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.
5500 Wayzata Blvd., Suite 1600
Golden Valley, MN 55416

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130008/S039

Date of FDA Notice of Approval: April 14, 2020

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. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Inspire® UAS system to include adolescent patients between 18 and 21 years of age.

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 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 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 and 21with moderate to severe OSA (15≤AHI≤65) 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
- 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® 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.

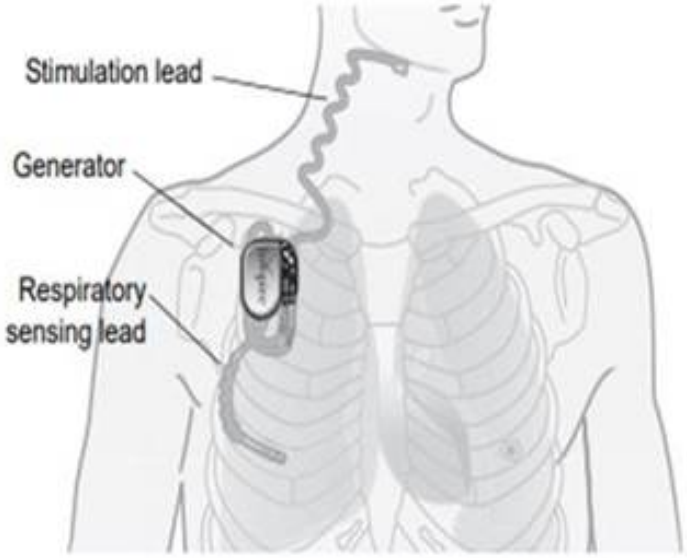

Figure 1: Inspire® system components and implant location

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 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 4340 Sensing Lead	The sensing lead is placed in the intercostal space and contains a piezoelectric differential pressure sensor for detecting respiratory signals.
External Components:	
Model 2500 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® UAS device has been commercially available in the U.S. since April 30, 2014 for treatment of adult patients 22 years and older. The device received CE Mark approval on October 20, 2010 and has been commercially available in the European Union since that time. The device also received approval for use in Japan on June 28, 2018.

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)
- Insomnia
- Pneumothorax

For the specific adverse events 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 in indications for use.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The clinical information below represents the additional information provided within this PMA Supplement in support of an expansion of the indications for use of this device to include a sub-population of older adolescents. This information in combination with the extensive clinical experience with the device in adult patients (P130008), which can be extrapolated to the pediatric patients being incorporated into the indications for use, is sufficient to demonstrate the safety and effectiveness of this device in that pediatric sub-population.

1. STAR Trial (adult study)

The primary study to support expansion in indications for use is the STAR trial in adult patients which was used to support the original PMA. A summary is provided below but additional details are available in the SSED of the original approval (P130008).

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® UAS therapy turned OFF for at least five (5) days leading up to the PSG study.

As demonstrated in the Table 2 below of the STAR trial population demographics, the median age was 55 and the minimum age was 31.

Table 2: 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*		

Safety of the Inspire® UAS system was determined through assessment of all reported adverse events. There was no formal statistical hypothesis. A detailed reporting of the safety information is available in the original SSED and currently approved labeling for the Inspire® UAS.

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).

The STAR Pivotal Trial met all primary and secondary effectiveness outcomes. 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%.

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.

2.Pediatric Down's Syndrome Study

Inspire has referenced the data from an ongoing feasibility study on use of Inspire® UAS in pediatric Down's syndrome patients. The most recent published update from this ongoing study included twenty (20) patients with 2 month data[1]. A prior publication of the same study also reported on 6- and 12-month follow-up results of the first six implanted patients[2]. The median age of implanted subjects was 16. The median baseline AHI was 24 events per hour and median preoperative OSA-18 was 3.56.

Safety

The primary outcome was to assess safety and monitor for adverse events. Based on interim data reported, safety results in the pediatric study population are consistent with those of the adult STAR trial population.

Effectiveness

The clinical feasibility study did not have a pre-specified effectiveness endpoint. Secondary outcomes included efficacy in reducing AHI, adherence to therapy and a change in validated quality of life (QOL) instrument (i.e. OSA-18).

Twenty participants completed the 2-month PSG study, with median percent reduction in AHI of 85% (interquartile range = 75%–92%). There was a median change in the OSA-18 score of 1.15, indicating a moderate, yet significant change.

A prior publication reporting on results from 6 subjects with longer term 6-month and 12-month follow-up indicated that patients demonstrated persistent improvement in AHI, with 56% to 85% reduction in AHI compared to baseline.

Limitations of the pediatric data

The data from this study is a small sample size and study is still ongoing. Additionally, the sub-population of patients with Down's syndrome in this study does not represent the intended general pediatric population. However, the results to date have demonstrated consistency with the adult study and have not identified any new safety signals.

3.Post-Approval Experience

As part of the conditions of approval of the original PMA, two post-approval studies were initiated. One study was a continuation of the original IDE cohort of the STAR trial out to 5 years. A new enrollment study was also initiated in a new cohort of patients to be

studied out to 5 years. In addition, Inspire has established a registry (ADHERE) which has been considered as part of this evaluation.

There have been no unanticipated adverse events identified in the post-approval information evaluated. The safety and effectiveness information reported were consistent with the original PMA data.

4.Pediatric Extrapolation

In this premarket application, existing adult clinical data was leveraged to support the reasonable assurance of safety and effectiveness of the proposed device in the pediatric sub-population of adolescents age 18 to 21. The leveraged data used to support the use of the device in a select group of older adolescents are discussed in more detail in Section X above.

The findings from the adult study including post-approval experience, coupled with the findings from the pediatric study in patients with Down's syndrome, can be partially extrapolated to a select group of older adolescents. This is supported by the lowering of AHI values as well as the OSA-18 scoring by caregivers. In terms of safety, the clinical data (Adult Trial and Pediatric Study of Down's Syndrome) presented may be leveraged in part to older adolescent patients, but not to the younger pediatric population where the impact of growth and development on the device may be different.

There is no data to support use of Inspire® UAS in a general pediatric population less than 18 years old. Additionally, published literature data[3, 4, 5, 6, 7] indicates there may be a significant chance for spontaneous remission of OSA in these patients who are still growing and may experience changes to their airway and disease characteristics.

Consideration was also given to whether the data could be used to support a sub-population of patients with Down's Syndrome. However, based on the limited data currently available from an ongoing feasibility study, it was determined that completion of this study and collection of the additional data will be required before a determination can be made as to whether there is reasonable assurance of safety and effectiveness in this sub-population.

5.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 the primary evidence to support approval.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None

XII. 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

1.Effectiveness Conclusions

In the adult pivotal study, Inspire® UAS 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. Inspire® UAS therapy has demonstrated a reasonable assurance of effectiveness for use in treating moderate to severe obstructive sleep apnea in 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. Interim data from the pediatric feasibility study in Down's syndrome patients has also demonstrated consistent results with the adult trial, and provides further support for extrapolation to a subset of older adolescents age 18 to 21.

2.Safety Conclusions

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

The device related adverse events (and the probability of experiencing an AE 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.

Interim safety data available from the pediatric feasibility study in Down's syndrome patients did not identify any additional safety concerns.

3.Benefit-Risk Determination

The probable benefits of the device are also 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

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

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 7-10 year intervals
- Increased risk of lead breakage/migration or damage to IPG, due to participation in vigorous physical activities/contact sports in 18-21 population
- Unknown consequences in the general pediatric population due to lack of data in the intended population
- Unnecessary intervention due to possibility of spontaneous remission of OSA

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 moderate to severe obstructive sleep apnea in a subset of older adolescents 18 to 21 years of age and older, who have been confirmed to fail positive airway pressure (PAP) therapy or who are intolerant to PAP, who have already undergone appropriate treatment for OSA (e.g. adenotonsillectomy, behavioral therapy for PAP adherence) and who have absence of complete concentric collapse at the level of the soft palate, the probable benefits outweigh the probable risks. This population may experience remission of OSA but less likely compared with younger children.

4. 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.

XIV. CDRH DECISION

CDRH issued an approval order on April 14, 2020. The final clinical conditions of approval cited in the approval order are described below.

The Inspire® UAS New Enrollment PAS will be a multi-center, single-arm, prospective post-approval registry to provide an ongoing safety and effectiveness assessment of Inspire® UAS in pediatric patients age 18 to 21, with moderate to severe sleep apnea, who are candidates for Inspire® UAS therapy. A total of 60 patients 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, tongue abrasion, insomnia/arousal. Effectiveness endpoints will also be collected to evaluate: AHI, ODI, T90, ESS.

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

XV. 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.

XVI. REFERENCES

1. Caloway CL, Diercks GR, Keamy D, et al. Update on hypoglossal nerve stimulation in children with down syndrome and obstructive sleep apnea. *The Laryngoscope.* Epub 2019 Jun 20. Doi: 10.1002/lary.28138

2. Diercks GR, Wentland C, Keamy D, et al. Hypoglossal Nerve Stimulation in Adolescents with Down Syndrome and Obstructive Sleep Apnea. *JAMA Otolaryngol Head Neck Surg*. 2018;144(1):37–42. doi:10.1001/jamaoto.2017.1871

3. Spilsbury JC, Storfer-Isser A, Rosen CL, Redline S. Remission and incidence of obstructive sleep apnea from middle childhood to late adolescence. *Sleep*. 2015;38(1):23–29. Published 2015 Jan 1. doi:10.5665/sleep.4318

4. Chan KC, Au CT, Hui LL, Ng SK, Wing YK, Li AM (2019 Jul) How OSA evolves from childhood to young adulthood: natural history from a 10-year follow-up study. Chest 156(1):120–130)

5. Edward O. Bixler, Julio Fernandez-Mendoza, Duanping Liao, Susan Calhoun, Sol M. Rodriguez Colon, Jordan Gaines, Fan He, Alexandros N. Vgontzas: Natural history of sleep disordered breathing in prepubertal children transitioning to adolescence.Respiratory Journal 2016 47: 1402-1409; DOI: 10.1183/13993003.01771-2015

6. Goodwin JL, Vasquez MM, Silva GE, Quan SF. Incidence and remission of sleep-disordered breathing and related symptoms in 6- to 17-year old children--the Tucson Children's Assessment of Sleep Apnea Study. *J Pediatr*. 2010;157(1):57–61. doi:10.1016/j.jpeds.2010.01.033

7. Chervin RD, Ellenberg SS, Hou X, et al. Prognosis for Spontaneous Resolution of OSA in Children. *Chest*. 2015;148(5):1204–1213. doi:10.1378/chest.14-2873