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 System

Device Procode: MNQ

Applicant's Name and Address: Inspire Medical Systems, Inc.
5500 Wayzata Blvd., Suite 1600
Golden Valley, MN 55416

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130008/S090

Date of FDA Notice of Approval: June 8, 2023

The original PMA (P130008) was approved on April 30, 2014 and is indicated to treat a subset of patients with moderate to severe obstructive sleep apnea (OSA) who have been confirmed to fail or cannot tolerate positive airway pressure (PAP) treatment and who do not have a complete concentric collapse at the soft palate level. The original PMA was approved in adult patients 22 years of age or older. Supplement P130008/S039 expanded the indications for the Inspire UAS system to include adolescent patients between 18 and 21 years of age and supplement P130008/S089 expanded the indications to include pediatric patients with Down syndrome between 13 and 18 years of age. Supplement P130008/S090 expands the indications further to include OSA patients, 18 years of age or older, with AHI ≤100. The supplement also updates the BMI warning to note that the BMI upper limit For which safety and effectiveness data is available has increased from BMI≤32 to BMI≤40.

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 than or equal to 15 and less than or equal to 100). 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 15 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).

Inspire UAS is also indicated for use in patients between the ages of 18 to 21 with moderate to severe OSA (15≤AHI≤100), and pediatric patients ages 13 to 18 years with Down syndrome and AHI greater than 10 and less than 50 who:

- Do not have complete concentric collapse at the soft palate level
- Are contraindicated for or not effectively treated by adenotonsillectomy
- Have been confirmed to fail, or cannot tolerate PAP therapy despite attempts to improve compliance
- Have followed standard of care in considering all other alternative/adjunct therapies

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. UAS therapy has not been evaluated for safety or efficacy during pregnancy.
- 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.
- Patients who require magnetic resonance imaging (MRI) other than what is specified in the MR Conditional labeling

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Inspire Upper Airway Stimulation System 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 remote. 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.

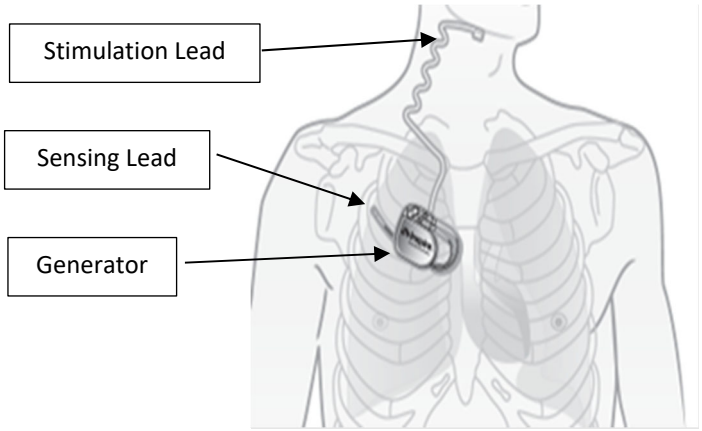

Figure 1: Inspire® system components and implant location

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 3028 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 3028 is a second generation IPG replacing the Model 3024 and is smaller and MR conditional.
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 and Model 4340 Sensing Leads	The sensing lead is placed in the intercostal space and contains a piezoelectric differential pressure sensor for detecting respiratory signals.
External Components:	
Model 2500 and Model 2580 Sleep Remote	The patient sleep remote is a handheld 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 obstructive sleep apnea in patients with AHI>65 and/or BMI ≤40 who have failed or are intolerant of PAP. These include upper airway surgical procedures and mandibular advancement devices (MAD). 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.

VII. MARKETING HISTORY

The Inspire UAS device has been commercially available in the U.S. since April 30, 2014. The device received CE Mark approval on October 20, 2010, and has been commercially available in the European Union since that time. The device has been commercially available in Japan since June of 2018, and in Australia since June 8, 2020.

The Inspire UAS device 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.

- 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)

- Scarring (due to picking at the device/ implant site) and keloid formation from implantation
- Cellulitis at surgical site
- Insomnia
- Pneumothorax
- Rhabdomyolysis

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

IX. SUMMARY OF NONCLINICAL STUDIES

All preclinical data to demonstrate safety and effectiveness of the Inspire UAS system has been reviewed by FDA under the original PMA (P130008) and subsequent supplements.
No new preclinical information was required for the expansion of the indications for use (IFU).

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Real world evidence data from Inspire Medical's ADHERE Registry (ongoing observational study) was used to support the expanded indication for use and update to the BMI warning. The ADHERE Registry is a multi-center, prospective, observational registry, conducted in the United States and Europe. The ADHERE registry is designed to capture data on 5,000 patients implanted with Inspire UAS, undergoing standard of care management following UAS implant. All patients who undergo implant of the Inspire UAS system are eligible to participate in the registry if they are willing to provide consent and have a life expectancy of at least one year. IRB approval is required for each clinical center to be included in the Registry. In addition, subjects must consent to have their data collected and reported (unless a waiver of consent was provided by the IRB).

Out of 3,988 subjects enrolled in the registry as of July 22, 2022, 57 patients were included in the analysis to support expanding the indication of the UAS to patients with 65<AHI≤100, and 279 patients were included in the analysis to support updating the BMI warning. Specific to the patient population of AHI>65 and BMI>32, Inspire evaluated efficacy using data from the ADHERE registry data using at least one of the following values recorded at final visit: AHI, ESS, Therapy Usage, CGI (Clinical Global Impression), and/or Patient Satisfaction data.:

Safety was evaluated via an analysis of all reported adverse events.

A. AHI ADHERE DATA ANALYSIS:

Table 2 below provides demographic characteristics of patients included in the analysis to support expanding the indication of the Inspire UAS to patients with AHI≤100. For the analysis data from patients with baseline AHI>65 was compared with data from patients

with baseline AHI of 15<AHI≤65 and data in each table below, therefore, includes these two groups.

Table 2: Demographics of High AHI Patients.

Variable	AHI≤65	65<AHI≤100 [1]
N	1483 (96.3%)	57 (3.7%)
Age	60.14±10.62 (61), 21 -85, N=1476	59.81±9.93 (61), 37 - 78, N=57
AHI- Baseline	34.58±12.62 (32.5), 15 - 65, N=1483	74.57±7.45 (72.4), 65.64 - 96.4, N=57
BMI- Baseline	28.99±3.76 (28.98), 17.71 - 47.19, N=1450	30.66±3.53 (30.75), 21.8 - 38.35, N=56
ESS- Baseline	11.36±5.55 (11), 0 -24, N=1298	10.54±5.48 (10), 0 - 22, N=52
Female	24% (355)	17.9% (10)
White	95.8% (1407)	93% (53)
Hispanic or Latino	1.9% (28)	1.8% (1)

Note: Format for numeric variables: Mean±SD (Median) Range

[1] Includes only patients with data related to AHI, ESS, therapy use, quality of life at annual visit

After initial therapy optimization, patients were followed by annual visits to assess effectiveness of the therapy with PSG or home sleep apnea testing (HSAT) and to provide necessary device setting adjustments. The registry captures data on each enrolled patient through their first annual visit. However, the visit window for the first annual visit can be up to 2 years post-implant to allow patients to get full therapy optimization. Table 3 below provides data on the final visit AHI, change in AHI from baseline, and responder rate.

Table 3: AHI Outcomes by Baseline AHI

Variable	AHI≤65	65<AHI≤100 [1]	p-value	Type of Test
Final AHI	15.6±14.8 (11.3), 0-96.2, N=1138	18.77±18.82 (11.9), 0- 70, N=39	0.66	Wilcoxon Test
Change in AHI - Baseline to Final	18.86±16.89 (18.5), -46.3 - 64.9, N=1138	54.79±20.26 (60.8), 4.8 - 92.3, N=39	<0.001	Students t-test
Responder - Sher	64.3% (732)	66.7% (26)	0.87	Fisher's Exact Test
Nonresponder-Sher	35.7% (406)	33.3% (13)		
Final ESS	6.88±4.54 (6), 0 - 23, N=1231	6.36±4.74 (5), 0 - 20, N=45	0.31	Wilcoxon Test
Change in ESS – Baseline to Final	4.53±5.21 (4), -13 - 23, N=1108	3.98±4.8 (4), -6 - 20, N=42	0.47	Student's t-test

Note: Format for numeric variables: Mean±SD (Median) Range
[1] Includes only patients with AHI and/or ESS data reported at the annual visit

At annual visit follow up (up to 2 years after treatment initiation with the Inspire UAS) there was no statistically significant difference observed in final AHI and responder rate between the groups with baseline AHI ≤65 (64.3%) and AHI>65 (66.7%). Thus, both groups received similarly effective treatment for their OSA. Given this finding, it follows that there was a significant difference when comparing reduction in AHI for these groups, with patients that had an AHI>65 at baseline showing greater reduction in AHI.

Further analysis of the ADHERE data similarly showed change from baseline to final ESS for both AHI groups, on average. There also was not a statistical difference in Final ESS or Change in ESS when both AHI groups were compared with each other. Thus, sleepiness symptoms were similar in both groups.

The safety profile reported in the population with baseline 65<AHI≤100 was similar to that of the AHI≤65 patient population. Table 4 and Table 5 summarize AEs in this population. No unanticipated adverse events were identified. The procedure related adverse event analysis includes all patients enrolled in the registry and implanted with the UAS System as of July 22, 2022 while prior Tables include only patients that completed the final visit.

Table 4: Procedure Adverse Events by Seriousness and Baseline AHI

Procedure AEs	AHI≤65 (N=3572)	65<AHI≤100 (N=123)
	Subjects with Events	Subjects with Events
Total	131 (3.7%)	3 (2.4%)
Serious	24 (0.7%)	0 (0%)
Non-Serious	105 (2.9%)	3 (2.4%)
Unrelated	2 (0.1%)	0 (0%)

Table 5 below includes all Adverse Events for patients who had follow-up visit completed.

Table 5: Follow-up Adverse Events by Seriousness and Baseline AHI

Follow-Up AEs	AHI≤65 (N=1483)	65<AHI≤100 (N=57)
	Subjects with Events	Subjects with Events
Total	432 (29.1%)	21 (36.8%)
Serious	42 (2.8%)	1 (1.8%)
Non-Serious	404 (27.2%)	20 (35.1%)
Unrelated	3 (0.2%)	0 (0%)

Table 6: Procedure Adverse Events by Characteristics and Baseline AHI

Characteristics	AHI≤65 (N=3572)	65<AHI≤100 (N=123)
	Subjects with Events	Subjects with Events
Serious Adverse Events		
Total	**24 (0.7%)**	**0 (0%)**
Revisions	13 (0.4%)	0 (0%)
Tachycardia	2 (0.1%)	0 (0%)
Pneumothorax	1 (0.03%)	0 (0%)
Infection	1 (0.03%)	0 (0%)
Hematoma	1 (0.03%)	0 (0%)
Hypotension	1 (0.03%)	0 (0%)
Rhabdomyolysis	1 (0.03%)	0 (0%)
Intraoperative arrest/bradycardia	1 (0.03%)	0 (0%)
Cervical Swelling with submandibular hematoma	1 (0.03%)	0 (0%)
Chest pain with Tachycardia	1 (0.03%)	0 (0%)
Bradycardia	1 (0.03%)	0 (0%)
Nonserious Adverse Events		
Total	**105 (2.9%)**	**3 (2.4%)**
Hematoma	14 (0.4%)	0 (0%)
Intraoperative bleeding	10 (0.3%)	0 (0%)
Speech Difficulties	7 (0.2%)	1 (0.8%)
Headache	6 (0.2%)	1 (0.8%)
Tongue weakness	6 (0.2%)	1 (0.8%)
Incision discomfort/irritation	5 (0.1%)	0 (0%)
Pneumothorax	5 (0.1%)	0 (0%)

Characteristics	AHI≤65 (N=3572)	65<AHI≤100 (N=123)
	Subjects with Events	Subjects with Events
Nonserious Adverse Events		
Neuropraxia	5 (0.1%)	0 (0%)
Tongue discomfort/irritation	4 (0.1%)	0 (0%)
Chest pain	4 (0.1%)	0 (0%)
Seroma	4 (0.1%)	0 (0%)
Infection	3 (0.1%)	1 (0.8%)
Lip weakness	3 (0.1%)	0 (0%)
Postoperative bleeding	3 (0.1%)	0 (0%)
Ecchymosis	3 (0.1%)	0 (0%)
Edema	3 (0.1%)	0 (0%)
Facial Swelling	3 (0.1%)	0 (0%)
Nerve Weakness	2 (0.1%)	0 (0%)
Urinary retention	2 (0.1%)	0 (0%)
Tongue deviation	2 (0.1%)	0 (0%)
Sore throat	2 (0.1%)	0 (0%)
Postoperative desaturation	2 (0.1%)	0 (0%)
Atrial fibrillation	2 (0.1%)	0 (0%)
Intraoperative nerve repositioning	1 (0.03%)	0 (0%)
Cuff placement challenges	1 (0.03%)	0 (0%)
Discomfort – swallowing	1 (0.03%)	0 (0%)
Allergic reaction at incision site	1 (0.03%)	0 (0%)
Tongue movement change	1 (0.03%)	0 (0%)
Neck pain	1 (0.03%)	0 (0%)
Difficult dissection	1 (0.03%)	0 (0%)
IPG reposition	1 (0.03%)	0 (0%)

Conversion disorder	1 (0.03%)	0 (0%)
Characteristics	**AHI≤65 (N=3572)**	**65<AHI≤100 (N=123)**
	Subjects with Events	**Subjects with Events**
Nonserious Adverse Events		
Cervical Swelling	1 (0.03%)	0 (0%)
Eye pain	1 (0.03%)	0 (0%)
Technical Challenges	1 (0.03%)	0 (0%)
Dysphagia	1 (0.03%)	0 (0%)
Wound Dehiscence	1 (0.03%)	0 (0%)
Discomfort – IPG	1 (0.03%)	0 (0%)
Neck swelling	1 (0.03%)	0 (0%)
Bradycardia	1 (0.03%)	0 (0%)
Incision swelling	1 (0.03%)	0 (0%)
Mouth pain	1 (0.03%)	0 (0%)
Nerve Damage	1 (0.03%)	0 (0%)
Hypotension	1 (0.03%)	0 (0%)

Table 7: Follow-up Adverse Events by Characteristics and Baseline AHI

Characteristics	AHI≤65 (N=1483)	65<AHI≤100 (N=57)
	Subjects with Events	Subjects with Events
Serious Adverse Events		
Total	42 (2.8%)	1 (1.8%)
Revisions	38 (2.6%)	1 (1.8%)
Swallowing, Chewing and Talking not possible immediately after surgery	1 (0.1%)	0 (0%)
Sore tongue, difficulty talking while Inspire is off and attacking pain in left lower jaw	1 (0.1%)	0 (0%)
System Explant	1 (0.1%)	0 (0%)
Unspecified	1 (0.1%)	0 (0%)
Nonserious Adverse Events		
Total	404 (27.2%)	20 (35.0%)
Stimulation related discomfort	181 (12.2%)	11 (19.3%)
Other device/therapy related event	81 (5.5%)	2 (3.5%)
Insomnia/arousal	80 (5.4%)	8 (14.0%)
Discomfort (incision/scar)	64 (4.3%)	0 (0%)
Other discomfort	61 (4.1%)	4 (7.0%)
Tongue abrasion	43 (2.9%)	3 (5.3%)
Other procedure-related event	41 (2.8%)	4 (7.0%)
Discomfort (device)	26 (1.8%)	3 (5.3%)
Swallowing or speech related	21 (1.4%)	0 (0%)
Tongue Weakness	10 (0.7%)	0 (0%)
Infection	8 (0.5%)	0 (0%)

B. BMI ADHERE DATA ANALYSIS

Table 8 provides demographic characteristics of patients included in the BMI analysis from ADHERE registry. Table 9 provides the outcomes analysis at the final visit for these same groups.

Table 8: Demographic Variables by Baseline BMI (BMI ≤32 vs. 32<BMI ≤40)

Variable	BMI≤32	32<BMI≤40[1]
N	1218 (81.40.%)	279 (18.6%)
Age	60.34±10.73 (61), 21 - 85, N=1212	59.44±10.04 (60), 28 - 81, N=279
AHI- Baseline	35.5±14.26 (32.7), 15 - 102.9, N=1218	38.94±16.97 (36.5), 15.1 - 118.7, N=279
BMI- Baseline	27.79±2.8 (28.18), 17.71 - 32, N=1218	34±1.64 (33.64), 32.01 - 39.95, N=279
ESS- Baseline	11.39±5.52 (11), 0 - 24, N=1069	11.17±5.61 (11), 0 - 24, N=248
Female	24.1% (292)	23.8% (66)
White	95.6% (1157)	96% (263)
Hispanic or Latino	2.2% (26)	1.1% (3)

Note: Format for numeric variables: Mean±SD (Median), Range.

[1] Includes only patients with data related to AHI, ESS, therapy use, or quality of life at annual visit.

Table 9: BMI Outcomes by Baseline BMI (BMI ≤32 vs. 32<BMI≤40)

Variable	BMI≤32	32<BMI≤40 [1]	p-value	Type of Test
Final AHI	15.34±14.44 (10.95), 0 – 83.8, N=930	17.31±16.83 (12.95), 0 – 96.2, N=216	0.09	Wilcoxon Test
Change in AHI - Baseline to Final	20.09±18.11 (19.25), -41.6 - 92.3, N=930	20.57±19.58 (18.95), -46.3 - 103.2, N=216	0.74	Students t-test
Responder - Sher	65.1% (605)	60.6% (131)	0.24	Fisher's Exact Test
Nonresponder - Sher	34.9% (325)	39.4% (85)		
Final ESS	6.87±4.57 (6), 0 - 23, N=1012	6.8±4.53 (6), 0 - 22, N=236	0.79	Wilcoxon Test
Change in ESS – Baseline to Final	4.59±5.08 (4), -13 - 23, N=906	4.29±5.78 (4), -13 - 19, N=217	0.47	Students t-test

Note: Format for numeric variables: Mean±SD (Median), Range.

[1] Includes only patients with AHI and/or ESS data reported at the annual visit

There is no statistically significant difference between the BMI groups (BMI≤ 32 vs. BMI>32) in regard to Final AHI and Change in AHI, nor response rate from Baseline to Final Visit. The response rate of both low and high BMI groups is higher than response rates (~50%) for other typical surgical options for OSA. When the data on the BMI groups was further analyzed using groups of BMI≤32, 32<BMI≤35, 35<BMI≤40, it was noted that the Sher responder rate was not statistically different across the three groups.

The safety profile reported in the BMI≤40 population was similar to that of the BMI≤32 patient population. Table 8 summarizes AEs in this population.

Table 10: Procedure Adverse Events by Seriousness and Baseline BMI

Procedure AEs	BMI≤32 (N=2832)	32<BMI≤40 (N=748)
	Subjects with Events	Subjects with Events
Total	105 (3.7%)	24 (3.2%)
Serious	19 (0.7%)	5 (0.7%)
Non-Serious	84 (3%)	19 (2.5%)
Unrelated	2 (0.1%)	0 (0%)

Table 11: Follow-up Adverse Events by Seriousness and Baseline BMI

Procedure AEs	BMI≤32 (N=1218)	32<BMI≤40 (N=279)
	Subjects with Events	Subjects with Events
Total	351 (28.8%)	91 (32.6%)
Serious	32 (2.6%)	9 (3.2%)
Non-Serious	331 (27.2%)	84 (30.1%)
Unrelated	1 (0.1%)	2 (0.7%)

Table 12: Procedure Adverse Events by Characteristics and Baseline

Characteristic	BMI≤32 (N=2832)	32<BMI≤40 (N=748)
	Subjects with Events	Subjects with Events
Serious Adverse Events		
Total	19 (0.7%)	5 (0.7%)
Revisions	12 (0.4%)	1 (0.1%)
Tachycardia	2 (0.1%)	0 (0%)
Pneumothorax	1 (0.04%)	0 (0%)
Hypotension	1 (0.04%)	0 (0%)
Intraoperative arrest/bradycardia	1 (0.04%)	0 (0%)
Cervical Swelling with submandibular Hematoma	1 (0.04%)	0 (0%)

Characteristic	BMI≤32 (N=2832)	32<BMI≤40 (N=748)
	Subjects with Events	Subjects with Events
Serious Adverse Events		
Bradycardia	1 (0.04%)	0 (0%)
Infection	0 (0%)	1 (0.1%)
Hematoma	0 (0%)	1 (0.1%)
Rhabdomyolysis	0 (0%)	1 (0.1%)
Chest pain with Tachycardia	0 (0%)	1 (0.1%)
Nonserious Adverse Events		
Total	84 (3%)	19 (2.5%)
Hematoma	12 (0.4%)	2 (0.3%)
Interoperative bleeding	9 (0.3%)	1 (0.1%)
Speech Difficulties	8 (0.3%)	0 (0%)
Headache	6 (0.2%)	1 (0.1%)
Tongue Weakness	6 (0.2%)	1 (0.1%)
Pneumothorax	5 (0.2%)	0 (0%)
Infection	4 (0.1%)	1 (0.1%)
Incision discomfort/irritation	4 (0.1%)	1 (0.1%)
Neuropraxia	4 (0.1%)	1 (0.1%)
Postoperative bleeding	3 (0.1%)	0 (0%)
Seroma	3 (0.1%)	1 (0.1%)
Tongue Discomfort/irritation	2 (0.1%)	2 (0.3%)
Unknown	2 (0.1%)	2 (0.3%)
Nerve weakness	2 (0.1%)	0 (0%)
Chest pain	2 (0.1%)	0 (0%)
Ecchymosis	2 (0.1%)	0 (0%)

Characteristic	BMI≤32 (N=2832)	32<BMI≤40 (N=748)
	Subjects with Events	Subjects with Events
Nonserious Adverse Events		
Sore throat	2 (0.1%)	0 (0%)
Atrial fibrillation	2 (0.1%)	0 (0%)
Lip weakness	1 (0.04%)	1 (0.1%)
Cuff placement challenges	1 (0.04%)	0 (0%)
Discomfort - swallowing	1 (0.04%)	0 (0%)
Allergic reaction at incision site	1 (0.04%)	0 (0%)
Tongue movement change	1 (0.04%)	0 (0%)
Neck pain	1 (0.04%)	0 (0%)
Urinary retention	1 (0.04%)	0 (0%)
IPG reposition	1 (0.04%)	0 (0%)
Conversion Disorder	1 (0.04%)	0 (0%)
Cervical Swelling	1 (0.04%)	0 (0%)
Tongue Deviation	1 (0.04%)	1 (0.1%)
Edema	1 (0.04%)	1 (0.1%)
Facial Swelling	1 (0.04%)	1 (0.1%)
Eye pain	1 (0.04%)	0 (0%)
Postoperative desaturation	1 (0.04%)	1 (0.1%)
Technical Challenges	1 (0.04%)	0 (0%)
Discomfort - IPG	1 (0.04%)	0 (0%)
Neck swelling	1 (0.04%)	0 (0%)
Bradycardia	1 (0.04%)	0 (0%)
Incision swelling	1 (0.04%)	0 (0%)
Mouth pain	1 (0.04%)	0 (0%)

Characteristic	BMI≤32 (N=2832)	32<BMI≤40 (N=748)
	Subjects with Events	Subjects with Events
Nonserious Adverse Events		
Nerve Damage	1 (0.04%)	0 (0%)
Hypotension	1 (0.04%)	0 (0%)
Intraoperative nerve repositioning	0 (0%)	1 (0.1%)
Difficult dissection	0 (0%)	0 (0%)
Dysphagia	0 (0%)	1 (0.1%)
Wound Dehiscence	0 (0%)	1 (0.1%)

Table 13: Follow-up Adverse Events by Characteristics and Baseline BMI

Characteristics	BMI≤32 (N=1218)	32<BMI≤40 (N=279)
	Subjects with Events	Subjects with Events
Serious Adverse Events		
Total	32 (2.6%)	9 (3.2%)
Revisions	29 (2.4%)	8 (2.9%)
Swallowing, chewing and talking not possible immediately after surgery	1 (0.08%)	0 (0%)
Sore tongue, difficulty talking while Inspire is off and attacking pain in left lower jaw	1 (0.08%)	0 (0%)
System Explant	1 (0.08%)	0 (0%)
Unspecified	0 (0%)	1 (0.5%)

Characteristics	BMI≤32 (N=1218)	32<BMI≤40 (N=279)
	Subjects with Events	Subjects with Events
Nonserious Adverse Events		
Total	331 (27.2%)	84 (30.1%)
Stimulation related discomfort	157 (12.9%)	29 (10.4%)
Other device/therapy related event	69 (5.7%)	12 (4.3%)
Insomnia/arousal	67 (5.5%)	20 (7.2%)
Discomfort (incision/scar)	56 (4.6%)	7 (2.5%)
Other discomfort	49 (4%)	15 (5.4%)
Other procedure related event	36 (3%)	9 (3.2%)
Tongue abrasion	30 (2.5%)	16 (5.7%)
Discomfort (device)	24 (2%)	4 (1.4%)
Swallowing or speech related	16 (1.3%)	5 (1.8%)
Tongue weakness	8 (0.7%)	2 (0.7%)
Infection	6 (0.5%)	2 (0.7%)

Note: Format for Subjects with Events: Number of subjects with at least one event (% of subjects per BMI group)

This evaluation demonstrated that patients with baseline AHI greater than 65 and less than 100 and BMI greater than 32 and less than 40 meet pre-specified criteria used in the STAR trial to demonstrate effectiveness of the Inspire UAS.

C. Pediatric Extrapolation

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

D. 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. Inspire provided this information in the original PMA which was used as evidence to support approval.

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 and Respiratory Therapy Devices 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 effectiveness results from the ADHERE registry in patients with 65<AHI≤100 and 32<BMI≤40 showed consistent results with those of the STAR trial subjects. Patients with AHI≤100 and BMI≤40 demonstrated significant reductions in the severity of OSA and improvements in quality of life.

B. Safety Conclusions

The safety profile of Inspire therapy was demonstrated in STAR trial data and post-approval studies through 60 months of extended follow up. The incidence of device or procedure related serious adverse events within 18 months was low (1.6%). While non-serious adverse events were frequent, 75% of such events were fully resolved primarily with either medication, device reprogramming or other measures. The device-related serious AE rate was relatively low (6.3%) over the 5-year follow up. All related serious AEs involved revisions or replacements to the system or components that have resolved without issue.

The ADHERE registry data demonstrated a consistent safety profile for patients with a baseline AHI≤100 with that of the STAR trial. When comparing the AHI≤65 and 65≤AHI≤100 groups there was no significant difference in the rate of serious or non-serious adverse events and there was no new adverse event noted in the analysis.

OSA patients with baseline 32<BMI ≤40 also demonstrated consistent result with the STAR trial. Rhabdomyolysis was reported in 1 patient in the 32<BMI≤40 group and all other adverse events were consistent with Inspire's labeling and prior clinical experience.

C. Benefit-Risk Determination

OSA is a sleep disorder characterized by recurrent airway narrowing or closures during sleep, OSA can result in severe complications if left untreated. These include neurobehavioral impairment, impaired memory, poor concentration, behavioral problems, cardiovascular comorbidities, reduced quality of life, metabolic disorder, and depression.

The most common first line treatment for OSA is CPAP therapy. However, multiple CPAP clinical trials have shown adherence at less than 50%, such as the APPLES study demonstrated only 39% of trial subjects were compliant to CPAP therapy 6-months after first being prescribed.[i] Alternative effective therapies to CPAP for patients with AHI>65 and BMI ≤ 40 is limited to upper airway surgeries and Mandibular Advancement Devices (MAD) intended to enlarge the airway.

Upper airway surgeries often have response rates less than 50%, and even lower response in patients with higher AHI and BMI[ii,iii]. Airway surgeries also have higher post-operative

complication rates than Inspire UAS, which may limit adoption of upper airway surgery in more severe OSA and obese patients[iv].

Oral Appliances also have challenges in this population[v]. Since 2012, it has been widely accepted that oral appliances are primarily indicated for mild-to-moderate OSA. Further, the Agency for Healthcare Research and Quality has also concluded that the clinical evidence for upper airway surgeries efficacy is insufficient.[vi] Therefore, the clinical needs of the CPAP-intolerant OSA patient population with AHI>65 and/or BMI>32 were not adequately met by currently available treatment options. Inspire therapy provides an alternative treatment option for OSA patients who are not effectively treated by current treatment options.
Given the seriousness of the co-morbidities associated with untreated OSA, and the low rate of CPAP compliance, the magnitude of Inspire therapy's benefits is substantial for OSA patient population with 65<AHI≤100 and/or 32<BMI≤40.

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

- Reduction in severity of obstructive sleep apnea
- Preserved sleep quality
- Improved subjective quality of life
- Potential improvement in therapy usage when compared to CPAP usage.

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

Inspire therapy demonstrated a sufficient safety profile to support PMA approval in 2014 and continued to do so in the post-approval study through 60 months of extended follow up (P130008/R012).

When considering the adverse events from ADHERE for patients with a baseline 65<AHI≤100 or baseline 32<BMI≤40, these groups have similar safety profiles to the patient groups with baseline 15<AHI<65 or BMI<32, respectively.

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
- Chance of revisions
- Battery replacements at 7-10 year intervals
- Increased risk of lead breakage/migration or damage to IPG, due to participation in vigorous physical activities/contact sports in the 18to 21-year-old population
- Permanent scarring
- Keloid formation particularly in patients of pigmented skin types

- Unnecessary intervention due to possibility of spontaneous remission of OSA

Common Adverse Events include:

- Tongue soreness/abrasion/weakness
- Stimulation discomfort/high stimulation
- Skin scratching/scarring
- 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 between Inspire UAS and CPAP were done in the ADHERE registry, showing 91% of patients preferred Inspire better than CPAP, and the high compliance and usage hours rate suggests that patients tolerated the risks well.

In conclusion, the data summarized above, for the expanded use of the Inspire Upper Airway Stimulation System in the treatment of severe obstructive sleep apnea for patients with 65<AHI≤100 and/or 32<BMI≤40 who:

- have been confirmed to fail positive airway pressure (PAP) therapy or who are intolerant to PAP or
- who have been contraindicated for or not effectively treated by adenotonsillectomy, and
- who have absence of complete concentric collapse at the level of the soft palate,

was found to be safe and effective and the probable benefits outweigh the probable risks.

Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

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. 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 (as reflected by AHI

and improved subjective quality of life. The safety profile of Inspire therapy in patients with 65<AHI≤100 and/or 32<BMI ≤40 was comparable to STAR trial with low rate of serious adverse events that resulted in revision, repositioning, or replacement of the Inspire system. Compliance with device usage was also similar to STAR Trial. Given the limited treatment options for OSA in CPAP intolerant patients, the adverse consequences associated with untreated, progressive OSA and the 50% compliance rate with PAP therapy, the probable benefits of Inspire® therapy for OSA patients with 65<AHI≤100 and/or 32<BMI≤40 outweigh the probable risks.

XIII. CDRH DECISION

CDRH issued an approval order on June 8, 2023. The final clinical conditions of approval cited in the approval order are described below.

In addition to the Annual Report requirements, you must provide the following data in post approval study reports (PAS).You must obtain approval of your post-approval study (PAS) protocol(s) within 60 days from the date of this order. Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study described below. Your PMA supplement should be clearly labeled as a "PMA Post-Approval Study Protocol" as noted below and submitted to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

The Inspire® UAS High AHI High BMI New Enrollment PAS will be a multi-center, two arms, prospective post-approval study to provide an ongoing safety and effectiveness assessment of Inspire® UAS in patients ≥18. One arm of the proposed PAS will include patients with severe sleep apnea (65<AHI≤100) who are candidates for Inspire® UAS therapy. The other arm will include patients with high BMI (32≤BMI≤40) who are candidates for Inspire UAS therapy. A total of 70 patients (35 in each arm) at a minimum of 5 qualified centers will be implanted and followed through 5 years of follow-up, with interim visits at pre-implant, post-implant, 6 months and yearly thereafter through 5 years of post-implant follow-up. Safety endpoints will be collected for device and procedure related adverse events, including but not limited to device explants, revision surgeries, malfunctions (relatedness to sport/activity), pneumothorax, and infection. Other non-serious adverse events to be collected include: tongue weakness, swallowing or speech related, discomfort (incision/scar), discomfort (device), post-operative, stimulation-related discomfort, isolated stimulation sensation events, tongue abrasion, dry mouth, headaches, intermittent fatigue, audible buzzing and insomnia/arousal. Effectiveness endpoints will also be collected to evaluate: AHI, ODI, T90, ESS. For patients within the high BMI cohort, Body Mass Index information should be monitored for the duration of the study.

From the date of study protocol approval, you must meet the following timelines for your PAS:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months

- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of your PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

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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