SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable Upper Airway Stimulation for Obstructive Sleep Apnea (OSA)

Device Trade Name: Inspire® Upper Airway Stimulation (UAS)

Device Procode: MNQ

Applicant's Name and Address: Inspire Medical Systems Inc.
9700 63rd Avenue North, Suite 200
Maple Grove, MN 55369

Date of Panel Recommendation: February 20, 2014

Premarket Approval Application (PMA) Number P130008

Date of FDA Notice of Approval: April 30, 2014

Priority Review: No

II. INDICATIONS FOR USE

Inspire® Upper Airway Stimulation (UAS) is used to treat a subset of patients with moderate to severe Obstructive Sleep Apnea (OSA) (Apnea-hypopnea Index [AHI] of greater or equal to 20 and less than or equal to 65). Inspire® UAS is used in adult patients 22 years of age and older who have been confirmed to fail or cannot tolerate Positive Airway Pressure (PAP) treatments (such as continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BPAP] machines) and who do not have a complete concentric collapse at the soft palate level.

PAP failure is defined as an inability to eliminate OSA (AHI of greater than 20 despite PAP usage) and PAP intolerance is defined as:

(1) Inability to use PAP (greater than 5 nights per week of usage; usage defined as greater than 4 hours of use per night), or

(2) Unwillingness to use PAP (for example, a patient returns the PAP system after attempting to use it).

III. CONTRAINDICATIONS

- Central + mixed apneas > 25% of the total apnea–hypopnea index (AHI)

- Any anatomical finding that would compromise the performance of upper airway stimulation, such as the presence of complete concentric collapse of the soft palate
- Any condition or procedure that has compromised neurological control of the upper airway
- Patients who are unable or do not have the necessary assistance to operate the sleep remote
- Patients who are pregnant or plan to become pregnant
- Patients who will require magnetic resonance imaging (MRI)
- Patients with an implantable device that may be susceptible to unintended interaction with the Inspire® system. Consult the device manufacturer to assess the possibility of interaction.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Inspire® UAS labeling.

V. DEVICE DESCRIPTION

The Inspire® UAS system consists of implanted components including the implantable pulse generator (IPG), stimulation lead and sensing lead, and external components such as the physician programmer and the patient programmer. See Figure 1 below depicting the implantable components and their relative positioning. The IPG detects the patient's respiratory effort and maintains airway patency with mild stimulation of the hypoglossal nerve during inspiration. The physician is able to configure the stimulation settings using the external physician programmer. The patient sleep remote allows the patient to turn therapy on before they go to sleep and to turn therapy off when they wake up. It also provides the ability to pause therapy and adjust stimulation amplitude within physician-defined limits that are within the therapeutic range of treatment.

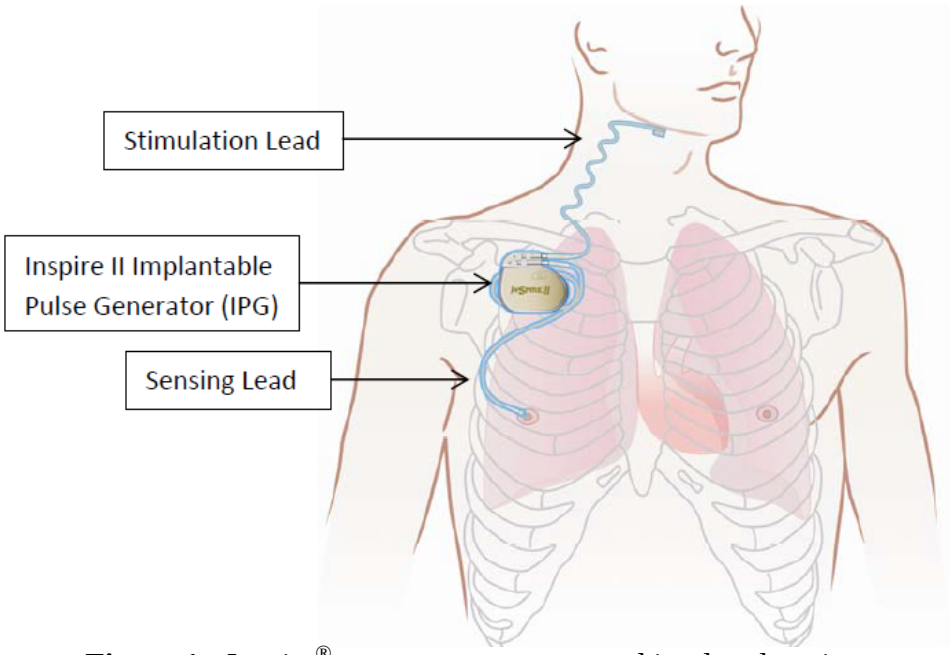

Figure 1: Inspire® system components and implant location

Table 1 provides a description of the implanted and external components of the Inspire® UAS system.

Table 1: Inspire® UAS System Components

Component	Description
Implanted Components:	
Model 3024 Implantable Pulse Generator (IPG)	The IPG contains electronics and a battery sealed inside a titanium case. The surgeon implants the IPG subcutaneously, below the clavicle in the upper chest, and connects to the stimulation lead and sensing lead. The algorithm synchronizes stimulation of the hypoglossal nerve to deliver stimulation during the late expiratory and through the inspiratory phase of respiration.
Model 4063 Stimulation Lead	The stimulation lead includes a cuff electrode with a guarded bipolar configuration. The surgeon positions the cuff around a patient's hypoglossal nerve and connects the connector tip end of the lead to the IPG. The cuff electrodes apply electrical current that stimulates the hypoglossal nerve, which causes the base of the tongue to protrude forward in order to open the upper airway.
Model 4323 Sensing Lead	The sensing lead is placed in the intercostal space and contains a piezoelectric differential pressure sensor for detecting respiratory signals.

Component	Description
External Components:	
Model 3032 Patient Programmer (Patient Sleep Remote)	The patient sleep remote is a hand held device. It is placed on the skin over the implant and provides a non-invasive means for patient to activate the IPG, to adjust the stimulation parameters (within the physician prescribed limits), and to check battery status.
Model 2740 Physician Programmer	The physician programmer consists of a tablet computer and a telemetry cable. The telemetry head communicates with the IPG through the skin via short-range radio-frequency (RF) telemetry. Telemetry communication allows the physician to noninvasively interrogate and configure the IPG settings. The physician programmer has the capability to monitor respiratory waveforms, configure stimulation modes, adjust stimulation parameter values, and store waveforms and settings.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of moderate to severe obstructive sleep apnea for those who have failed or are intolerant of PAP. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

The treatment alternatives for this patient population include oral appliances and surgical procedures to enlarge the airway. A patient should thoroughly discuss the risks and benefits of treatment alternatives with his/her physician in order to select the treatment option which best meets their needs.

VII. MARKETING HISTORY

The Inspire® therapy received CE Mark approval on October 20, 2010 and has been commercially available in the European Union since that time.

Inspire® therapy has not been withdrawn from the market in any country. The device has not been marketed in the United States.

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.

- Damage to blood vessels in the vicinity of implant
- Excessive bleeding

- Nerve trauma or damage
- Allergic and/or rejection response to the implanted materials
- Infection
- Local irritation, seroma, hematoma, erosion, or swelling
- Persistent pain, numbness, or inflammation at the implant site
- Discomfort from the stimulation
- Tongue movement restrictions, irritation resulting from tongue abrasions on preexisting sharp or broken teeth
- Tongue soreness or weakness
- Problems with swallowing or speaking
- Undesirable change in stimulation over time, possibly related to tissue changes around the electrode(s), shifts in electrode position, loose electrical connections, or lead fractures
- Fibrosis to the extent that it makes it difficult to remove the system without damaging surrounding structures
- Dry mouth
- Other acute symptoms (i.e., headaches, coughing, choking, dysphasia, and speech related events)
- Insomnia

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Model 4323 and Model 4063 Leads

Table 2 summarizes the testing conducted for the implantable stimulation and sensing leads, including information about the test, purpose, acceptance criteria, and results.

Samples were pre-conditioned prior to performance testing. Pre-conditioning procedures included ETO sterilization, thermal shock, environmental conditioning, shipping simulation (free fall and vibration), and shelf life (accelerated aging).

- Thermal Shock: The lead shall survive a thermal shock of 5 cycles, from -10°C to 55°C with transfer time of 1°C per minute.
- Environmental conditioning: Temperature and humidity cycling per ASTM D4332
- Shipping simulation: Package free fall (Mechanical shock), loose load, and random vibrations (Mechanical vibration).
- Accelerated aging (55°C +/-2 @ <20%RH for 75 days, per ASTM F1980)

Following pre-conditioning, leads were tested for tensile strength, fatigue testing, and electrical continuity as outlined below.

Table 2: Implantable Leads Bench Testing Summary

Test	Purpose	Acceptance Criteria	Results
Model 4063 Stimulation Lead:			
Tensile Load Testing Following 10 day saline soak (0.9% saline), leads must remain electrically and mechanically functionally intact following tensile testing.	Test the tensile strength of lead to anchor	Withstand a pull test (lead to anchor) of 0.5 lbf	PASS
	Test the tensile strength of conductor to connector pin	Withstand a pull test of 2.5 N (0.56 lbf)	PASS
	Test the tensile strength of conductors & polyurethane tubing to lead connector	Withstand a pull test of 5.0 N (1.12 lbf)	PASS
	Test the tensile strength of conductor to electrode tab	Withstand a pull test of 2.5 N (0.56 lbf)	PASS
	Test the tensile strength of conductor & polyurethane tubing to cuff strength	Withstand a pull test of 5.0 N (1.12 lbf)	PASS
	Test the tensile strength of the cuff flap	Withstand a pull tests of 2.5 N (0.56 lbf)	PASS
Fatigue Testing Leads must remain electrically and mechanically functionally intact following fatigue testing.	Test the ability of the lead body to withstand cyclical fatigue.	Withstand 400,000 cycles when flexed +/- 60 degrees at central lead body bend radius of 4.76 mm	PASS
	Test the ability of the distal cuff to withstand cyclical fatigue.	Withstand 80,000 cycles when flexed +/- 60 degrees at central lead body bend radius of 4.76 mm.	PASS
	Test the ability of the proximal connector to withstand cyclical fatigue.	Withstand a vertical load of 100 g oscillated at 45 degree angle for 82,000 cycles	PASS
	Test the ability of the lead body sigmoid section to withstand cyclical fatigue when straightened.	Withstand a displacement of 1 cm over 80,000 cycles. Extension cycling shall take place at a rate of 2 cycles per second	PASS
	Test the ability of the cuff to withstand crush cycles. The cuff surrounds a silicone tube and is crushed between a reciprocating plunger and plate. The plunger displacement shall be 1 mm or approximately 33% of the cuff inner	Withstand 80,000 flex (crush) cycles	PASS

Test	Purpose	Acceptance Criteria	Results
	diameter.		
Electrical Continuity	Test the resistance of the conductors	DC resistance of the lead should be no greater than 70 Ω.	PASS
	Test intermittence of the lead. The test is performed while manually flexing the lead at the proximal and distal junctions.	Intermittence of the complete lead including connector shall be less than 50 microseconds.	PASS
	Test dielectric withstand voltage (hipot)	The insulation shall withstand a dielectric strength in which the peak voltage experienced is a minimum of 2 times the maximum stimulation output voltage (2 times 10.5 V)	PASS
	Test insulation resistance of the lead body	The minimum insulation resistance of the lead body shall exceed 50,000 Ω	PASS
Model 4323 Respiration Sensing Lead:			
Tensile Load Testing Following 10 day saline soak (0.9% saline), leads must remain electrically and mechanically functionally intact following tensile testing.	Test the tensile strength of the suture sleeve (anchor)	Withstand a pull test (lead to anchor) of 5 N (1.12 lbf)	PASS
	Test the tensile strength of the conductor to connector pin	Withstand 2.5 N (0.56 lbf)	PASS
	Test the tensile strength of the conductor to connector ring	Withstand 2.5 N (0.56 lbf)	PASS
	Test the tensile strength of the conductors and tubing to lead connector	Withstand 5.0 N (1.12 lbf)	PASS
	Test the tensile strength of the conductor to sensor pin	Withstand 2.5 N (0.56 lbf)	PASS
	Test the tensile strength of the conductor to sensor adapter barrel	Withstand 2.5 N (0.56 lbf)	PASS
	Test the tensile strength of the conductors and tubing to sensor	Withstand 5.0 N (1.12 lbf)	PASS
	Test the tensile strength of the nose cone to sensor	Withstand 2.5 N (0.56 lbf)	PASS

Test	Purpose	Acceptance Criteria	Results
	Test the lead body flexibility proximal to sensor	Maximum force of 0.20 N in order to hold a 90 degree bend over a 1 cm diameter cylinder, at a distance of 2 cm from the mid-point of the radius.	PASS
Fatigue Testing Leads must remain electrically and mechanically functionally intact following fatigue testing.	Test the ability of the sensor to withstand cyclical fatigue	A vertical load of 100 g will be applied and the fixture oscillated at 45 degree angle for 82,000 cycles	PASS
	Test the ability of the connector to withstand cyclical fatigue	A vertical load of 100 g will be applied and the fixture oscillated at 45 degree angle for 82,000 cycles	PASS
Electrical Continuity	Test dielectric withstand voltage (hipot)	The insulation shall withstand a dielectric strength test in which the peak voltage is not less than twice the peak voltage experienced with a maximum current leakage of 1 μA.	PASS
	Test the resistance of the conductors	DC resistance of the lead should be no greater than 80 Ω for the outer conductor and 40 Ω for the inner conductor (120 Ω total)	PASS
	Test intermittence of the lead. The test is performed while manually flexing the lead at the proximal and distal junctions.	Intermittence of the complete lead including connector shall be less than 50 microseconds.	PASS
	Test insulation resistance of the lead body	Electrical leakage between the inner conductor coil and the outer coil (sensor) shall be 300 kΩ minimum impedance at 100 Hz and electrical leakage between the inner coil (sensor feed through) and indifferent electrode shall be 50 kΩ	PASS

Test	Purpose	Acceptance Criteria	Results
		minimum impedance at 100 Hz.	
	Test the response to defibrillation	The pressure transducer shall not be damaged when subjected to defibrillation pulse delivered directly over the pressure transducer. The pressure transducer's output shall be stable within 10 minutes.	PASS

B. <u>Model 3024 Implantable Pulse Generator (IPG)</u>

Table 3 summarizes the testing conducted for the IPG, including information about the test, purpose, acceptance criteria, and results.

Table 3: Implantable Pulse Generator (IPG) & System Level Testing

Test	Purpose	Acceptance Criteria	Results
IPG & System Functional Testing	Verify accuracy of device output specifications for amplitude	Function correctly and amplitude accuracy (+/- 10%) was acceptable at all tested amplitudes (0.1 V, 0.2 V, 0.5 V, 5 V, and 10.5 V) and load impedances (200, 510, 2000 Ω).	PASS
	Verify accuracy of device output specifications for rate	All measured rates were within 1% and the measured impedances were within 11%, which meets specifications.	PASS
	Verify accuracy of device output specifications for pulse width	The measured pulse widths were within 1% which meets specifications.	PASS
	Test that the IPGs have proper functionality in upper airway stimulation mode at the minimum and maximum pressure inputs	Verify the IPG's synchronized stimulation to the input pressure waveform and the measured peak pressure corresponded to the input pressure. The measured accuracy of the pressure was 3-20%.	PASS

Test	Purpose	Acceptance Criteria	Results
	Test that the IPG diagnostic model charts the sine wave signal and the onset and offset markers indicate where stimulation is occurring.	Verify all IPGs properly entered diagnostic mode and properly charted the sensor signal along with the onset and offset markers.	PASS
	Use physician programmers to measure IPG battery voltage (at 3.7 V) and load impedance (510, 1000, 1500 Ω) based on the manufacturing programmed calibration.	Verify all IPGs successfully pass the manufacturing console battery test (+/- 10%) and qualification tests. Verify all lead impedances (510, 1000, 1500 Ω) stay within the +/- 30% accuracy.	PASS
	Test that the physician programmer nominal command successfully downlinks with the IPG.	Verify all IPGs were successfully programmed to the nominal parameters using the nominal command.	PASS
	Test IPG programming and output in saline tank tests	Verify no erratic behavior (overshoot in voltage, parameter changes, polarity changes, intermittence) of the IPG-lead assembly output while in saline solution. Verify proper telemetry performance (telemetry found to be reliable within 2 inches). Verify lead impedance measurements met the required specification of +/- 30% for voltages > 1 volt	PASS

C. Model 2740 Physician Programmer and Model 3032 Patient Sleep Remote

Table 4 summarizes the testing conducted for the external programmers, including information about the test, purpose, acceptance criteria, and results.

Table 4: Physician and Patient Programmer Testing

Test	Purpose	Acceptance Criteria	Results
Model 2740:			
Electrical Safety Testing	Verify the Model 2740 meets international	Meets the requirements of IEC/EN 60601-	PASS

Test	Purpose	Acceptance Criteria	Results
	standards for electrical safety	1:1990+A1:1993+A2:1995 Medical electrical equipment Part 1: General requirements for safety	
Electromagnetic compatibility (EMC) Testing	Verify the Model 2740 meets international standards for electromagnetic compatibility	Meets the requirements of IEC/EN 60601-1-2:2007 Medical electrical equipment. General requirements for basic safety and essential performance	PASS
Radio-Frequency Wireless Technology Followed FDA Guidance for Radio-Frequency Wireless Technology in Medical Devices. In addition, the following tests were conducted.	Verify the Model 2740 meets electromagnetic compatibility for wideband data communication.	Meets the requirements of EN 301 489-17 V1.2.1 (2002-08) and EN 301 489-31 V1.1.1 (2005).	PASS
	Verify the Model 2740 meets electromagnetic compatibility requirements of Industrial, Scientific and Medical (ISM) Radio-Frequency Equipment.	Meets the requirements of EN 55011:2007+A2:2007 Limits and Methods of Measurement of Radio Disturbance	PASS
	Verify the Model 2740 meets the requirements of US FCC 47 CFR Part 15 Subpart B	Meets the requirements of the FCC regulations	PASS
Mechanical & Environmental Testing	Validation for the Model 2740 Physician Programmer included climate conditioning, free fall shock test, vehicle stacking, loose load vibration, low pressure high altitude testing, random vibration. Followed by visual inspection and functional performance	Meets the requirements of IEC 60601-1 3rd edition.	PASS
Software Verification & Validation Testing	The Model 2740 Physician programmer is the only component containing software. Verification and	Verify the software meets the system requirements and functions as intended.	PASS

Test	Purpose	Acceptance Criteria	Results
	validation testing was conducted on the Model 2740 Programmer's software to confirm that it met user needs and performed as intended. This software testing was done in accordance with the FDA Guidance titled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." In addition, the software testing demonstrates compliance to the ANSI/AAMI/IEC 62304:2006 Medical device software - Software life cycle processes industry standard.		
Model 3032:			
Electrical Safety Testing	Verify the Model 3032 meets international standards for electrical safety	Meets the requirements of IEC/EN 60601-1:1990+A1:1993+A2:1995 Medical electrical equipment Part 1: General requirements for safety	PASS
Electromagnetic compatibility (EMC) Testing	Verify the Model 2740 meets international standards for electromagnetic compatibility	Meets the requirements of IEC/EN 60601-1-2:2007 Medical electrical equipment. General requirements for basic safety and essential performance	PASS
Radio-Frequency Wireless Technology Followed FDA Guidance for Radio-Frequency	Verify the Model 3032 meets electromagnetic compatibility for radio equipment in the frequency range 9 kHz to 25 MHz and inductive loop systems	Meets the requirements of EN 300 330-2 V1.1.1:2001 Sub-clauses 7.2, 7.3, 7.4	PASS

Test	Purpose	Acceptance Criteria	Results
Wireless Technology in Medical Devices. In addition, the following tests were conducted.	in the frequency range 9 kHz to 30 MHz.		
	Verify the Model 3032 meets electromagnetic compatibility for Short-Range Devices (SRD) Operating on Frequencies between 9 KHz and 40 GHz.	Meets the requirements of EN 301 489-3:2002 Electromagnetic Compatibility and Radio Spectrum Matters (ERM); Electromagnetic Compatibility (EMC) Standard for Radio Equipment and Services; Part 3	PASS
	Verify the Model 3032 meets limits of radio disturbance characteristics of Industrial, Scientific and Medical (ISM) Radio-Frequency Equipment.	Meets the requirements of EN 55011:1998 and EN 55022:1998 for conducted emissions, radiated emission, interference power and equivalent radiated emissions	PASS

D. Biocompatibility

Biocompatibility of all patient-contacting components of the Inspire® UAS system was evaluated in accordance with ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. The model 4323 Pressure Sensing Lead and the Model 4063 Stimulation Lead are considered permanent implants in contact with tissue/bone. The biocompatibility of these leads was supported by a combination of available data on the lead materials in the device master files as well as additional biocompatibility testing on the finished sterilized leads and chemical analyses of extractables from these finished leads. The Inspire® UAS system is considered biocompatible for its intended use.

E. Sterility & Shelf Life

The only components of the Inspire® system which are provided sterile are the implantable pulse generator (IPG) and leads. Both the leads and the IPG are sterilized through 100% ethylene oxide (EtO).

Standard/Method: AAMI/ANSI/ISO/EN 11135-1:2007 Sterilization of Health Care Products –Ethylene Oxide – Part I: Requirements for development, validation and routine control of a sterilization process for medical devices.

SAL: 10^{-6}

Residuals: Both the Sensor Leads and the Cuff Leads meet the requirements of ANSI/AAMI/ISO/10993-7:2008(E) for the limit of toxic sterilant residuals. An exhaustive extraction procedure was performed on the leads, and the ethylene oxide levels were < 4mg, the ethylene chlorohydrin levels were < 9mg, and the ethylene glycol levels < 11.2mg.

Packaging: Both lead Models 4063 and 4323 utilize the same packaging - a PETG tray with a Tyvek lid packaged in a fiberboard shelf box. The packaging meets the standards in EN/ISO 11607-1:2006 (2009), "Packaging for Terminally Sterilized Medical Devices Part I: Requirements for Materials, Sterile Barrier Systems, and Packaging Systems."

Shelf life: Accelerated aging testing was conducted per ASTM F1980 to validate a 2-year shelf life of the leads. Following accelerated aging, samples were tested for Bubble Leak (per ASTM F2096-04), Seal Strength (per F88-08a), visual inspection, and functional testing. The device met the requirements of the applicable standards and passed all inspection and functional testing following accelerated aging studies. Therefore, the 2-year shelf life claim was accepted. Real time aging studies are ongoing in order to confirm the shelf life claim based on real time data.

The Model 3024 IPG uses the same case and mechanics as FDA approved Medtronic Model 7425 Itrel® 3 IPG (P840001/S37, approved 8/29/1995) with identical sterilization process, packaging, and manufacturing as this device. The firm provided sterilization certification and documentation, which supports the 100% EtO sterilization of the device. The shelf life of the Model 3024 IPG is 2 years based on the battery shelf life and real time use of the approved IPG which has identical sterilization process, packaging, and manufacturing.

F. Animal Studies

Inspire Medical Systems has performed two (2) canine studies to evaluate the Inspire® UAS system. Results are summarized below.

Table 5: Canine Studies

Study Objectives	Number of Subjects	Duration	Results
Evaluate the performance of the stimulation lead and sensing leads.	4 canine animals; bilateral lead implantation	8-12 weeks	Stimulation thresholds were consistent and stable. Respiratory pressure signals showed consistent respiratory waveform morphology and system testing demonstrated synchronized electrical stimulation.
Evaluate the complete Inspire®	4 canine animals; bilateral lead	12 weeks	The system performed as intended in delivering

Study Objectives	Number of Subjects	Duration	Results
II system performance and safety.	implantation		stimulation synchronous with respiration. The animals tolerated chronic stimulation well and there were no instances where therapy had to be discontinued, reduced in intensity or duration due to discomfort or untoward effects. Chronic implantation of the stimulation and sensing leads resulted in mild to moderate inflammation and fibrosis associated with the foreign body response and typical of chronically implanted devices.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A total of four (4) clinical studies were submitted in support of the application. Inspire conducted three (3) earlier feasibility studies with the Inspire® UAS system as well as a single pivotal study. Inspire conducted the pivotal clinical study in the US and Europe under IDE # G080122, to establish a reasonable assurance of safety and effectiveness of upper airway stimulation with the Inspire® UAS system for the treatment of moderate to severe OSA. Data from this clinical study were the basis for the PMA approval decision. The clinical studies are summarized in Table 6 and further discussed below.

Table 6: Summary of Clinical Studies

Document Number	Title	Study Type	Duration	Sample Size	Conclusion
G950075	Inspire® 1	Feasibility	1998-2001	8	Demonstrated that nightly stimulation in patients with moderate to severe OSA markedly diminished apnea severity without arousing patients from sleep. Technical issues with the first generation Inspire® UAS system design led to product redesign of stimulation lead which was redesigned to improve the

Document Number	Title	Study Type	Duration	Sample Size	Conclusion
					robustness of the electrode and the implant location of the sensing lead was moved between intercostal muscles to minimize surgical risk and to improve performance.
G080122	Inspire® 2/3 Feasibility Group I	Feasibility	2008-2010	22	Demonstrated 2nd generation Inspire® UAS system design was robust. Established viability of pressure sensor placement between intercostal muscles. Identified predictors of therapy success to be AHI < 50, body mass index (BMI) < 32, no concentric collapse on drug induced sleep endoscopy (DISE) which became part of patient selection criteria for future studies/enrollment (Feasibility Group II and Pivotal).
G080122	Inspire® 2/3 Feasibility Group II	Feasibility	2010-2012	12	Validated the narrower selection criteria developed from Feasibility Group I. Data used to support Pivotal Study protocol.
G080122 / S28	STAR Trial	Pivotal	2010-	126	Achieved primary and secondary endpoints to establish reasonable assurance of safety and effectiveness. Achieved at least a 50% responder rate for AHI and oxygen desaturation index (ODI) (co-primary endpoints). Met all secondary endpoints.

Feasibility Studies

The first feasibility study was a chronic study in 8 patients (G950075). It demonstrated that nightly stimulation in patients with moderate to severe obstructive sleep apnea markedly diminished apnea severity without arousing patients from sleep. It also identified the need to improve the durability of the stimulation leads design, and to change the implant location of the sensing lead to avoid cardiac artifact interfering with the pressure signal.

The second feasibility study was a larger global study with 22 patients (G080122 – Group 1). This study validated the current Inspire® system and further demonstrated the effect of Inspire® therapy in reducing the severity of OSA by evaluating the change in AHI and ODI. Patients were initially enrolled using broad selection criteria in order to identify therapy response predictors. Those predictors were a pre-implant AHI of 20 to 50, a BMI of ≤ 32, and the absence of a complete concentric collapse at the level of the soft palate.

A third feasibility study (G080122-Group 2) with 12 patients prospectively validated these therapy predictors, which were then used as patient selection criteria in the pivotal trial. These feasibility studies demonstrated therapeutic potential, facilitated design enhancements, determined objective criteria for identifying the patients most likely to benefit from Inspire® therapy, and supported IDE approval of the STAR pivotal trial.

STAR Pivotal Study

A. <u>Study Design</u>

Patients were treated between November 10, 2010 and October 16, 2013. The database for this PMA reflected data collected through October 16, 2013 and included 126 patients. There were 22 investigational sites.

The STAR trial was a multi-center, prospective trial with a 12-month single arm study and a randomized controlled therapy withdrawal study at 13 months. The primary objective was to evaluate Inspire® UAS therapy and determine if the therapy provides a clinically significant reduction in OSA. The study collected primary and secondary endpoint data during an in-laboratory sleep study 12 months after the device implantation and were compared against the baseline sleep studies. In addition, the study administered quality of life (QoL) questionnaires (Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ)) at baseline and at the 12-month visit to further assess the effectiveness of Inspire® UAS therapy.

Upon completion of the in-laboratory overnight sleep study at the 12-month visit, a randomized controlled therapy withdrawal study was conducted. The first 46 responders, based on the AHI primary endpoint, were randomized 1:1 to either the therapy maintenance group (ON group) or the therapy withdrawal group (OFF group), resulting in 23 patients in each group. The study required a subsequent

polysomnogram (PSG) at month 13 on patients in each group and results were compared between the two (2) groups. Responders randomized to the therapy withdrawal group had the Inspire therapy turned OFF for at least five (5) days leading up to the PSG study. An independent core lab scored all sleep studies. A Registered Polysomnogram **(**PSG) Technician (RPSGT) conducted the scoring and followed standard techniques according to the American Academy of Sleep Medicine (AASM) Manual of Scoring Sleep (2007).

Device Programming and Adjustments

The Inspire® UAS system is programmable in order to optimize a patient's response to therapy. The physician programs the initial device settings in an office setting. Additional adjustments (titrations) are made during an overnight sleep study whereby real time review of the PSG is available to aid in device setting adjustments during the 2 and 6-month visit. The physician can adjust the device stimulation and sensing parameters in response to (1) acute observations during a PSG sleep study, and (2) overall therapy efficacy as indicated by PSG study results. During a PSG study, the physician may also increase the stimulation strength if persistent apneas and hypopneas occur. The study protocol did not allow any adjustments to be made within 30 days of the 12-month PSG or during the 12-month PSG. Similarly, the study did not allow for adjustments to be made during the 13-month PSG or during the randomization period prior to the 13-month PSG.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the STAR Pivotal study was limited to patients who met the following inclusion criteria:

   - Likely suffer from moderate to severe OSA based on history and physical, or have an established diagnosis of OSA (AHI ≥ 20) based on a prior PSG conducted within 12 months of enrollment
   - Have failed or have not tolerated CPAP treatment
   - Age 22 or older

   Patients were not permitted to enroll in the STAR Pivotal study if they met any of the following exclusion criteria:

   - BMI of > 32
   - Surgical resection or radiation therapy for cancer or congenital malformations in the larynx, tongue, or throat (Note that some prior surgeries to remove obstructions related to obstructive sleep apnea were allowed; such as uvulopalatopharyngoplasty (UPPP), tonsillectomy or adenoidectomy)
   - Hypoglossal nerve palsy (obvious limited tongue movement, such as inability to protrude tongue, or unintended lateral deviation of the tongue when protruding)

- Previous surgery on the soft tissue of the upper airway (e.g., uvula, soft palate or tonsils) performed within 12 weeks of scheduled implant
- Obvious fixed upper airway obstructions (tumors, polyps or nasal obstruction)
- Intrinsic neuromuscular disease or other neurologic deficits (e.g., multiple sclerosis, muscular dystrophy, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy, transient ischemic attack or cerebrovascular accident)
- Other severe co-morbid conditions.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations. The key time points are shown below in the tables summarizing safety and effectiveness. After successful pre-implant screening, the surgeon implanted patients with the Inspire® UAS system and the study allowed patients to recover for 1-month. At 1-month, the study required a second in-laboratory PSG sleep study prior to activating the Inspire® UAS device. The results of this 1-month sleep study and the pre-implant sleep study were averaged with the results defined as the patient's baseline. Regular follow-ups with performance of PSG studies occurred at 2, 6, 12, 13, and 18-months. Follow-ups in which PSG studies were not required occurred at 3, 9, 15, 24-months, and every 6 months thereafter.

Primary evaluations of safety and effectiveness results occurred at the 12-months follow-up visit, but follow-up of the study patients has continued through 18-months according to the approved study protocol. See Table 7 for a summary of follow-up visits and data collected.

Table 7: STAR Pivotal Study Follow-Up Schedule

Visit (Section number)	Window (days)	Eligibility/ Infomed Consent (8.2.1)	Subject Information /Physician Exam (8.2.2)	Functional Tongue Exam (8.2.3)	ESS (8.2.4)	FOSQ (8.2.5)	Polysomnography (8.2.6)	Surgical Consultation (8.2.7)	Drug Induced Sleep Endoscopy (8.2.8)	Adverse Event (8.2.9)	Patient Programmer Instruction (8.2.10)	Device Check (8.2.11)	System Settings during PSG (8.2.12)
Baseline Visit (8.4.1)	-90	√[1]	√	√	√	√				√			
Pre-Implant Screening (8.4.2)	-90						√[2]	√[2]	√[2]	√			
Implant (8.4.3)	0									√		√	
Post-op Check (8.4.4)	4-14		√							√			
1 Month Visit (8.4.5)	±10		√	√	√	√	√			√	√	√[3]	
1 Month + 1 Week Visit (8.4.6)	±10		√							√			
2 Month Visit (8.4.7)	±14		√	√	√	√	√			√		√	√
3 Month Visit (8.4.8)	±14									√		√	√
6 Month Visit (8.4.9)	±21		√	√	√	√	√			√		√	√
9 Month Visit (8.4.10)	±21									√		√	√
12 Month Visit (8.4.11)	±21		√	√	√	√	√			√		√[4]	
13 Month Visit (8.4.12) Randomize period prior to PSG	±14 5-10		√	√	√	√	√			√		√[4]	
15 Month Visit (8.4.13)	±21									√		√	√
18 Month Visit (8.4.14)	±21		√	√	√	√	√			√		√	√
Long-term Visit (8.4.15)	±30		√	√	√	√				√		√	√[5]
Interim Visit (8.4.17)			√[5]				√[5]			√		√[5]	√[5]

The study required collection of data for the primary effectiveness endpoint at the 12-month follow-up PSG study. After the 12-month follow-up visit sleep study, the first 46 patients who responded to the therapy participated in a therapy withdrawal study. These subjects were randomized 1:1 into either a therapy ON arm or a therapy OFF arm and were followed for an additional month (13-month visit). After a therapy "wash out" period of at least 5 days for the OFF arm, the study required another PSG. See Figure 2 for a flow chart of the follow-up schedule after the 12-month follow-up visit.

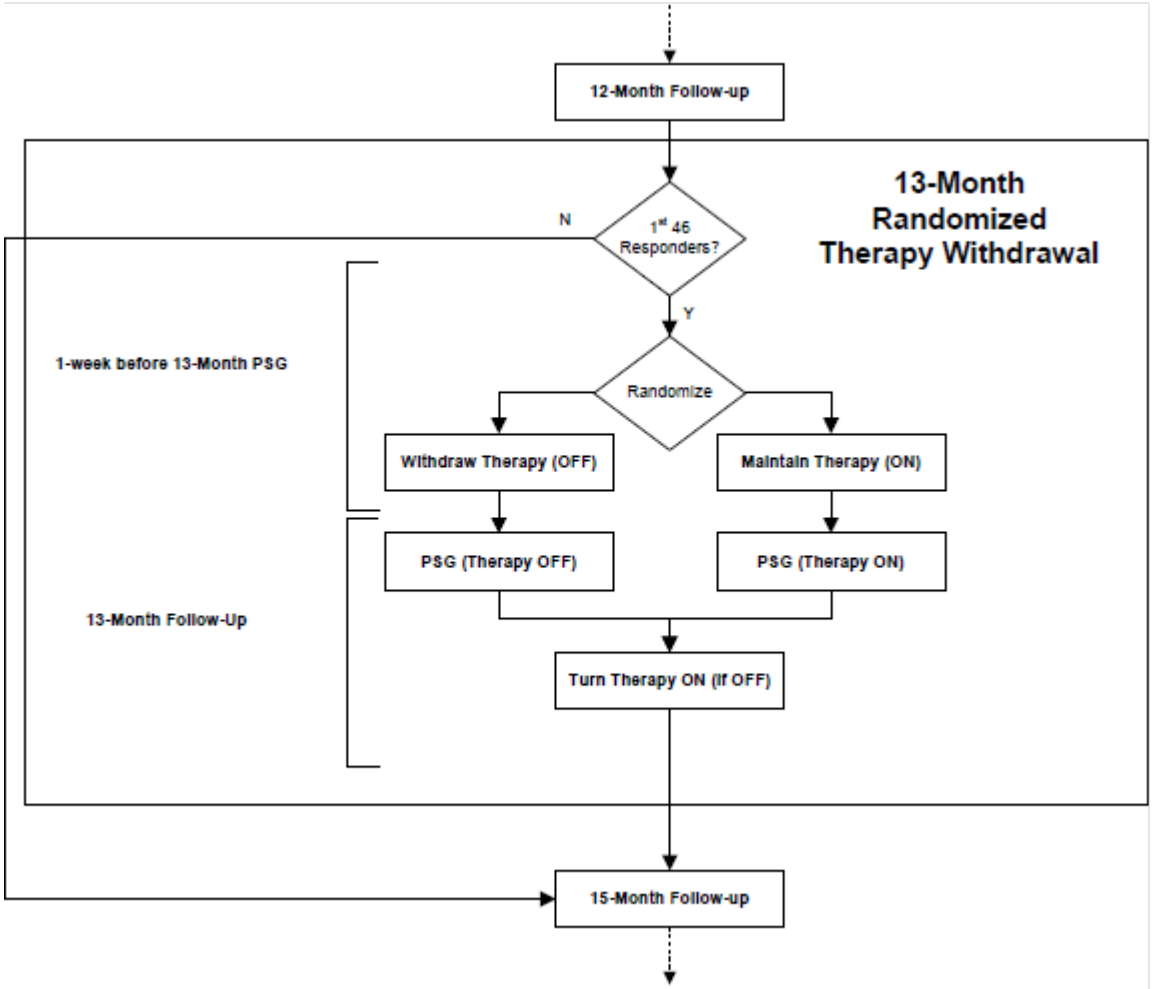

Figure 2: STAR Pivotal Study 13-Month Randomized Therapy Withdrawal

3. Clinical Endpoints

Safety
Safety of the Inspire® UAS system was determined through assessment of all reported adverse events. There was no formal statistical hypothesis.

Effectiveness
The study had two (2) co-primary effectiveness endpoints based on patient-level reductions in the AHI and the ODI from baseline to month 12.

For the first co-primary endpoint, the study defined a responder to the Inspire® UAS therapy as a patient with least a 50% reduction in the AHI compared to the mean of the pre-implant screening and 1-month visit (post-implant but prior to therapy activation) and AHI less than 20 events per hour.

For the second co-primary endpoint, the study defined a responder as a patient with a 25% or greater reduction in ODI at the 12-Month visit compared to baseline (i.e., the mean of the pre-implant screening and 1-month visit).

Secondary endpoints included the following:

- **Randomized controlled therapy withdrawal:**
  The randomized therapy withdrawal test occurred at the 13-month PSG in order to evaluate the influence of confounders on the efficacy results. The randomized controlled therapy withdrawal allowed for measurement of the extent to which AHI change is due to Inspire® UAS therapy versus other potential health changes over the 12-month follow-up period such as a change in BMI, which may confound the effect of Inspire® UAS therapy on AHI. The first 46 therapy responders were randomized to the controlled therapy withdrawal study during the 13-nonth visit. To meet this endpoint, there needed to be a statistically significant difference between the therapy OFF arm and the therapy ON arm in their mean AHI results from the 12-month and 13-month sleep studies.

- **Modified intent-to-treat (ITT) analysis:**
  The primary analysis was an intent-to-treat analysis, so any patient missing 12-month data was automatically presumed to be a treatment failure. The modified ITT included all implanted patients with AHI collected at pre-implantation, 11-month, and 12-month follow-ups. All implanted patients that had pre-implantation and 11-month data but not 12-month data had their last data values carried forward, provided they had at least 6-month AHI data. Any implanted patient that did not have 12-month data available due to failure of therapy (e.g., study withdrawal due to therapy failure) was included in the primary analysis as a treatment failure.

- **Functional Outcomes of Sleep Questionnaire (FOSQ):**
  The FOSQ is a quality of life measure used in clinical evaluation and management of OSA. This validated instrument assesses the effect of a patient's daytime sleepiness on activities of ordinary living scored on a 4-point scale. The total scores can range from 5 to 20, with higher scores associated with better functional status. For each patient, the study measured the change in FOSQ from baseline to the 12-month visit.

- **Epworth Sleepiness Scale (ESS):**
  The ESS is a quality of life measure used in clinical evaluation and management of OSA. This validated instrument rates a patient's daytime sleepiness. The ESS asks people to rate their usual chances of dozing off or falling asleep in 8 different situations or activities that most people engage in as part of their daily lives, although not necessarily every day. The ESS scores items on a 4-point scale. Possible scores range from 0 to 24, with higher scores indicating a greater chance of falling asleep during normal

daytime activities. The ESS identifies a score of 10 or greater to be abnormal daytime sleepiness. The study recorded changes between baseline and 12 Months.

- **Percentage of sleep time with oxygen saturation (SaO_2) below 90%:** This secondary endpoint assessed the change between baseline and 12 Months, with the objective of finding a statistically significant decrease in the percentage of time below a SaO_2 level of 90%.

4. Statistical Analyses

The analysis of the primary and secondary endpoints was pre-specified. The study defined success by a responder rate that was statistically significantly greater than 50% for each of the co-primary endpoints. In statistical terms, the hypothesis test for each co-primary endpoint was:

Ho: $\pi \leq 50\%$
Ha: $\pi > 50\%$

(π is the probability of success and 50% is the pre-specified performance goal)

The statistical analysis tested both primary effectiveness endpoints at a significance level of 2.5% (based on a 2-sided significance level of 5%). The study is successful if the null hypothesis could be rejected in favor of the alternative for both co-primary endpoints, thereby preserving an overall significance level of 2.5%.

The statistical analysis tested the secondary effectiveness endpoints according to a hierarchical strategy in order to preserve an overall Type I error rate of 5%.

The required sample size was based on the hypothesis tests of the co-primary effectiveness endpoints (i.e., patient-level success based on sufficient reductions in AHI and ODI). With a one-sided significance level of 2.5%, desired power of 80%, and assuming that the true probability of success (π) is 64%, the required sample size is 108 implanted patients.

There was no randomization for the first 12 months of the study due to the single arm trial design. The study only called for randomization of the therapy withdrawal at 13-months. Following the 12-Month visit, the first 46 responders based on the AHI primary endpoint were randomized 1:1 to either a therapy maintenance group (ON group) or a therapy withdrawal group (OFF group).

Blinding was not possible during the study since the stimulation therapy evokes a physiological response in the patients. However, the primary endpoints were objective measures of AHI and ODI which were collected during an overnight

sleep study using PSG. An independent core lab scored all the sleep studies in order to minimize assessment bias.

B. Accountability of PMA Cohort

At the time of database lock, of the 929 patients screened in the PMA study, 126 patients were implanted and 124 were available for analysis at the completion of the study at the 18-month post-operative visit.

Table 8: Patient Accountability through 18-Months

Patients	Implant	1-Month visit	2-Month visit	3-Month visit	6-Month visit	9-Month visit	12-Month visit	18-Month visit
Implanted	126	126	126	126	126	126	126	126
Died	0	0	0	0	0	0	1	0
Withdrawn	0	0	0	0	0	0	1	0
Eligible at visit	126	126	126	126	126	126	124	124
Visit at interval	126 (100%)	126 (100%)	126 (100%)	126 (100%)	125 (99%)	125 (99%)	124 (100%)	123 (99.2%)
Visits within window	77 (61%)	122 (97%)	120 (95%)	115 (91%)	119 (94%)	115 (91%)	118 (95%)	111 (90%)
Visits outside window	49	9	12	11	7	10	6	12
Missed visit	0	0	0	0	1	1	2	1

C. Study Population Demographics and Baseline Parameters

Table 9 list the patient demographics for the STAR Study. During the February 20, 2014 Advisory Meeting, the Panel was asked to comment on the demographics of the STAR trial and concluded that while the majority of patients were male and Caucasian there are no clinical or physiologic reasons why the results cannot be extrapolated to the general intended population who may be treated by the device.

Table 9: Study Population Demographics

Demographic Measures	Mean N= 126	Median (Min, Max)
Age, year	54.5	55 (31.0, 80.0)
Body Mass Index, kg/m²	28.4	29.2 (18.4, 32.5)
Neck Size, cm	41.2	41.9 (31.8, 48.3)
Systolic BP, mmHg	128.7	128 (96, 180)
Diastolic BP, mmHg	81.5	80.5 (60.0, 105.0)
Male	105 (83%)	

Demographic Measures	Mean N= 126	Median (Min, Max)
Race Caucasian African American Hispanic Asian Others*	 122 (97%) 0 (0) 1 (1%) 1 (1%) 2 (2%)	
**1-Surinam, 1-Turkey*		

The baseline sub-ranges for AHI and ODI are provided in the table below. The baseline AHI range in the STAR trial was between 13.3 and 65.1 and the baseline ODI range was between 4.5 and 63.5. The patients' baseline AHI showed a mean of 32.0 and a median of 29.3, and the baseline ODI showed a mean of 28.9 and a median of 25.4.

Table 10: AHI & ODI Baseline Sub-ranges

Baseline AHI Ranges	**n**
10<x<20	19
20<x<30	46
30<x<40	32
40<x<50	16
50<x<60	10
60<x<70	3
Baseline ODI Ranges	**n**
0<x<10	2
10<x<20	30
20<x<30	45
30<x<40	24
40<x<50	15
50<x<60	9
60<x<70	1

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the assessment of all reported adverse events.

Adverse events that occurred in the PMA clinical study

There were a total of 680 adverse events during the 18 month post-implantation period, with 557 at 12-month endpoint and another 123 adverse events (AEs) between 12 and 18 months. An additional 43 AEs are reported beyond 18 month post-implantation follow up. Adverse events occurred in 117 subjects (93%) through 18 months.

All adverse events observed in the pivotal study are summarized in the table below:

Table 11: Adverse Events Summary

AE Type	Number of AEs from baseline to 12 months (n=126)	Number of AEs from 12-18 months (n=124)	Number of AEs from 18+ months (n=124)
Total Adverse Events*	557	123	43
Serious Adverse Events (SAEs)	17 (n=14) (12%)	15 (n=11) (9%)	11 (n=6) (5%)
All Non-Serious Adverse Events	540 (n=115) (91%)	108 (n=61) (49%)	32 (n=25) (20%)
AEs unrelated to Inspire® Procedure or Device	202 (n=76) (60%)	58 (n=41) (33%)	22 (n=18) (15%)
AEs related to Inspire® Procedure or Device	338	50	10
-Procedure Related Events	170 (n=73) (58%)	1 (n=1) (0.8%)	0
-Device Related Events	168 (n=84) (67%)	49 (n=33) (27%)	10 (n=9) (7%)

**Does not include two (2) explanted devices discussed in more detail below.*

Serious Adverse Events

Of the 680 total number of adverse events observed in the pivotal study through 18 months, 32 (5%) constituted SAEs.

The pivotal study had a total of 17 SAEs in 14 patients during the first 12 months post-operative time period. The 17 SAEs included one (1) IPG revision, one (1) death, 13 independent conditions or pre-existent diseases (i.e., coronary artery disease, atrial fibrillation, chest pain, recurring syncope, angina, acute enterocolitis, exacerbation of benign prostatic hypertrophy, right renal artery stenosis, hernia surgery, knee/shoulder injuries, and trigger finger), and two (2) motor vehicle accidents reported as other.

In the 12-18 months post-operative period, an additional 15 SAEs were reported in 11 patients. Of the 15 SAEs, one (1) device repositioning related event and fourteen (14) SAEs of independent conditions or pre-existing diseases (i.e,. thyroid cancer, drug reaction to clindamycin, kidney stone, coronary artery disease, atrial fibrillation, UPPP) and seven (7) listed under Other AEs (i.e., UPPP, heart catheterization, anesthesia reaction or fall) were reported.

Beyond the 18-month visit, additional 11 SAEs are reported in six (6) patients. These include two (2) deaths and nine (9) pre-existing or independent conditions (i.e., concussion, prostate cancer/prostatitis, fractured nose, fall with rib fractures, melanoma, kidney stone/pain, diaphragmatic hernia, orthostatic hypotension). All of the SAEs beyond 18 months are unrelated to the Inspire® UAS system.

The incidence of device or procedure-related serious adverse events that occurred within 18 months was low (i.e. 1.6%)

Table 12: Serious Adverse Events

SAE Type	SAEs(n)from 0-12 months	SAEs (n) from 12-18 months	SAEs (n) from 18+ months	Related to Inspire® procedure or device
Device Revision-Repair suture or reposition IPG in the pocket	1	1†	0	Yes
Pre-existing or independent condition	13	7	9	No
Death	1	0	2	No
Explant	1††	0	0	Yes
Other	2*	7#	0	No

†† Elective explant requested by non-responder patient and withdrawn from study @10 months

† This SAE originally reported as an AE, became SAE in June 2013 (post 12 months) as a surgical procedure was performed to reposition the neurostimulator.

** Motor Vehicle Accident (1) and accident (1)*

 # Heart catheterization procedure (1); sleep surgeries (4); anesthesia reaction (1); fall (1).

Death Related SAEs

Of the three (3) deaths reported during and after the 18-month follow up visit of the pivotal trial, one (1) implanted patient died prior to completing the 12-month assessment and two (2) others died after the 18-month follow up visit from causes unrelated to the Inspire® UAS therapy.

The one (1) patient who died prior to completing the 12-month assessment suffered from 11 separate AEs including death. These adverse events included: tongue did not move to front, stimulation too strong, sleep interruption, skin rash, throat and ear-ache, pain in ribs, phlegm, painful hip, and pain in esophagus. Three (3) of the eleven (11) events were related to neurostimulation therapy (two (2) were due to high stimulation and one (1) included an unknown cause for the

event of tongue not moving to the front) and were resolved through reprogramming of the IPG.

One (1) of the two (2) patients who died after 18-months of therapy also had 10 adverse events including death. These adverse events included hyperhidrosis, tinnitus, abdominal pain, high stimulation (x2) restless leg, itchy right ear, hypertension, ticking in mouth, and back pain. Three (3) of the ten (10) events were related to neurostimulation therapy and are reported to have been resolved with reprogramming.

The second of the two (2) patients who died after 18-months of therapy experienced four (4) adverse events - one (1) adverse event was related to stimulation (tongue irritation), two (2) events were related the to the programmer, and the remaining adverse event was related to a fall.

Non-Serious Adverse Events

Of the 680 total number of adverse events observed in the pivotal study through 18 months, 95% were categorized as non-serious in 115 of 126 patients (91%).

The following table summarizes all non-serious adverse events.

Table 13: Non-Serious Adverse Events Summary

AE Type	Number of AEs from 0-12 months (n=126)	Number of AEs from 12-18 months (n=124)	Number of AEs from 18+ months (n=124)
All Non-Serious Adverse Events	540 (n=115) (91%)	108 (n=61) (49%)	32 (n=25) (20%)
AEs unrelated to Inspire® Procedure or Device	202 (n=76) (60%)	58 (n=41) (33%)	22 (n=18) (15%)
AEs related to Inspire® Procedure or Device	338	50	10
-Procedure Related Events	170 (n=73) (58%)	1 (n=1) (0.8%)	0
-Device Related Events	168 (n=84) (67%)	49 (n=33) (27%)	10 (n=9) (7%)

The following tables provide a breakdown of the non-serious procedure-related and device-related events.

Table 14: Procedure-Related Adverse Events (and the probability of experiencing them within the first 18 months)

Event	Number of Subjects with Event	Percent of Subjects (n=126)
Incision pain	35	28%
Post-operative discomfort	31	25%
Temporary tongue weakness	23	18%
Sore throat from intubation	15	12%
Other post-operative symptoms (such as gastrointestinal [nausea, vomiting, abdominal pain, constipation], body pain [back, knee, wrist, hand], allergy to antibiotics, anxiety, ineffective airway clearance, loss of some taste, and inability to void)	14	11%
Headache	8	6%
Mild infection	1	1%

The most commonly reported procedure related events were incision pain (28%), post-operative discomfort (25%), temporary tongue weakness (18%), and sore throat due to intubation. These are typical for these types of procedures. At the completion of the 18-months follow-up visit, 93% of procedure related events were fully resolved with either no intervention or medication.

Table 15: Device-Related Adverse Events (and the probability of experiencing them within the first 18 months)

Event	Number of Subjects with Event	Percent of Subjects (n=126)
Discomfort due to electrical stimulation	59	47%

Event	Number of Subjects with Event	Percent of Subjects (n=126)
Tongue abrasion	30	24%
Other acute symptoms (i.e., headaches, coughing, choking, dysphasia, and speech-related events)	23	17%
Mouth Dryness	14	11%
Complaints related to temporary usability or functionality issues with an implanted device	13	11%
Complaints related to temporary usability or functionality issues with an external device	13	10%
Mechanical pain associated with presence of device	10	8%
Mild infection	1	1%

The most commonly reported device related AEs were discomfort due to electrical stimulation (47%) and tongue abrasion (24%), which are not unexpected given that this is a neurostimulation device. At the completion of the 18-months follow-up visit of all study patients, 75% of device related events were fully resolved primarily with either medication, device reprogramming, dental work to fix a jagged tooth, with the aid of a lower tooth guard used during sleep to prevent tongue abrasions, or with no intervention.

The following table summarizes unresolved non-serious adverse events through 18 months post-implant.

Table 16: Unresolved Adverse Events through 18 Months

AE Type	AEs (n) from 0-12 months (n=126)	AEs (n) from 12-18 months (n=124)	AEs (n) from 18+ months (n=124)
All Non-Serious Adverse Events	95 (n=50)	40 (n=29)	17 (n=14)
AEs unrelated to Inspire® Procedure or Device	48 (n=29)	23 (n=19)	14 (n=12)

Procedure Related Events	9 (n=8)	0	0
Device Related Events	38	17	3
-Neurostimulation	**29 (n=22)**	**12 (n=11)**	**2 (n=2)**
-Non-neurostimulation	9 (n=8)	5 (n=5)	1 (n=1)
** Includes Partially Resolved Non-Serious Device-Related Adverse Events through 18-months Post-Implantation*			

As of data closure on October 16, 2013, 55 device-related events at 18 months remained unresolved (38 at a 12 month endpoint and 17 between 12 months and 18 months). Of the 55 events, 41 neurostimulation related events were unresolved in 28 patients. These neurostimulation-related events to the Inspire® UAS therapy were the most common device-related events in the pivotal study. The unresolved events include reports of discomfort due to stimulation, tongue abrasion and various stimulation related events including dry mouth, headaches, intermittent waking, isolated stimulation sensation events, audible buzzing, and intermittent fatigue.

Only nine (9) of 171 procedure-related adverse events remain unresolved, including three (3) tongue weakness, one (1) event of parosmia, and five (5) events related to incision issues which include three (3) events of numbness at incision site, one (1) event of scar pain, and one (1) event of hypertrophic scar.

Despite these reported events, patients continued to report high (85%) compliance with the therapy at 18 months.

Explant/Re-implantation/Revisions

In the pivotal study of 126 subjects, one (1) elective explantation of the IPG was performed at the request of the patient at 332 days (10 months) following implantation, as the patient was not satisfied with the effectiveness of the therapy. In addition, their leads were capped and left in place. The patient's IPG was returned to the Inspire Medical after explant. Analysis of the explant (included visual inspection and electrical testing) revealed the device was functioning and met its specifications. Subsequently, the patient was withdrawn from the study and considered a non-responder in the effectiveness analysis.

A second explant was reported after the data closure (October 16, 2013). This patient was diagnosed with septic arthritis of the right sterno-clavicular joint and sternocleidomastoid muscle insertion with associated methicillin sensitive staphylococcal aureus bacteremia. After initial debridement of the affected site and treatment with I/V antibiotics, a second surgery was required to drain the large persistent abscess within the substance of sternocleidomastoid (SCM) muscle extending down through the insertion of the SCM behind the head of the right clavicle and behind superior portion of the sternum. Operative surgeon explanted all of the implantable components of the device, because of proximity of infection. Given the patient had several different infective sites simultaneously

while the sterno-clavicular area abscess developed, the original source of infection was difficult to identify.

Both explants were successfully completed without damage to the surrounding structures. However, for one explant only partial removal of the implant was accomplished. The lead could not be removed in order to avoid injuring the hypoglossal nerve.

Two (2) other patients underwent revision surgeries, one (1) at 12 month post implantation and the other between 12-18 months, both for repositioning of the IPG to address patient discomfort.

2. Effectiveness Results

The analysis of effectiveness was based on the 124 evaluable patients at the 12-month time point. Two (2) patients were withdrawn from the study (one (1) unrelated death and one (1) elective explant) prior to the 12-month study. Patients without evaluable data were counted as failures in the ITT analysis (therefore, n=126). Key effectiveness outcomes for the ITT population are presented in Tables 17 through 23.

Primary Effectiveness Endpoints

The STAR Pivotal Trial met its primary effectiveness outcome. The overall responder rate based on AHI measurement was 66% (83 of 126) with a corresponding lower 97.5% confidence level of 57%. This lower confidence bound was above the pre-specified performance goal of 50%. The overall responder rate based on ODI measurements was 75% (94 of 126) with a corresponding lower 97.5% confidence level of 66%, which was also above the pre-specified performance goal of 50% (see Table 17).

Table 17: Co-Primary Effectiveness Results (ITT population)

	Responder Rate	Performance Goal	Lower 97.5% Confidence Level	p value
Primary Endpoint: AHI Responder, 12 months	66% (83/126)	50%	57%	0.0002
Primary Endpoint: AHI Responder, 18 months	65% (80/124)	50%	55%	0.0008
Co-Primary Endpoint: ODI Responder, 12 months	75% (94/126)	50%	66%	<0.0001
Co-Primary Endpoint: ODI	80% (99/124)	50%	72%	<0.0001

Responder, 18 months				

The average reduction of AHI from baseline to 12-months was 68% and for ODI was 70%. Baseline AHI showed a mean of 32.0. In comparison, the AHI at the 12-month PSG study showed a mean of 15.3. Baseline ODI showed a mean of 28.9. In comparison, ODI at the 12-month PSG study showed a mean of 13.9.

Secondary Effectiveness Endpoints
The STAR Pivotal Trial met all five (5) secondary effectiveness objectives.

Randomized Controlled Therapy Withdrawal
The first 46 responders, based on the AHI primary endpoint, were randomized 1:1 to either the therapy maintenance group (ON group) or the therapy withdrawal group (OFF group), resulting in 23 patients in each group. The randomized controlled therapy withdrawal study provided further evidence that improvements were attributed directly to the Inspire therapy. AHI increased significantly in the therapy withdrawal (OFF) group compared to AHI scores in the therapy maintenance (ON) group. The results from the randomized control therapy withdrawal study showing the difference between the therapy OFF arm and the therapy ON arm are provided in Table 18.

Table 18: Randomized Controlled Therapy Withdrawal Study Results

AHI	Mean AHI		Change (13M-12M) Mean	95% CL for Mean Change	p-value
	12-Month	13-Month			
Therapy ON	7.2	8.9	1.7	(-1.1, 4.5)	<0.0001
Therapy OFF	7.6	25.8	18.2	(11.4, 24.9)	

The mean AHI at the 12-month visit for the Therapy On group was 7.2 ± 5.0, and 8.9 ± 9.1 at the 13-month visit, a change of 1.7 ± 6.4 between the two (2) visits. For the Therapy Off group, AHI at the 12-month visit (prior to their therapy being turned off) was 7.6 ± 4.0, and at the 13-month visit (with therapy off) it was 25.8 ± 16.2, a change of 18.2 ± 15.6 between the two (2) visits. AHI increased significantly in the Therapy Off group compared to AHI change in the Therapy On group (See Table 19). This demonstrated that the decreases in OSA severity were due to Inspire® therapy.

Table 19: Mean Difference in AHI of Randomized Therapy Withdrawal Study

	Difference Mean AHI increase "ON" vs. "OFF" (OFF – ON)	95% CL for Difference in means	p value

Randomized Therapy Withdrawal	16.4 ± 12.0	9.2, 23.7	<0.0001

Modified Intent to Treat

Since there were only two (2) patients who did not complete the 12 month visit, a modified intent to treat analysis was performed. The modified intent to treat analysis showed the same outcome as the intent to treat analysis. The overall AHI responder rate of the modified intent to treat group was 66% (83 of 126) with a corresponding lower 97.5% confidence level of 58% (See Table 20).

Table 20: Modified Intent to Treat Results

	Responder Rate	Performance Goal	Lower 97.5% Confidence Level	p value
Modified ITT analysis AHI Responder	66% (83/126)	50%	57%	0.0002

Functional Outcomes of Sleep Questionnaire (FOSQ)

A total 123 patients completed FOSQ measurement at the 12 month visit. The mean FOSQ score at the pre-implant visit from all 126 patients was 14.3 ± 3.2. The mean FOSQ score from 123 patients at the 12-month visit was 17.2 ± 3.1 and at the 18-month visit it was 17.3 ± 3.0. The mean change from pre-implant to the 12-month visit was -2.9 ± 3.1, showing a statistically significant improvement in FOSQ score at the 12-month visit (See Table 21).

Table 21: FOSQ Results

	Mean Change (BL-12M) (SD)	95% CL for Mean Change	p value
FOSQ	2.9(3.1)	2.4, 3.5	< 0.0001

Epworth Sleepiness Scale (ESS)

A total 123 patients completed their ESS measurement at the 12 month visit. The mean ESS score at the pre-implant visit for all 126 patients was 11.6 ± 5.0. The mean ESS score from 123 patients at the 12-Month visit was 7.0 ± 4.2, and at the 18-month visit it was 7.0 ± 4.0. The mean change from pre-implant to the 12-month visit was 4.6 ± 5.0, showing a statistically significant improvement in the ESS score at the 12-month visit (See Table 22).

Table 22: ESS Results

	Mean Change (BL-12M) (SD)	95% CL for Mean Change	p value
ESS	4.7 (5.0)	3.8, 5.5	<0.0001

Percentage of Sleep Time at SaO2 < 90%

A total 124 patients completed SaO_2 measurement during PSG study at the 12-month visit. The mean percentage of sleep time at SaO_2 < 90% at baseline for all 126 patients was 8.7 ± 10.2. The mean SaO_2 measurement from 124 patients at

the 12-month visit was 5.9 ± 12.4 and at the 18-month visit was 5.6 ± 12.0. The mean change from the baseline to the 12-month visit was 2.7 ± 11.1, showing a significant reduction in the percentage of sleep time at SaO_2 < 90% at the 12-month visit (See Table 23).

Table 23: Percentage Sleep Time at SaO_2 < 90

	Mean Change (BL-12M) (SD)	95% CL for Mean Change	p value
Percentage sleep time SaO_2 < 90%	2.5 (11.1)	0.6, 4.5	0.01

3. Subgroup and Additional Analyses

Prior history of upper airway surgeries, including uvulopalatopharyngoplasty, for potential association with outcomes was analyzed. While the responder group had a higher proportion of patients with prior upper airway surgeries this trend was not found to be statistically significant.

The study protocol allowed stimulation adjustments (titrations) to occur up to 1 month prior to the 12 month endpoint evaluation. Because many patients required stimulation adjustments over the study duration in order to achieve a therapeutic effect, data on stimulation adjustments at each time point for all patients as well as data out to 18 months was evaluated. A total of 14 patients from the 83 responders (16.9%) required multiple titrations throughout the study prior to achieving a therapeutic effect. Titrations occurred between the 2 and 11 month time points. Sixty seven percent (67%) of responders and 44% of non-responders required 1 to 3 titrations. Thirty four percent (34%) of all patients required 4 to 5 titrations during the study and this number of titrations was equally distributed between responders and non-responders.

Due the number of titrations that were required for more than half of the patients (67%), the Anesthesiology and Respiratory Therapy Devices Panel was asked to comment on the need for multiple titrations and the durability of the therapeutic effect. The comments from the Panel are discussed in Section XI below.

Information is provided in the Inspire® UAS Physician implant labeling describing how the stimulation adjustments are performed during a titration sleep study.

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 25 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: $42,299 USD over a 3-year period
- 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. To address the compensation for this one investigator, FDA conducted statistical analyses without that site's data to determine whether the financial interests/arrangements of this one investigator had any impact on the clinical study outcome. The exclusion of data from this one site did not impact the overall study results. The information provided does not raise any questions about the reliability of the data.

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

A. Panel Meeting Recommendation

At an advisory meeting held on February 20, 2014, the Anesthesiology and Respiratory Therapy Devices Panel voted 12-0-1 (yes, no, abstain) that there is reasonable assurance the device is safe, 12-0-1 (yes, no, abstain) that there is reasonable assurance that the device is effective, and 12-0-1 (yes, no abstain) that the benefits of the device outweigh the risks in patients who meet the criteria specified in the proposed indication.

The Panel meeting summary is available at the following link: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/AnesthesiologyandRespiratoryTherapyDevicesPanel/UCM386960.pdf.

B. FDA's Post-Panel Action

The Panel drew the following conclusions at the February 20, 2014 meeting:

- The Panel acknowledged that multiple titrations may be necessary in order to fine tune the efficacy of the device for a given patient. The Panel felt that the need for multiple stimulation adjustments and titrations was consistent with typical neurostimulation therapies for other conditions. The Panel was not concerned

with the number of titrations experienced by patients in the STAR trail. The Panel suggested that information in the labeling be included for patients in order to clarify the number of titrations which may be needed to establish a relevant clinical effect.

- The Panel suggested that titration information would be useful in the patient and physician labeling in order to guide prescription of the device and inform patients (e.g., number of titrations, severity of discomfort, and duration of discomfort).

- The Panel discussed the STAR pivotal trial study population demographics, which consisted of 97% Caucasians, 0 African Americans, 1% Hispanic, 1% Asian and 2% other ethnicity. The Panel believed that the data from the STAR pivotal study population can be extrapolated to the intended population of moderate to severe obstructive sleep apnea failing or intolerant of PAP due to both the published data and the fact that there is no mechanistic reason to restrict this device to a demographic simply due to the fact that they were not included in the study. The Panel agreed that Inspire Medical should be diligent in being inclusive of different ethnicities in their post-approval studies.

- The Panel generally believed that screening patients with DISE (Drug-Induced Sleep Endoscopy) alone for implantation with Inspire® system was an adequate metric. The Panel agreed that most otolaryngologists; however, may opt to use DISE in conjunction with other medical metrics to screen their patients for this particular medical treatment.

- The Panel agreed that a proper training program was necessary for physicians planning to use this technology and only qualified experts should be allowed to screen patients using the DISE examination.

- The Panel agreed that future patients would not need prior surgical procedures to address upper airway collapse (e.g., UPPP, Tonsillectomy/Adenoidectomy), in order to fit the criteria for implantation with the Inspire® UAS system.

- The 648 non-serious adverse events reported through 18-months included 158 with tongue soreness, irritation/abrasion, and discomfort due to electrical stimulation, mouth dryness, and mechanical pain. Some of these adverse events remained unresolved at the end of the study. The Panel did not have any major concerns regarding the adverse event profile due to the high level of compliance of the patients in continuing to use the device. The Panel agreed that patients should be informed about these possible side effects prior to surgery.

- Based on the device description, the proposed indication, STAR trial study results, and currently available treatments for OSA, the Panel agreed that patients should be given full disclosure about what the procedure entails, that multiple titrations may be required, that long-term effects (beyond 18-months) are unknown, and that implantation of this device may lead to other non-serious

adverse events. The Panel also indicated patients should be informed that the device may not work for everyone (1/3 of the study population did not respond) and that this device is non MRI compatible. Furthermore, fibrosis around the nerve could complicate full device removal. The Panel agreed that PAP trial should be done before considering this device and that Inspire® UAS therapy should only be performed as a second line treatment after PAP failure.

- The Panel concluded that there is a need for postmarket evaluation of the real-world device performance, and believed it should include: appropriate study design, safety and effectiveness endpoints, appropriate follow-up for long-term evaluation, and need for evaluation of performance. In addition, the Panel recommended that while sleep-related Quality of Life (QoL) questionnaires such as the Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaires (FOSQ) were adequate for addressing many of the effectiveness issues, other broader metrics would be clinically useful (e.g., additional questionnaires concerning quality of life, general health metrics, and/or depression scales). In addition, the Panel encouraged the development of a patient registry in order to follow long term effectiveness.

- The Panel was satisfied with the anticipated magnitude in mean changes in AHI and ODI at 3 years proposed in the post-approval study.

- The Panel generally agreed that the use of adverse event data from other types of neurostimulator implants to generate the performance goal for the evaluation of long-term safety may not be the most useful tool, due to the different modalities of neurostimulator implants, but specific device failures may be used as a benchmark (i.e., lead fractures).

- The Panel generally agreed that 5 year safety data should be collected in the post-approval studies but that hypothesis testing at 5 years was not essential.

The FDA concurs with the Panel recommendations. The physician and patient labeling have subsequently been revised to address the comments from Panel. A post-approval study has also been agreed upon which takes into account the feedback received from Panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the pivotal study, Inspire® therapy provided the majority of patients with clinically meaningful reductions in the severity of their obstructive sleep apnea and improvements in their quality of life. The FDA concurs with the Panel conclusions that Inspire® therapy has demonstrated a reasonable assurance of effectiveness for use in treating moderate to severe obstructive sleep apnea in adult patients who have failed or who are

intolerant to PAP, and who have absence of complete concentric collapse at the level of the soft palate.

B. Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

The device related adverse events (and the probability of experiencing within the first 18-months) included: discomfort due to electrical stimulation (47%); tongue abrasion (24%); mouth dryness (11%); mechanical pain associated with presence of device (8%); complaints regarding temporary usability or functionality issues with an implanted device (11%); complaints regarding temporary usability or functionality issues with an external device (10%); mild infection (1%); and other acute symptoms (i.e., headaches, coughing, choking, dysphasia and speech related events) (11%). At the time of the completion of 18-months follow up of all study patients, 75% of device related events were fully resolved, primarily with either medication, device reprogramming, dental work to fix a jagged tooth, with the aid of a lower tooth guard used during sleep to prevent tongue abrasions, or no intervention.

The incidence of device or procedure related serious adverse events within 18 months was low (1.6%). While non-serious adverse events were frequent the majority of such events resolved with stimulation adjustments and other measures. The Panel felt that the number of stimulation adjustments and frequency of non-serious adverse events were consistent with what could be expected from this type of neuro-stimulation therapy. The FDA concludes that the Inspire® UAS has demonstrated a reasonable assurance of safety.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. The benefits include:

- Reduction in severity of obstructive sleep apnea
- Preserved sleep quality
- Improved subjective quality of life

Additional factors to be considered in determining probable risks and benefits for the Inspire® UAS device include:

- Requires surgical procedure
- Permanent implant; if explanted possibility of cuff/partial leads remaining

- Battery replacements at 8yr intervals
- MRI unsafe

Common Adverse Events include:

- Tongue soreness/abrasion/weakness
- Stimulation discomfort/high stimulation
- Dry mouth
- Mechanical pain
- Headache
- Infection

Despite the frequency of non-serious adverse events the study exhibited a high device compliance rate (85%) suggesting that the non-serious adverse events did not prohibit device use on a regular basis. Direct assessments of patient preference were not done; however, the high compliance rate suggests that patients tolerated the risks fairly well.

In conclusion, given the available information above, the data support that for the treatment of a subset of patients with moderate to severe obstructive sleep apnea in adult patients 22 years of age and older who have been confirmed to fail or are intolerant to positive airway pressure (PAP) and who have absence of complete concentric collapse at the level of the soft palate, the FDA concurs with the Panel that 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 provided preclinical testing for the device was acceptable. Based on the clinical study results, it is reasonable to expect that a significant portion of the patient population will achieve clinically significant results in reduction in severity of OSA and improved subjective quality of life. The Inspire® therapy is associated with a low rate of serious adverse events. While non-serious adverse events were frequent, the majority of these events resolved. Compliance with device usage was quite high suggesting that patients regarded therapy as beneficial despite the minor discomforts and need for multiple stimulation adjustments. The therapeutic effect appears to be durable out to at least 18 months. Given the increased morbidity associated with untreated, progressive OSA and the 60% compliance rate with PAP therapy, the probable benefits of Inspire® therapy outweigh the probable risks.

XIII. CDRH DECISION

CDRH issued an approval order on April 30, 2014. The final conditions of approval cited in the approval order are described below.

1. *Extended Follow-up of the Premarket Cohort (Inspire® 4 STAR Trial):* This study will be conducted as per protocol dated December 28, 2011, Version 9.1. This is a prospective, single arm cohort study to evaluate the long-term safety of the device in 124 subjects implanted with the Inspire® UAS system under the premarket study. The subjects will be followed 5-years post procedure. Any adverse events will be summarized by seriousness, severity, relatedness to the device and temporal relationship to the procedure. Data will be analyzed in a descriptive fashion using 95% confidence limits for the estimates.

2. *New Enrollment Study:* This study will be conducted as per protocol dated March 19, 2014, Version 1.5. This is a multi-center, prospective, single arm cohort study to evaluate long-term device safety and effectiveness. Accounting for a 10% attrition rate a total of 127 subjects will be implanted with the Inspire® UAS system and enrolled in the study. The study will also evaluate effectiveness of physicians' training program in a postmarket setting. The subjects will be followed 5-years post-procedure. Safety endpoints will be collected to evaluate: long-term device-related serious adverse events, therapy-specific adverse events (i.e., stimulation discomfort, tongue abrasions weakness, and deviation) at 12 months, and long-term therapy-related adverse events.

   Physician training measures of post-operative safety outcomes must include surgical times, post-operative pain recovery, procedure related adverse events, and post-operative comments. Effectiveness endpoints to evaluate quality of life measures using Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaires (FOSQ) will be collected annually. The study must be powered to assess if the mean score at 12 months post-implant is less than 10 for ESS and more than 2 for FOSQ. Therapy efficacy measured by Apnea Hypopnea Index (AHI), Oxygen Desaturation Index (ODI) should be evaluated by using mean differences compared to baseline using single night in-lab Polysomnography (PSG) at 3 years, while two-night home sleep testing (HST) would be conducted for descriptive purposes at 2, 4, and 5-year follow-up visits. Subjects must be evaluated at baseline, during implant, at 1-, 2-, 6-, and 12-months post-implant, and every six months thereafter through 5 years of post-implant follow-up.

   A one-sided binomial exact test will be used to test if long term device related serious adverse events is less than a performance goal of 24% at 5 years. For therapy-specific adverse events non-inferiority test with a margin of 5% using the Bayes Factor at 12 months post implant will be used. All therapy- and procedure-related adverse events will be described and summarized by seriousness, severity, relatedness, and temporal relationship to the device and/or procedure.

   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.