds ratio of 11.81. Baseline OAI and baseline neck size also remained in the model after accounting for the other variables, but both had p>0.05 (odds ratios of 0.79 and 0.9 respectively). This suggested that subjects who have a higher baseline OAI and larger neck size may be less likely to achieve ≥50% reduction in AHI; however, no obvious cut-points for higher baseline OAI and neck size were indicative of a subject's response to **rem**edē System therapy.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 172 investigators of which none were full-time or part-time employees of the sponsor and one (1) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Anesthesiology Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint of the **rem**edē System Pivotal Trial was met: the proportion of the subjects who achieved a clinically meaningful (≥50%) reduction in AHI in the Treatment group was significantly greater than the Control group with a between-group difference of 41% ($p<0.0001$). In the modified ITT population, 51% of the Treatment subjects achieved a ≥50% reduction in AHI versus 11% in the Control group. The benefits experienced by the Treatment group continued over time with similar effects through 12 months and through the available 18-month data, and were also confirmed by the results of the Control group after 6 months of active

therapy. In addition, all of the hierarchically tested secondary endpoints (CAI, AHI, ODI4, REM sleep, PGA, ArI, and ESS) were met. Reductions in CAI and AHI demonstrate that the **rem**edē System therapy reduces apnea. The results of all hierarchically tested secondary sleep endpoints support the primary effectiveness endpoint outcome.

Beyond the improvements in respiratory and sleep metrics, improvements in the hierarchically tested secondary patient-centered endpoints in quality of life metrics and sleepiness were demonstrated. In the PGA, Treatment group subjects reported improved quality of life as evidenced by 76% of subjects reporting improvement and 60% recording a "moderate" or "marked" improvement. Subjects were less sleepy, as evidenced by the magnitude of the difference in improvement in the ESS between Treatment and Control groups. Both the Treatment group as well as the Control group had a positive experience with **rem**edē System therapy with 94% and 97% respectively, stating that they would have this medical device implanted again.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above. The primary safety endpoint of freedom from related serious adverse events associated with the implant procedure, the **rem**edē System, or the delivered therapy through the 12-month visit, was high (91%), and comparable with implanted systems for other applications [1, 2, 3]. There were no UADEs and no deaths related to the implant procedure, the **rem**edē System, or the delivered therapy. The implant success rate was high (97%). Serious implant procedure related complications, including lead dislodgements, were low and comparable to those of other implantable transvenous systems [3, 4]. Due to the programming flexibility of the **rem**edē System, most of the AEs related to delivered therapy were resolved with non-invasive reprogramming. Unrelated SAEs were observed at rates expected in subjects with similar co-morbidities [5, 6, 7]. Recognizing that the sample size was small, the Kaplan-Meier curves showing the time to death for both the Treatment and Control groups showed no evidence of increased risk of death.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. Central sleep apnea is a chronic disease that is associated with hypoxia and sympathetic surges which can lead to cardiovascular complications and is associated with poor outcomes. There are currently no effective alternative treatments available. The **rem**edē System is an implantable system developed to treat CSA by transvenously stimulating the phrenic nerve to restore a normal breathing pattern. This sponsor studied 151 subjects (73 treatment and 78 control) with CAI at least 50% of all apneas, with at least 30 central apnea events during the qualifying PSG.

This was a well-conducted randomized sham controlled study of the **rem**edē System. The study has met the primary effectiveness endpoint on both the ITT population (under multiple imputation method) and modified ITT population. All of the primary and secondary endpoints have been found statistically and clinically significant. Results showed a reduction from baseline in AHI of ≥50% in 51% of patients. The secondary effectiveness endpoints were also met. The effects appear to persist up to 18 months in the subjects that have been followed that long. An improvement in these parameters can potentially impact the long term care of these patients.

Risks of the procedure are similar to other implantable devices. Adverse events of subclavian vein dissection and thrombotic disease also occurred that can potentially be serious and patients will need to be monitored for these events. There was no device related mortality or unexpected adverse events.

Additionally, the patient preference was positive for use of this device.

Patient perspectives considered during the review included:

- Epworth sleep scale
- Patient Global Assessment (PGA)

This group of patients has limited options for treatment of their CSA. This device provides a therapy option for this group of patients and the probable benefits outweigh the probable risks.

In conclusion, given the available information above, the data support that for treatment of moderate to severe central sleep apnea in adults the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The primary effectiveness endpoint of the **rem**edē System Pivotal Trial was met demonstrating there was a clinically meaningful reduction in AHI in the treatment group as compared to the control group. Additionally, all hierarchically tested secondary endpoints were met. There were no device related mortalities or unexpected adverse events and risks were similar to other similar implantable medical devices. The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on October 6, 2017. The final conditions of approval cited in the approval order are described below.

The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The remedē System Post Approval Study will be an extended follow-up study of patients enrolled in the premarket trial. It will be a prospective, single arm cohort study to evaluate the long-term safety, long-term effectiveness, and survival rate in subjects implanted with the remedē System under the premarket study. The subjects will be followed 5-years post procedure. All adverse events will be summarized by seriousness, severity, relatedness, and temporal relationship to the procedure and will be analyzed in a descriptive fashion. Safety endpoints will be collected to evaluate survival rate in comparison to historical controls, device-related adverse events and therapy-related adverse events. Effectiveness endpoints will be collected to evaluate: AHI, CAI, OAI, and ESS. Interim analyses will be conducted at three and five years.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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