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/S089

Date of FDA Notice of Approval: March 20, 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 indication for the Inspire UAS system to include adolescent patients between 18 and 21 years of age, and this supplement, P130008/S089 expands the indication further to include pediatric patients with Down syndrome between 13 and 18 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 21 with moderate to severe OSA (15≤AHI≤65), and pediatric patients ages 13 to 18 years with Down syndrome and severe OSA (10≤AHI≤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
- 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.

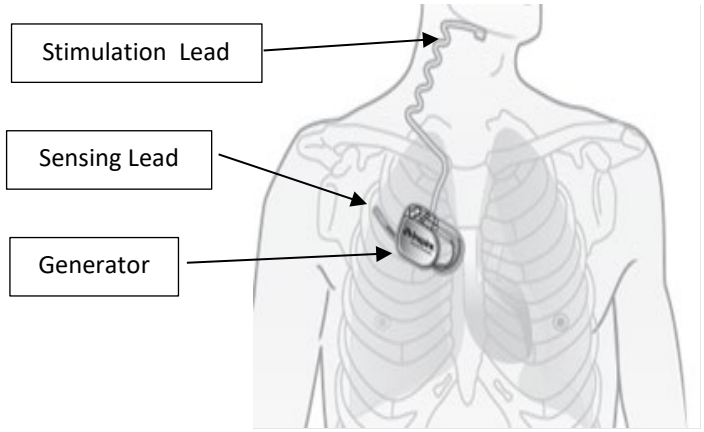

Figure 1: Inspire® system components and implant location

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. The expandable stimulation lead allows for body growth.
Model 4323 Sensing Lead	The sensing lead is placed in the intercostal space and contains a piezoelectric differential pressure sensor for detecting respiratory signals. The expandable sensing lead allows for body growth.
External Components:	
Model 2580 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 obstructive sleep apnea in pediatric Down Syndrome patients 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 such as adenotonsillectomy 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. 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, and in Australia on 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 cheloid formation from implantation
- Cellulitis at surgical site
- Insomnia
- Pneumothorax

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

The clinical information summarized below was used in support of the expansion of the indications for use of this device to include Pediatric patients with Down syndrome. This information was found to be sufficient to demonstrate the safety and effectiveness of this device in the proposed Pediatric Down syndrome patient population.

1. Pediatric Down Syndrome Study

The data from a pediatric Down syndrome study was used to support the expanded IFU. This study was a prospective single arm multicenter study with a 12 month follow up. Forty-two (42) subjects were implanted with the Inspire UAS . Table.2 provides demographic characteristics of patients. Eligibility criteria for the study included:

- Down syndrome patients, 10 to 21 years of age, with persistent severe OSA defined as 10<AHI<50
- Previous adenotonsillectomy
- CPAP intolerance
- Absence of complete concentric collapse (CCC)
- Central sleep apneas make up < 25% of total AHI
- BMI < 95th percentile for patient's age per CDC growth curves

Table 2 Demographics of Pediatric Down Syndrome Patients.

Characteristics	Patients, No. (%) (N=42)
Sex	
Male	28 (66.7)
Female	14 (33.3)
Age, y	
10-13	13 (31)
14-17	19 (45.2)
18-21	10 (23.8)
BMI, percentile	
Normal (<85th percentile)	23 (54.8)
Overweight (85th – 95th percentile)	19 (45.2)

Subjects underwent polysomnogram (PSG) studies at 1, 2, 6, and 12 months and also completed OSA-18 and Epworth Sleepiness Scale (ESS) quality of life assessments. The primary efficacy endpoint was change in AHI while the primary safety endpoint was the report of all AEs. Secondary outcomes included percentage of time with oxygen saturation < 90%; the percentage of time with end-tidal carbon dioxide > 50 mm Hg; and OSA-18 and ESS quality of life scores.

The safety profile reported in the pediatric Down syndrome population was similar to that of the adult population (P130008), with the exception of higher readmission rates (5 of 42 patients or 11.9%). The most common complication was temporary tongue or oral discomfort, which occurred in 5 patients (11.9%). Table.2 summarizes AEs in this population.

Table 3 Summary of AEs in Pediatric Patients with Down Syndrome

Characteristics	**Frequency, No. (%)**
Nonserious AEs	
Tongue or oral pain or discomfort	5 (11.9)
Rash at surgical site	4 (9.5)
Acute insomnia	2 (4.8)
Cellulitis at surgical site	2 (4.8)
Cheek swelling	1 (2.4)
Perioperative urinary retention	1 (2.4)
Oral ulcers	1 (2.4)
Postobstructive central hypoventilation	1 (2.4)
Serious AEs	
Readmission	5 (11.9) *
Reoperation	2 (4.8)
Pressure ulcer	1 (2.4)

*Four related to surgery and 1 unrelated to surgery

The effectiveness was reported at 12-month follow-up where a mean decrease of 12.9 (SD 13.2) was observed in AHI. Also, 65.9% of patients (27 of 41) had at least a 50% reduction in AHI and 73.2% (30 of 41) had an AHI of less than 10. There was also 0.8% (SD 3.1%) decrease in these subjects' mean time with oxygen saturation below 90%. Results for 13-18 years subpopulation (N=25) showed reduction in AHI from 24.3 (SD 10.8) in baseline to 11.2 (SD 15) after12-months.

The improvement in quality of life was assessed using OSA-18 survey scores and ESS. At the 12 month follow up, 28 of the 36 (77.8%) patients saw an improvement in their overall OSA-18 score by a mean of 1.8 points (SD 1.2). The ESS showed similar improvement with a mean reduction of 5.1 points (SD 6.9), changing the mean score from baseline of 10.0 to 5.0.

In addition, the study reported improvement in therapy usage with an average nightly duration of 9 hour (SD 1.8) and 40 patients (95.2%) used their upper airway stimulation device for at least 4 hours a night for 70% of the nights during the follow-up time period.

2. STAR Trial (adult study)

The other 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 (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.

Safety of the Inspire UAS system was determined through assessment of all reported adverse events. A detailed reporting of the safety information is available in the original SSED and currently approved labeling for the Inspire UAS. Table.3 summarizes device-related AEs during the first 18 months.

Table 4: Device-Related AEs for STAR trial during the first 18 months

Adverse Events	Number of Subjects with Event (n=126)	Percent of Subjects
Discomfort due to electrical stimulation	59	47%
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 study had two (2) co-primary effectiveness endpoints based on patient-level reductions in the AHI and the oxygen desaturation index (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 at the 12-Month visit 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%. The overall responder rate based on ODI measurements was 75% (94 of 126) with a corresponding lower 97.5% confidence level of 66%. The average reduction in median values of AHI from baseline to 12-months was 68% (29.3 to 9) and for ODI was 70% (25.4 to 7.4).

3. Post-Approval Experience

As part of the conditions of approval of the original PMA, two post-approval studies (PAS) were initiated. One study was a continuation of the original premarket cohort of the STAR trial out to 5 years. The safety and effectiveness information reported in 5-year follow up study were consistent with the original PMA data. The average reduction of AHI from baseline was 52%, 64% and 61% for visits at 12, 36 and 60 months, respectively. The average reduction of ODI from baseline was 52%, 68% and 66% for visits at 12, 36 and 60 months, respectively. There were significant improvements in the QoL as measured by ESS and a mean reduction of 4.4 (SD 5.1), 4.8 (SD 5), 4.4 (SD 5.6), 4.4 (SD 5.3), 4.5 (SD 5.4) and 4.4 (SD 5.) points were observed at 24, 30, 36, 48, 54 and 60 months, respectively.

During the five-year follow-up period in the STAR pivotal trial there were nine related serious AEs in eight (6%) patients resulted in revision/repositioning or replacement of the Inspire system. There were five subject deaths reported during the study, all unrelated to the Inspire device, procedure or therapy. A summary of AEs during the five years is provided in table below.

Table 5: Summary of AEs of STAR trial PAS for up to 5 years

Type of AE	**Number of Events**	**Subjects (%) N=126**
Procedure-related AEs		
Events specifically related to an Incision	52	38 (30.2%)
Post-operative discomfort independent of any surgical incision	42	34 (27%)
Acute tongue weakness	34	23 (18.3%)
Intubation Effects	18	15 (11.9%)
Headache	8	8 (6.3%)
Other post-op symptoms	22	14 (11.1%)
Infection (mild or moderate)	1	1 (0.8%)
Device-related AEs		
Discomfort due to electrical stimulation	142	76 (60.3%)
Tongue abrasion	49	34 (27%)
Mouth dryness	20	19 (15.1%)
Mechanical pain associated with presence of the device	14	14 (11.1%)
Temporary Internal Device Usability or Functionality Complaint	25	21 (16.7%)
Temporary External Device Usability or Functionality Complaint	45	33 (26.2%)
Other acute symptoms*	39	31 (24.6%)
infection (mild or moderate)	1	1 (0.8%)
Serious AEs		
Device Revision	5	4 (3.1%)
Device Replacement	4	4 (3.1%)
Preexisting or independent condition	80	40 (31.7%)
Death	5	5 (4%)
Other	14	11 (8.7%)

Another PAS was a new enrollment study initiated in a new cohort of patients (n=127) to be studied up to 5 years. Of the 127 subjects enrolled and implanted, 96 have completed the ESS and 97 completed the FOSQ assessments for the effectiveness endpoints at 12-month. Improvement in daytime sleepiness is demonstrated by a decrease in ESS from 12.02 (SD 5.39) to 7.62 (SD 5.11). FOSQ score as another QoL improvement parameter showed an increase of 2.05 (SD 4.48) points. Serious AEs reported in 27 patients (21.3 %) which resulted in device explant or revision in 11 patients (8.7%). A total of 112 non-serious AEs were reported for 51 subjects (40.2%). Non-serious AEs in 26 subjects (20.57%) were procedure-related and in 34 subjects (26.8%) were device/therapy-related.

Table 6: Summary of AEs for New Enrollment PAS during the 12 Months

Type of AE	**Number of Events**	**Subjects (%) N=127**
Procedure-related AEs		
Pain or discomfort	13	9 (7.1%)
Incision – Irritation	3	3 (2.4%)
Damage to nerves	2	2 (1.6%)
Wound dehiscence, headache, tongue numbness, speech lisping, scar numbness, hypertrophic scar, hematoma and infection	8	8 (6.4%)
Other	12	9 (7.1%)
Device-related AEs		
Pain or discomfort	24	20 (15.7%)
Mouth dryness	6	6 (4.7%)
Tongue abrasion	5	4 (3.1%)
Tongue movement change, headache, lead migration, speech difficulties and tongue irritation	6	6 (4.7%)
Other	11	9 (7.1%)
Therapy-related AEs		
Pain or discomfort	6	3 (2.4%)
Tongue irritation	1	1 (0.8%)
Infection – urinary tract infection	1	1 (0.8%)
Other	14	9 (7.1%)
Serious AEs		
Device Revision	11	9 (7.1%)
Device Replacement	2	2 (1.6%)
Infection	4	3 (2.4%)
Preexisting, independent condition and others	31	21 (16.5%)

4. Real World Evidence

Inspire also has an ongoing registry called the ADHERE Registry. The ADHERE registry has enrolled 1017 patients from 2016-2019 and 382 patients (74% male; 60 ± 11 years) have completed the 12-month follow up. The safety profile for this registry was found to be comparable to the PAS and no unanticipated adverse events were identified. Effectiveness was 71% and 45% reduction in AHI and ESS at 12 months, respectively.

5. Pediatric Extrapolation

Due to the limited and scattered sample size of pediatric Down Syndrome clinical trial, in order to evaluate the expansion of indications for use of the Inspire UAS device in this new pediatric population i.e., Down Syndrome, an attempt was made to extrapolate existing adult data using FDA's guidance, "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices". The guidance document outlines a roadmap and circumstances to determine whether extrapolation is appropriate and to what extent the data can be borrowed for pediatric inferences. The adult OSA population, and the pediatric OSA patient population with Down syndrome are similarly situated regarding their condition's risks of ineffective treatment and their need for alternative therapies. The pathophysiology of OSA is similar in both populations and therefore implant procedure, location, activation, and titration process remain the same in both the adult and proposed pediatric populations.

Here, the outstanding question regarding the extrapolation of adult's data for pediatric population is the impact of unique characteristics for pediatric Down syndrome population (e.g., post-implant growth) and disease characteristics differences between adult and pediatric on the safety and effectiveness of Inspire therapy. The relatively higher prevalence of OSA in individuals with Down syndrome likely reflects the presence of many risk factors contributing to airway obstruction like anatomical abnormalities (macroglossia, adenotonsillar hypertrophy, midface hypoplasia, etc.) and other associated conditions such as obesity, stunted growth, craniofacial features, narrow airways, cognitive ability, hypothyroidism, hypotonia, and enlarged adenoids, tonsils and tongue. Given these unique characteristics for the pediatric sub-population, adult data cannot serve as a complete substitute for pediatric data to demonstrate safety or effectiveness and therefore full extrapolation of adult data is not acceptable. However, since the endpoints used in the adult data (e.g., AHI) are relevant to the pediatric subpopulation and quality of adult data is sufficient, a partial extrapolation from the STAR trial and post-approval evidence to pediatric OSA patients with Down syndrome was considered to be appropriate.

To further support the extrapolation, direct clinical evidence was collected from Down syndrome pediatric patients. While the effectiveness was comparable to the adult STAR trial, the safety profile was not found to be the same across the entire population in this study when considering growth and development as well as intellectual and cognitive challenges in younger pediatric subpopulation (i.e., <13 years). For ages 13-18, safety concerns regarding adolescent growth spurts were adequately addressed and benefits of the device in Down syndrome pediatric subpopulation were proved to outweigh risks. In conclusion, the safety and effectiveness profile of the Inspire UAS has been reasonably demonstrated in adult clinical studies. Additionally, the evidence from pediatric study supports the current data while considering different characteristics such as growth spurt in the intended population. Together, it is appropriate to leverage the available clinical data

from the STAR adult trial and findings from the pediatric study to support extrapolation to pediatric patients 13 to 18 years with Down syndrome.

6. 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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None

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

In accordance with the provisions of section 515©(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

The effectiveness results from the study in pediatric OSA patients with Down syndrome were consistent with those of the STAR trial in adults. Both showed significant reductions in the severity of OSA and improvements in quality of life. In the adult pivotal study, Inspire therapy provided clinically significant reduction of AHI and ODI in 66% and 75% of enrolled patients, respectively. A significant improvement in the quality of life was also observed as clinically significant reduction in mean ESS. The minimum clinically important improvement in the ESS lies between −2 and −3 and results showed -4 to -5 points improvement. Data from the pediatric study in Down syndrome patients have also demonstrated consistent results with the adult trial, where 50% reduction in AHI was observed in 66% of subjects at the 12-month follow up. The average reduction of ESS was -5.1 points which is considered significant improvement in the quality of life for the pediatric cohort. However, due to concerns regarding earlier puberty and growth spurt in pediatric Down syndrome patients, benefits of the device in the pediatric subpopulation age 13-18 were only proved to outweigh risks. These findings, together with existing study data from adults as well as real-world evidence, provide further support for extrapolation to a subset of OSA patients with Down syndrome ages 13 to 18.

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 safety profile of Inspire therapy was demonstrated in adult clinical 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 pediatric Down syndrome study also demonstrated a consistent safety profile with that of the STAR trial with the exception of higher readmission rates. All implanted subjects made it through the implant procedure without any intraoperative complications, and none of the subjects subsequently had their system removed. Similar to adult data, temporary tongue or oral discomfort was the most common complication occurring in 5 patients (11.9%).

3. Benefit-Risk Determination

OSA is a sleep disorder characterized by recurrent airway narrowing or closures during sleep. In the pediatric population, OSA can result in severe complications if left untreated. These include neurocognitive impairment, behavioral problems, failure to thrive, cardiovascular comorbidities, reduced quality of life, and depression. OSA is a common pediatric health problem affecting up to 5.7% of the general pediatric population. However, its prevalence is much higher in the Down syndrome population, with estimates ranging from 53% to 76% according to the National Down Syndrome Society. The most common first line treatment for children with OSA is adenotonsillectomy. However, 60% of pediatric OSA patients with Down syndrome will continue to have OSA symptoms following this procedure. Patients not effectively treated by adenotonsillectomy may go on to try CPAP therapy. Unfortunately, CPAP intolerance rates for the pediatric population are quite high, 40% to 50%, just as they are with the adult OSA patient population. Inspire therapy provides OSA patients who are not effectively treated by CPAP with a safe, and effective, treatment alternative that is not subject to the factors which limit compliance with CPAP therapy (e.g., therapeutic air pressure too high to tolerate, or discomfort from the mask). Given the seriousness of the co-morbidities associated with uncontrolled OSA, and the low rate of CPAP compliance, the magnitude of Inspire therapy's benefits is substantial for pediatric Down syndrome patient population.

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 and neurocognitive functioning
- 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.

Safety results show that the majority of adverse events reported in the pediatric study were not serious and were consistent with those in the adult patient population. One difference was adverse events related to skin issues at surgical site. Children and adolescents with Down syndrome often have sensory integrative disorders and may have heightened sensory responses to certain types of touch and noise. When considering the adverse events from the pediatric Down syndrome patient study, it should be noted that they have an intellectual disability and therefore are not always aware of the consequences of their actions. Taken together, this means that children and adolescents with Down syndrome are more prone to scratching their surgical wounds, which could lead to requiring additional treatment and pain control.

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

- Requires surgical procedure including modified 2-incision technique for pediatric population
- Permanent implant; if explanted possibility of cuff/partial leads remaining
- Chance of revisions due to growth or development in pediatric patients with Down syndrome.
- 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 13 to18 year old population
- Unknown long-term consequences in the pediatric population with Down syndrome due to lack of data in the intended population, as implantation was done at early ages
- Poor wound healing due to scratching in patients with Down syndrome
- Permanent scarring
- Cheloid 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 were not done; however, the high compliance rate suggests that patients tolerated the risks fairly well.

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

In conclusion, the data summarized above for the use of the Inspire Upper Airway Stimulation System in the treatment of severe obstructive sleep apnea in adolescents 13 to 18 years of age with Down syndrome, 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.

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. 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 ODI) and improved subjective quality of life. The safety profile of Inspire therapy in pediatric Down syndrome patients was comparable to adults with low rate of serious adverse events that resulted in revision, repositioning or replacement of the Inspire system. While procedure-related or therapy-related non-serious adverse events were frequent in pediatric patients, they were found to be comparable in number and type with adults and majority of these events resolved. Compliance with device usage was quite high suggesting that patients regarded therapy as beneficial despite the reported non-serious adverse events. The therapeutic effect appears to be durable out to at least 60 months, as shown in adult

studies. Given the limited treatment options for OSA in pediatric patients with Down syndrome, adverse consequences associated with untreated, progressive OSA and considering the totality of the scientific evidence available (pediatric DS data, extrapolation of adult STAR trial and PAS, real-world evidence-Registry), the probable benefits of Inspire® therapy outweigh the probable risks.

XIV. CDRH DECISION

CDRH issued an approval order on March 20, 2023. 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 with Down syndrome age 13 to 18, with moderate to severe sleep apnea, who are candidates for Inspire® UAS therapy. A total of 60 patients with even distribution across the age range 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.

From the time of study protocol approval, you must meet the following timelines for you 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
- Submission of Final study report: 3 months from study completion (i.e., last subject, last follow-up date)

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.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports (i.e., every 3 months), in addition to your periodic (6-months) 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).

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

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