SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cochlear Implant System

Device Trade Name: Nucleus 24 Cochlear Implant System

Device Procode: MCM

Applicant's Name and Address: Cochlear Americas
10350 Park Meadows Drive
Lone Tree, CO 80124

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P970051/S205

Date of FDA Notice of Approval: January 10, 2022

The original PMA (P970051) was approved on June 25, 1998 and is indicated for children and adults with bilateral severe to profound sensorineural hearing loss. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement to add an indication for single sided deafness or unilateral hearing loss (SSD/UHL) in children and adults.

II. INDICATIONS FOR USE

The Cochlear Nucleus 24 Cochlear Implant System is indicated for individuals with unilateral hearing loss who meet the following criteria:

- Individuals 5 years or older who have one ear with a severe to profound sensorineural hearing loss and obtain limited benefit from an appropriately fitted unilateral hearing device and one ear with normal or near normal hearing.
    - In the ear to be implanted, a severe to profound sensorineural hearing loss defined as a PTA at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz of > 80 dB HL.
    - In the contralateral ear, normal or near normal hearing is defined as a PTA at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz ≤ 30 dB HL.
- Limited benefit from an appropriately fit unilateral hearing device is defined as a score of less than or equal to 5% on a Consonant Nucleus Consonant (CNC) word test. For individuals between 5 years and 18 years of age, insufficient functional access to sound in the ear to be implanted must be determined by aided speech perception test scores of 5% or less on

developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone.

- It is recommended that prior to cochlear implantation, individuals with SSD have at least two (2) weeks to one (1) month experience wearing appropriately fit Contralateral Routing of Signal (CROS) hearing aid or another suitable hearing device (i.e., traditional hearing aid).

III. CONTRAINDICATIONS

A Cochlear Nucleus Cochlear Implant (CI) is not suitable for individuals with the following conditions:

- Absence of cochlea development
- Absence of a cochlear nerve
- Active middle ear infections
- Tympanic membrane perforation in the presence of active middle ear disease.

For individuals with single sided deafness the following contraindication is also applicable:

- Duration of profound sensorineural hearing loss greater than ten years.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Nucleus 24 Cochlear Implant System labeling.

V. DEVICE DESCRIPTION

No design changes to the approved devices in the Nucleus 24 Cochlear Implant System are required for the new indication.

The Nucleus 24 Cochlear Implant System consists of the following main components:

- Cochlear Implants (consisting of a stimulator, a coil with a magnet within its center, a variant of an active electrode, and a reference electrode):
  - Nucleus CI600 series
  - Nucleus CI500 series
  - Nucleus CI24RE series
- Sound Processors (a Behind-The-Ear (BTE) or Off-The-Ear (OTE) processor consisting of an external coil with a magnet of various strengths for positioning and holding it at the implant site by attracting to the magnet inside the implant and a driver for the radio frequency (RF) inductive stage)
  - Nucleus 7 Sound Processor
  - Kanso Sound Processor
  - Kanso 2 Sound Processor
- Fitting Software:
  Custom Sound Pro Fitting Software

In the Nucleus 24 Cochlear Implant system, the external sound processor captures sound with two microphones and converts it to a digital signal. The sound processor coil is magnetically held in place over the implant coil so that power and the digital information can be transmitted to

the internal implant via an inductive link. The implant receiver/stimulator receives the digital signals. The internal implant converts the digital signals into electrical pulses that are sent to the electrode array implanted in the cochlea. The electric pulses stimulate the auditory nerve, bypassing the damaged hair cells and allowing the brain to perceive sound. Within the Cochlear Nucleus Cochlear Implant System, Custom Sound software allows for programming of the system components to the optimal benefit of the individual user.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of SSD/UHL conditions. These treatments include bone conduction hearing aids, bone anchored hearing aids, implantable bone conduction hearing aids, and CROS hearing aids. Each alternative has its own advantages and disadvantages. A patient should discuss these alternatives with his/her audiologist and physician to select the method that best meets their expectations and lifestyle.

VII. MARKETING HISTORY

The Nucleus 24 Cochlear Implant System was first approved in the United States in October 1985.

The indications for use in countries other than the US do not have identical age or audiometric indications. Countries with unilateral and bilateral indications include Australia, China, Hong Kong, Taiwan, South Korea, India, the Philippines, Vietnam, Thailand, Malaysia, Singapore, Argentina, Columbia, Mexico, Brazil, Peru, Uruguay, Paraguay, Costa Rica, Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Iceland, Liechtenstein, Switzerland, and the United Kingdom.

The devices have not been withdrawn from any market due to a change in indications for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g., complications) associated with the implantation and use of the Nucleus 24 Cochlear Implant System:

- Normal risk associated with surgery and general anesthesia.
- Increased surgical and anesthetic risks for certain populations.
- Complications most frequently associated with this surgical procedure are stimulation of the facial nerve, taste disturbance, and tinnitus.
- Complications that may require addition medical treatment, surgery, and/or removal of the device, such as:
    - Acute Otitis Media (AOM)
    - facial nerve injury leading to temporary facial nerve weakness
    - perilymph fistula

    - Concurrent Cerebrospinal Fluid (CSF) leakage
    - vestibular dysfunction
    - subdural injury
    - subcutaneous hematoma
    - irritation, inflammation or breakdown of the skin flap; infection; and in some cases, extrusion of the device caused by the presence of a foreign body under the skin
    - decreased hearing ability caused by the electrode array migrating partially or completely out of the cochlea
    - perforation of external ear structures, such as the tympanic membrane or canal wall, by the electrode lead
    - perception of non-auditory sensations and poorer performance than expected from misplacement of the electrode array.
- Electrical stimulation may result in increased tinnitus, temporary facial nerve stimulation, temporary dizziness, or temporary pain.
- The long-term effects of electrode insertion trauma or chronic electrical stimulation are unknown. Such effects may include new bone growth in the cochlea or deterioration of the nerve cells. These effects may preclude replacement of the electrode array or may lead to eventual deterioration of cochlear response.
- Failure of component parts (both external and internal) could result in the perception of an uncomfortably loud sound sensation, intermittent sound, or no sound.
- Failure of various component parts of the implanted device could require removal or replacement of the implant, or a reduction in the number of electrodes used.

Meningitis

Before implantation, candidates should consult their primary care physician and implanting surgeon regarding vaccination status against micro-organisms that cause meningitis. Meningitis is a known risk of inner ear surgery and candidates should be appropriately counselled of this risk. Certain preoperative conditions may increase the risk of meningitis with or without an implant. These conditions include:

- Mondini's syndrome and other congenital cochlear malformations
- CSF shunts or drains
- recurrent episodes of bacterial meningitis before implantation
- perilymph fistulas and skull fracture/defect with CSF communication.

For information on the use of vaccines to prevent meningitis in persons with cochlear implants refer to: https://www.cdc.gov/vaccines/vpd/mening/hcp/dis-cochlear-gen.html. For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The preclinical studies (bench and animal) that were previously submitted to FDA in the original PMA (P970051) and its supplements continue to support the safety and effectiveness of the commercially available Cochlear Nucleus Cochlear Implant System.

No additional preclinical studies were required to evaluate the performance of the Nucleus 24 Cochlear Implant System for the treatment of patient populations under the expanded indications for SSD/UHL. The previously approved supplements which support the device system and its components are listed below in Table 1.

Table 1. Summary of System/Device Components and Their Respective Approval References

Device	Approval Reference
Cochlear Implants:	
Nucleus CI600 series	P970051/S183 and S191
Nucleus CI500 series	P970051/S048, S116, S126, and S133
Nucleus CI24RE series	P970051/S028
Nucleus 24 series	P970051
Sound Processors:	
Kanso 2	P970051/S193
Nucleus 7	P970051/S151
Kanso	P970051/S143
Fitting Software:	
Custom Sound Pro Software	P970051/S193

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant provides clinical performance data, including results from a feasibility study and a supporting systematic literature review to establish a reasonable assurance of safety of the use of Nucleus 24 Cochlear Implant System for patients with SSD/UHL. The systematic literature review was based on bilateral implantation, as it is not expected safety concerns will differ with unilateral implantation.

The applicant provides results from a feasibility study and real-world evidence in accordance with the FDA guidance "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" (issued August 31, 2017) to establish a reasonable assurance of effectiveness of the use of the Nucleus 24 Cochlear Implant System for patients with SSD/UHL who meet the proposed indication.

Safety data from the extant literature as well as effectiveness evidence from a prospectively designed, retrospective analysis and a supporting literature review for both adult and pediatric patients were the basis for the PMA approval decision.

A summary of the feasibility study combined with real-world data is presented below.

A. Study Design

Cochlear conducted a prospective analysis of data gathered from one Cochlear sponsored feasibility study and real-world data from two CI centers that have clinical and research

protocols for the treatment of SSD/UHL with cochlear implantation. The feasibility study was conducted under Institutional Review Board (IRB) and/or Research Ethics Board (REB) oversight.

The primary goal of the combined feasibility study + real-world data analysis was to gather pre-specified data points to demonstrate reasonable assurance of safety and effectiveness of cochlear implantation in individuals with SSD/UHL. The population of interest are individuals with a severe to profound (PTA of 500, 1000, 2000, and 4000 Hz > 70 dB HL) sensorineural hearing loss (SNHL) in the ear to be implanted, and aided CNC word scores of ≤ 10% and normal or near-normal hearing (PTA 500, 1000, 2000, and 4000 Hz) ≤ 30 dB HL in the contralateral ear (refer to Section XIII(C), Benefit-Risk Determination, for details on final approval of 80 dB HL PTA and <5% aided CNC word scores).

A total of 4 US sites (House Ear Research Institute, New York University, University of Iowa, Washington University) are represented in this analysis, where two of the sites (New York University (NYU) and University of Iowa) also provided RWD on patients who were not part of the Cochlear feasibility study. Table 2 shows the number of study participants at each study site.

Table 1. Study participants per site

Study Site	Number of participants
House Ear Research Institute	2 (Feasibility)
New York University (NYU)	4 (Feasibility) 17 (RWD)
University of Iowa	2 (Feasibility) 15 (RWD)
Washington University	2 (Feasibility)

There were two data sources for the study analyses:

1) A Cochlear sponsored feasibility study, "The Implantation of the Cochlear Nucleus System in Adults with Single-Sided Deafness Feasibility Study" (n=10) and
2) Real-world data (RWD) collected from two CI centers that have clinical and research protocols for the treatment of SSD with cochlear implantation (n=32).

1. Clinical Inclusion and Exclusion Criteria
   To be included in the prospective analysis study, the following inclusion and exclusion criteria were met.

Inclusion Criteria

- Patients who received a Nucleus cochlear implant (excluding the Hybrid L24 implant) in the last 10 years for the treatment of single-sided deafness.
- Aged 18 years or older at time of implantation.
- **Ear to be implanted:** Moderate to profound sensorineural hearing loss (PTA of 500, 1000, 2000 Hz and 4000 Hz) ≥ 70 dB HL and an aided CNC word score ≤ 10%.

- **Contralateral Ear:** Normal or near normal hearing (NH; PTA of 500, 1000, 2000, and 4000 Hz < 30 dB HL).

Exclusion Criteria

- A subject was excluded if there was no pre to post data available with the same test metric or no data available post-activation at any interval in the bimodal condition (CI + NH) versus NH alone (CI off).

2. Follow-up Schedule
   All patients were scheduled to return for follow-up examinations at 6, 12, and 24 months postoperatively, with 12 months being the primary endpoint time interval.

   Preoperatively, cochlear implant candidacy was determined based on current standards of care; additionally, the below tests were conducted for post-operative comparison. Postoperatively, the test metrics measured during the study included pure-tone audiometry, the Hearing in Noise Test (HINT), the Bamford Kowal Bench Sentence in Noise test (BKB-SIN), the Consonant Nucleus Consonant (CNC) Word Recognition Test, and localization testing. Patient reported outcomes with the Speech, Spatial, and Qualities of Hearing (SSQ-49) Scale, the Iowa Tinnitus Handicap Questionnaire were collected. Audiometric thresholds were also collected at each visit. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

   There were no defined safety endpoints for this indication expansion. Safety data was gathered from the currently approved indications for individuals with bilateral sensorineural hearing loss with the same device. Since it is not expected unilateral implantation will differ from bilateral implantation in rate or severity of adverse events, a safety analysis of the current literature was conducted (see Section XI).

   Effectiveness testing included speech recognition testing using the CIDirect Binaural Test System to complete the Hearing in Noise Test (HINT), Bamford Kowal Bench Sentences in Noise test (BKB-SIN). Localization testing was also assessed by delivering a broadband noise from one of 12 virtual locations in the rear hemi field. The locations are numbered 1 through 12 on a response sheet, from right to left, and positioned to represent an arc from 97.5° (on the right) to 262.5° (on the left) with 15° separations between source locations. The task for the subject involved a verbal response corresponding to the perceived location of the sound. Patient reported outcomes were evaluated with the Speech, Spatial, and Qualities (SSQ) Questionnaire. Audiometric thresholds were also obtained for each ear.

Primary Effectiveness Endpoint

1. The improvement in sentence in noise scores obtained post-activation in the bimodal listening condition (CI + NH) compared to scores obtained preoperatively in the best listening condition (NH+HA or NH alone) when the speech is presented from the front and noise to the normal hearing ear (S_ON_{NH}).

2. The improvement in sentence in noise scores obtained in the bimodal (CI +NH) listening condition at the most recent evaluation interval compared to scores obtained with the NH ear alone (CI off) when speech is presented from the front speaker and noise is presented to the normal hearing ear (S_ON_{NH}).

   The pre-specified null and alternative hypotheses are as follows:

   $$\text{Ho: } \Delta \leq \text{P } 1.5 \text{ dB}$$
   $$\text{Ha: } \Delta > \text{P } 1.5 \text{ dB}$$

   Where Δ is the mean difference between the preoperative best-aided condition and post-activation CI+NH or the mean difference post-activation between performance in the bimodal condition (CI + NH) and better hearing ear alone (CI off), and P was a performance goal with a pre-specified value of Δ 1.5 dB on the HINT or BKB-SIN.

   Thought a pre-specified success criterion of 1.5 dB was selected for this study, there is no widely accepted precedent as to what the minimal clinical meaningful difference should be. It possible a 1.5 dB cutoff may be a conservative clinical success criterion. Consequently, an additional post hoc analysis for the co-primary endpoints was completed where the confidence bounds exclude zero. Additionally, an analysis related to proportion of subjects showing a clinically meaningful improvement of 1 dB was completed. Some studies have concluded that a 1 dB improvement in speech understanding corresponds to approximately a 10% improvement (Litovsky et al., 2006; Soli et al., 2008) which aligns with the minimal clinically meaningful difference used for other test metrics such as CNC words and AzBio sentences. Therefore, results from the co-primary effectiveness endpoints data analysis are provided for both the 1.0- and 1.5-dB cut-off values (see below section for data tables).

Secondary Effectiveness Endpoint

Improvement in the bimodal (CI+NH) localization scores (Root Mean Square or RMS error) compared with NH ear alone (CI off) scores at the most recent post-activation evaluation.

The secondary effectiveness endpoint was the assessment of the within-subject difference of localization ability. Two conditions – bimodal condition (CI+NH) and NH ear alone (CI off) were measured at post-activation. Performance was then compared.

The pre-specified null and alternative hypotheses are as follows:

$$\text{Ho: } \Delta \leq 0$$
$$\text{Ha: } \Delta > 0$$

Where Δ was the mean difference between CI +NH and better hearing ear alone (CI off) in at the most recent post-activation test interval.

B. Accountability of PMA Cohort

Data from a total of 42 subjects was analyzed. Ten subjects participated in the Cochlear SSD Feasibility study and data from an additional 32 subjects was retrospectively collected from two US clinics.

- For the primary effectiveness endpoint, data from 23 participants was available for the Bimodal (CI+NH) performance relative to preoperative performance condition and 38 participants for the Bimodal (CI+NH) performance relative to NH ear alone (CI off) performance condition.
- For the secondary effectiveness endpoint, data from 24 participants were available.

Participant numbers are provided for each test below.

C. Study Population Demographics and Baseline Parameters

The subjects ranged in age at the time of implantation from 26 years to 73 years with a mean age of 53 years. The duration of hearing loss ranged from 0.4 years to 20 years with a mean of 4.5 years. Twenty-six (62%) of the subjects were female and 16 (38%) were male. Group demographics are shown in Table 3 below and the etiology of hearing loss for the group is shown in Table 4.

Table 3. Descriptive statistics for subject demographics

Characteristic	**Mean (S.D.) Entire Study Cohort**	**Mean (S.D.) Feasibility Study**	**Mean (S.D.) Real World Data**
Age at implantation	53.1 years (± 11.8yrs) *Range 26-73 years*	52.8 years (± 11.3yrs) *Range 27-65 years*	53.2 years (± 12.1yrs) *Range 26-73 years*
Gender	16 males (38%) 26 females (62%)	3 males (30%) 7 females (70%)	13 males (41%) 19 females (59%)
Duration of Hearing Loss	4.5 years (± 5.1 yrs)	3.2 years (± 3.4 yrs)	4.9 years (± 5.5 yrs)
Pre PTA (500– 4000 Hz) – Poorer Hearing Ear	99 dB (± 15.9 dB) *Range 70 – 120 dB*	103 dB (± 13.3 dB) *Range 83 – 120 dB*	98 dB (± 16.7 dB) *Range 70-120 dB*
Pre PTA (500–4000 Hz) – Better Hearing Ear	16 dB (± 6.3 dB) *Range 0 – 28 dB*	14 dB (± 6.2 dB) *Range 0 -24 dB*	17 dB (± 6.3 dB) *Range 3 -28 dB*

Table 2. Etiology of hearing loss

Etiology	**Number of subjects**
Idiopathic Sudden SNHL (ISSNHL)	13 (31%)
Menieres/Labyrinthitis	6 (14%)

Etiology	Number of subjects
Unknown	5 (12%)
Meniere's Disease	4 (10%)
Labyrinthitis	3 (7%)
Vestibular Schwannoma	2 (5%)
Viral	2 (5%)
Autoimmune hearing disease	1 (2%)
Bell's palsy	1 (2%)
Head injury	1 (2%)
Iatrogenic	1 (2%)
Noise exposure/fluctuating/Labyrinthitis	1 (2%)
Trauma	1 (2%)
Viral Labyrinthitis/ISSNHL	1 (2%)

D. Safety and Effectiveness Results

1. Safety Results

No systematic RWD data on device safety was collected. Study sites were asked if any unanticipated or serious adverse events occurred, and no events were reported. Safety data were primarily collected in the Cochlear feasibility study, where one anticipated adverse event was reported. A literature review of safety data for currently approved, bilateral indication for cochlear implants is included.

Cochlear SSD Feasibility Study Safety Data (n = 10)

- There were no unanticipated adverse events reported. One subject was reported as having an anticipated adverse event to sudden ventilation restriction upon induction of anesthesia during preparation for surgery. The event was quickly resolved and determined to be anesthesia related.

Adverse effects that occurred in the PMA clinical study:
The reported adverse event was anticipated for this procedure. Please see the literature review of safety data for rates of occurrence for adverse events in the broader cochlear implant population (see Section XI).

2. Effectiveness Results

The analysis of effectiveness was based on pre-specified co-primary and secondary effectiveness endpoints. These pre-specified endpoints are analyzed based on the combined data from the Cochlear feasibility study (n = 10) and RWD (n = 32), for a total of 42 available subjects. Key effectiveness outcomes are presented in **Tables 5 to 7**.

Co-Primary Effectiveness Endpoint 1:

The first co-primary endpoint was defined as the difference between HINT or BKB-SIN scores (from either the Cochlear feasibility study or RWD) obtained at 12-month post-activation in the bimodal condition (CI + NH) and pre-operative best aided scores. Out of 42 subjects total, 23 subjects had pre to post-activation performance data at 12 months available for analysis.

As shown in Table 5**,** when speech was presented from the front speaker and noise to the normal hearing ear (S_ON_{NH}), there was statistically significant improvement in the bimodal listening condition (CI + NH) compared to the best preoperative listening condition. The success criterion for the primary average clinical benefit at 12 months was 1.5 dB. On average, subjects experienced score -2.8 dB ($p<0.001$); a negative value connotates improvement on this test. This equates to approximately a 28 percentage point improvement (Litovsky et al., 2006; Soli et al, 2008). The null hypothesis is rejected, indicating that the mean clinical benefit at 12 months for the HINT/BKB-SIN met the pre-specified success criterion. Therefore, this co-primary effectiveness endpoint was met.

Table 3. Statistical summary for co-primary effectiveness endpoint 1: (Bimodal (CI+NH) performance relative to preoperative performance (N=23). Mean, median and interquartile range (IQR) values are shown.

	Preoperative (HA+NH/NH alone)	**Post-activation (CI + NH)**	**Difference**		
	Mean ± SD Median (IQR)	**Mean ± SD Median (IQR)**	**Mean ± SD Median (IQR)**	**95% CI**	**1-sided p-value**
Sentence recognition in noise HINT/BKB SIN S_ON_{NH}	0.9 ± 3.3 0.6 (-1.0, 2.7)	-1.9 ± 2.6 -1.6 (-3.1, -1.0)	-2.8 ± 3.1 -2.5 (-4.3, -1.2)	(-4.1, -1.4)	<0.001

Co-Primary Effectiveness Endpoint 2:

The second co-primary endpoint was defined as the difference between HINT or BKB-SIN scores (from either the Cochlear feasibility study or RWD) obtained at 12-month post-activation in the bimodal condition (CI + NH) and the NH ear alone (CI off). Out of 42 subjects total, 38 subjects had pre to post-activation performance data at 12 months available for analysis.

As shown in Table 6, a statistically significant improvement was found in the bimodal condition (CI + NH) compared to NH alone (CI off) for speech

understanding in noise (S_0N_{NH}). The success criterion for the primary average clinical benefit at 12 months was -1.5 dB (a negative value connotates improvement on this test). Participants on average experience a 1.5 dB improvement ($p<0.001$) in the bimodal condition compared to listening with the NH alone. This improvement equates to approximately 15 percentage point improvement with the CI + NH versus NH alone (CI off), (Litovsky et al., 2006; Soli et al, 2008). The null hypothesis is rejected, indicating that the mean clinical benefit at 12 months for the HINT/BKB-SIN met the pre-specified success criterion. Therefore, this co-primary effectiveness endpoint was met.

Table 4. Statistical summary for co-primary effectiveness endpoint 2: Speech understanding in noise post-activation (S_0N_{NH}) (N=38).

	Post-activation (CI off) NH alone	Post-activation (CI + NH)	Difference		
	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	95% CI	1-sided p-value
Sentence recognition in noise HINT/BKB SIN S_0N_{NH}	-0.7 ± 2.3 -1.2 (-1.6, 1.0)	-2.2 ± 2.5 -1.9 (-4.1, -1.0)	-1.5 ± 1.8 -1.6 (-2.8, 0.0)	(-2.1, -0.9)	<0.001

An additional correlational analysis with a cutoff of 1.0 dB was also included to compare co-primary endpoint 1 to co-primary endpoint 2 with a less conservative cutoff value. This analysis showed 47.6% (n = 10) of subjects received benefit on both endpoints and 9.5% (n=2) of subjects did not receive benefit in either endpoint. The remaining 42.9% of subjects showed benefit on one co-primary endpoint and not the other. These outcomes were similar when separating the feasibility study from the real-world data subjects. For the 1.5 dB cutoff value, 19% (n= 4) subjects did not receive benefit for either endpoint. However, the remaining 81% (n = 19) showed benefit in one or both of the co-primary endpoints. Although 1.5 dB was a more conservative cut-off value, most subjects showed benefit in one or more of the co-primary endpoints.

Secondary Effectiveness Endpoint

The secondary effectiveness endpoint was the difference in localization ability between the bimodal condition (CI+NH) and NH ear alone (CI off) measured at 12 months post-activation. Out of 42 subjects total, 24 subjects had pre to post-activation performance data at 12 months available for analysis. The success criterion for the difference in localization ability in these two conditions was > 0° (i.e., any statistically significant difference was observed). Table 7 summarizes

the results on the localization test showing the RMS error. The RMS error was significantly improved by 18.8^0 ($p < .0001$), in the bimodal condition (CI +NH) compared to the NH (CI off) ear alone. Based on the pre-specified success criterion of 0°, the secondary effectiveness endpoint was met.

Table 5. Localization Outcomes (n=24).

	CI Off	CI On	Difference		
	Mean ± SD Median (IQR)	**Mean ± SD Median (IQR)**	**Mean ± SD Median (IQR)**	**95% CI**	**1-sided p-value**
Localization (RMS error)	54.3 ± 16.8 52.2 (41.8, 63.0)	35.5 ± 16.7 33.0 (26.4, 44.5)	-18.8 ± 16.1 -18.9 (-26.7, -11.8)	(-25.6, -12.0)	<0.001

Patient Reported Outcomes

Speech, Spatial, and Qualities of Speech Questionnaire

The Speech, Spatial, and Qualities of Speech Questionnaire or SSQ-49 (Gatehouse & Noble, 2004) was administered as a self-assessment of hearing (dis)abilities across a range of listening situations that fall within three hearing domains. There are three subscales: 1) Speech hearing, 2) Spatial hearing, and 3) Sound qualities. Each question is scored by the patient using a line marked from 0 through 10, where 0 corresponds to minimal ability and 10 corresponds to complete ability. There were 14 subjects who completed the SSQ preoperatively and 10 subjects who completed it at 6 months post-activation.

- **Speech and Hearing Scale:** Preoperative scores obtained in the bilateral listening condition ranged from 2.4 to 6.0, with a mean score of 4.26, and at the 6-month evaluation in the bimodal listening condition (CI+NH), scores ranged from 3.8 to 8.3 with a mean of 6.18. Individual comparisons showed that 8 (80%) of the subjects perceived benefit. Two subjects (20%) reported no change in pre- to post-activation scores.

- **Spatial Hearing Scale:** Preoperative scores obtained in the bilateral listening condition ranged from 0.2 to 4.9, with a mean score of 3.19, and at the 6-month evaluation in the bimodal listening condition (CI+NH), scores ranged from 0.9 to 7.9 with a mean of 5.66. Individual comparisons showed that 7 (70%) of the subjects reported benefit. Three subjects (30%) reported no change in pre- to post-activation scores.

- **Sound Qualities Scale:** Preoperative scores obtained in the bilateral listening condition ranged from 4.2 to 8.5, with a mean score of 6.24, and

at the 6-month evaluation in the bimodal listening condition (CI+NH), scores ranged from 5.4 to 9.6 with a mean of 6.89. Individual comparisons showed that 6 (60%) of the subjects perceived benefit. Three subjects (30%) reported no change in pre- to post-activation scores. One subject (10%) indicated a decrement in pre- to post-activation scores.

3. Subgroup/Covariate Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender, median age at implant, median duration of hearing loss at baseline, median preoperative 4PTA for the implanted ear, median preoperative speech score for S_0N_{NH}, median CI off speech score (NH alone) for S_0N_{NH}, post-activation interval, and etiology of hearing loss.

- Results indicated that the only baseline characteristics that affected co-primary endpoint 1 (post-activation bimodal (CI+NH) performance relative to preoperative performance) were duration of hearing loss, etiology of hearing loss and pre-op speech in noise score. A shorter duration of deafness or higher pre-op speech in noise score yielded more clinical benefit. The result for etiology should be interpreted with caution as many were classified as "other."

- Results indicated that the only baseline characteristic that affected co-primary effectiveness endpoint 2 (i.e., performance obtained in the bimodal condition (CI + NH) and the NH ear alone (CI off) was the baseline speech in noise score. Subjects with poorer speech understanding in noise in the CI off condition demonstrated more improvement than in the bimodal listening condition (CI +NH).

- Results indicated that the only baseline characteristics that affected secondary effectiveness endpoint 2 (i.e., difference in localization ability post-operatively between CI + NH and NH (CI off) conditions) and the NH ear alone (CI off) was preoperative PTA (500, 1000, 2000 and 4000 Hz) in the implanted ear. Subjects with a higher pre-operative 4PTA showed less benefit than those with a lower PTA, as may be expected.

An additional covariate analyses examining the relationship between baseline characteristics for each co-primary effectiveness endpoint was conducted.

- For co-primary effectiveness endpoint 1, results suggest that age at implant, duration of hearing loss, preoperative speech in noise score and

preoperative PTA (500, 1000, 2000 and 4000 Hz) were related to the performance in the bimodal condition (CI + NH).

- For co-primary endpoint 2, there was a relationship between baseline speech in noise score (NH ear alone (CI off) and performance in noise in the bimodal condition (CI +HA).
- These results should be interpreted with some caution as there was no control for type I error (i.e., control for multiple comparisons). These additional analyses show some variation in clinical benefit related to duration of deafness, age at implant (related to duration of deafness in adults), pre-operative speech scores, etiology, and 4PTA. Variability in outcomes due to these factors is common in the cochlear implant population, so this variation in clinical benefit is expected.

Stratified Analysis for Co-Primary Endpoints

Stratified analyses were performed between preoperative hearing in the best listening condition to post-activation performance in the bimodal condition (CI +HA) (co-primary endpoint 1) and between NH performance compared to performance with a CI +HA (co-primary endpoint 2). The stratified analysis was completed based on the following performance level categories.

- Better performance (change >1 dB)
- Similar performance (change >-1 and <1)
- Worse performance (change < -1 dB)

For co-primary endpoint 1, results show that 18/23 (78%) of subjects had better performance (≥ 1 dB) change in their post-activation performance compared to preoperative performance, 3/23 (13%) had similar performance and 2/23 (8.7%) had worse performance. For co-primary endpoint 2, results show that 24/38 (63.2%) of the participants had better performance, 12/38 (31.6%) demonstrated similar performance and 2/38 (5.3%), had worse performance. When stratifying by patient characteristic (similar to the above subgroup analyses), there was no discernible difference in performance level categories depending on any characteristic.

Stratified Analysis of Investigational Sites

An analysis of variance (ANOVA) was done to examine the consistency of the primary effectiveness endpoints across investigational sites. There was no difference across the sites or study for any endpoint.

Stratified Analysis by Device Type

A subgroup analysis was conducted to determine the effect of device type on performance for co-primary effectiveness endpoint 1). There was no difference in performance for co-primary effectiveness endpoint 1 when stratified by device

either receiver stimulator or by electrode type. A similar result was found for co-primary effectiveness endpoint 2.

Patient Reported Outcomes

1. Speech, Spatial and Qualities Questionnaire (SSQ-49)
2. Iowa Handicap Tinnitus Questionnaire

Discussion of Results

This study analyzed outcome data on a group of SSD/UHL adult patients who received a cochlear implant in one ear. Data were combined from a feasibility study (n=10) and RWE (n = 32). Taken together, there were 23 subjects with post-operative data available for the first co-primary endpoint, and 38 with data available for the second co-primary endpoint. Overall, the effectiveness data demonstrated that for most subjects, the cochlear implant provided clinical benefit both in noise and with localization.

When comparing speech understanding in noise in the best pre-operative listening condition (HA+NH or NH alone) to the post-activation in the bimodal condition (CI +NH), significant improvements were found when noise was directed to the better hearing ear (S_0N_{NH}). In this configuration, a statistically significant improvement of -2.8 dB was observed ($p < .001$), meaning that, on average, subjects had improved sentence understanding at a more aversive signal to noise ratio (SNR) with the presence of the CI. Likewise, when performance with CI +NH was compared to performance in the better hearing ear alone (CI off), a significant improvement of -1.5 dB was found in the S_0N_{NH} spatial configuration ($p < .001$).

In the S_0N_{NH} spatial configuration, it was found that 78% of subjects demonstrated a clinically significant improvement of 1.0 dB (approximately 10%) in the post-operative bimodal condition (compared to pre-operative). Similarly, 66% of the participants demonstrated a clinically significant improvement of 1.0 dB at the most recent post-activation evaluation interval when performance with CI +NH was compared to NH alone (CI off).

Participants also demonstrated better sound localization, with the CI on (CI +NH) compared to the CI off (better hearing ear alone), an average improvement of 18.8° RMS. In other words, when asked to localize a sound emanating from the speaker array, the participants could locate the source within a range of 35° RMS with the CI on, whereas with the CI off they could perform the same task within a larger range of 54° RMS.

On a patient reported outcome, the SSQ-49, participants showed an improvement on all three subscales: hearing for speech in quiet and in noise, spatial hearing, and sound qualities. The biggest improvement was seen on the spatial hearing subscale, consistent with the improved spatial hearing measured objectively.

For those participants who were administered the Iowa Tinnitus Handicap Questionnaire, it was observed that at 6 months 67% of the participants reported an improvement in their self-reported tinnitus at 6 months and 70% at 12 months. This is an important finding as many individuals with SNHL also report tinnitus as an associated debilitating symptom.

In conclusion, the outcomes of these data analyses provide valid scientific evidence that cochlear implantation in individuals with SSD/UHL is an effective treatment option that has the potential to restore binaural hearing and improve an individual's everyday communication ability.

4. Pediatric Extrapolation

In this premarket application, existing clinical data were leveraged to support the reasonable assurance of safety and effectiveness the proposed device in pediatric patients aged 5 years and older.

The FDA published a guidance document entitled, Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices (issued on June 21, 2016). The guidance offers recommendations on when and why extrapolation of available clinical data (e.g., adult data) is appropriate for use in pediatric patients aged 5 years and older. The guidance provides a decision tree to evaluate the suitability of extrapolating data sets.

In the following paragraphs, questions from the pediatric extrapolation decision tree, as presented in figure 1 of the FDA guidance document, are answered in order to determine whether a full or partial extrapolation could be applied to the available clinical data.

Question A: Does the treated disease or condition in question occur in pediatric (sub)populations?

Yes. Unilateral sensorineural hearing loss has an estimated incidence of 1 in 1000 live births in the United States, (Lieu, 2018). The US Centers for Disease Control and Prevention (CDC) reported in the 2018 Annual Data Early Hearing Detection and Intervention (EHDI), Type and Severity data report that permanent hearing loss was identified in 5,778 children. There were 2,181 unilateral cases, of which 657 children were classified as having a moderately severe or poorer sensorineural hearing loss. There were also 126 children who had a unilateral SNHL of unknown severity. It has been reported that 3 to 6% of schoolchildren have some degree of UHL (Ross, et al., 2010). The proportion of cases with severe to profound hearing loss is probably around 30-50% (Boyd, 2015).

Question B: Is there an endpoint present in the existing data source that measures device effects relevant to the intended pediatric (sub)population(s)?

Yes. The effectiveness measures of the adult clinical study were the comparisons between speech understanding in noise between the preoperative best bilateral (unaided or HA + NH) condition and 6-month post-activation (CI +NH) condition when the speech was directed from the front speaker and noise to the NH side. Effectiveness endpoints measured speech understanding in noise and the ability to localize sound. Both speech understanding in noise and the ability to localize are relevant to the intended pediatric population. Most children are educated in classrooms with notoriously noisy environments. Gremp et al., 2018 reported that the average intensity level in an occupied classroom was 63.77 dB (range 44.20 and 76.40 dB). While an appropriate listening environment is desirable for individuals of all ages, it is particular important for children who are still developing mature linguistic skills, which continues through to 15 years (Wróblewski et al., 2012). This is particularly relevant for children with hearing loss, including SSD.

Further, a systematic literature review on outcomes of cochlear implantation in children with SSD provided 11 relevant articles. These pediatric studies evaluated similar device effects as reported in the adult literature, specifically; speech understanding in noise in different spatial configurations, localization of a sound source and patient reported outcomes. Collectively, these studies reported improved speech understanding in noise after cochlear implantation and also improved ability to localize a sound source with the addition of a cochlear implant. These reported device effects are similar to what is reported in adult literature. For full details of these published studies refer to the systematic literature review.

Question C-1: Is the device implanted or in contact with the body, and, if so, does either the location or duration of implantation differ between the adult and intended pediatric (sub)population(s) in such a way that the safety or effectiveness of the device could be impacted in a clinically meaningful way?

No. Though the device is implanted, the location of the implantation does not differ between the adult and the intended pediatric population in such a way that either the safety or effectiveness of the device would be impacted. For both pediatric and adult populations the device is implanted in the same location. Of note, Nucleus Cochlear Implants are approved for use in a population aged 9 months and older so the use of cochlear implants in a pediatric population is already deemed safe and effective by the Food and Drug Administration. This PMA supplement seeks approval for an expanded indication but in no way changes the surgical procedure of the device.

Question C-2: Are there differences in device characteristics between pediatric and adult use that could impact either device safety or effectiveness in the pediatric (sub)population(s) in a clinically meaningful way?

No. The same device is used for adult and pediatric patient populations, including the electrode array type and the external sound processors that are worn by the patient. Therefore, there are no differences in device characteristics between pediatric and

adult use that could impact either device safety or effectiveness in the pediatric population in a clinically meaningful way.

Question C-3: Are there characteristics unique to the intended pediatric (sub)population(s) that could impact either the effectiveness or safety of the device when used in the pediatric (sub)population(s) in a clinically meaningful way?

No. Cochlear implants are already used for the treatment of children aged 9 months and older with bilateral sensorineural hearing loss. The benefit-risk profile of the device is established in the pediatric population and does not change with the requested indication. For children who present with SSD, implantation is occurring in the affected ear only; the better hearing ear remains intact. Evaluation of auditory benefit can be determined in this pediatric population. By age 5 years language should be developed, so this age group can be evaluated and treated similarly to adults.

Question C-4: Are there differences in disease characteristics between adult and pediatric (sub)population(s) that could impact either device safety or effectiveness in the pediatric (sub)population(s) in a clinically meaningful way?

No. Although the disease characteristics that cause the hearing loss may be different in the pediatric population, the underlying diagnosis of sensorineural hearing loss is the same. The hearing mechanism presents with the same damage or absence of the hair cells needed for the transmission of sound. Just as in adults, children need to meet the candidacy criteria for cochlear implantation before receiving a cochlear implant.

Question C-5: Are there other differences between adult and pediatric (sub)population(s) that could impact either device effectiveness or safety in the pediatric (sub)population in a clinically meaningful way?

No. There are no other differences between adults and children that could impact either device effectiveness or safety in a clinically meaningful way.

The safety profile of cochlear implantation has been well-established and confirmed among children aged 12 months and older with bilateral, profound, sensorineural hearing loss. Device effectiveness for the SSD/UHL indications among adult patients has been demonstrated in Cochlear feasibility study and collected RWE in terms of improved speech perception in quiet and noise, improved localization performance, and higher subjective quality of hearing (see Section X). Additionally, published studies have also provided evidence to confirm and support the prospective analysis among both adult and pediatric patients for the proposed SSD/UHL indications (see Section XI). Therefore, the adult clinical data from the feasibility study and literature articles may be extrapolated to support the SSD/UHL pediatric population down to 5 years of age with severe to profound degrees of hearing loss (i.e., defined as (PTA4)

of 80 dB HL or greater at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz) with less than 5% speech score in the ear to be implanted. This pediatric indication is consistent with the Bone Anchored Hearing Aid (BAHA)'s age indications (BAHA is a 510(k)-device cleared for the same SSD patient population). Data extrapolation is not considered suitable for children younger in age (< 5 yrs), given the uncertainty to obtain ear-specific hearing and amplification related information among them for the SSD/UHL indications.

Overall Conclusions

Analysis of the data for 23 subjects (first co-primary endpoint) and 38 subjects (second co-primary endpoint) who received a cochlear implant for the treatment of SSD/UHL demonstrated that most subjects received clinical benefit from the cochlear implant, both for speech in noise and for localization.

When comparing speech understanding in noise from preoperative in the best listening condition (bilateral HA+NH or NH alone) to post-activation in the bimodal condition (CI +NH), significant clinical benefit was observed for the most challenging spatial configuration ear (S_0N_{NH}; co-primary endpoint 1). Similarly, when subjects were tested post-activation and performance in the bimodal condition (CI +NH) was compared with performance in the better hearing ear alone, an improvement of -1.5 was found in the S_0N_{NH} spatial configuration (co-primary endpoint 2). No changes were seen in the S_0N_0 and S_0N_{CI} spatial configurations.

Subjects also showed an improvement in sound localization with the CI on (CI +NH) compared to CI off (Better ear alone), with an improvement in root mean square error of 18.8°. On a patient reported outcome, the SSQ49, subjects showed an improvement on all three subscales: speech and hearing, spatial hearing, and sound qualities. The biggest improvement was seen on the spatial hearing subscale.

In conclusion, the outcomes of these data analyses provide valid clinical evidence that cochlear implantation in individuals with SSD is a safe and effective treatment option that has the potential to restore binaural hearing for both an adult and for pediatric patients aged 5 years and older. As previously stated, this pediatric indication is consistent with the Bone Anchored Hearing Aid (BAHA) age indication (a device cleared for the SSD/UHL population). In this submission, no prospective clinical data in the pediatric population was provided and the systematic literature review yielded a very small number of children under the age of two. Finally, for children under 5 years of age there is significant uncertainty when obtaining ear-specific hearing information, particularly related to speech perception. Therefore, data extrapolation is not currently considered suitable for children under 5 years of age.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The

pivotal clinical study included four investigators of which none were full-time or part-time employees of the sponsor and two had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: 1
- Significant equity interest held by investigator in sponsor of covered study: 0

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

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Literature Search Strategy (SSD)

In support of this application, Cochlear has completed a systematic review of the literature for cochlear implantation in children and adults with SSD. This review was completed following The PRISMA Statement guidelines (Liberati et al., 2009; Moher et al., 2009).

The search terms and inclusion and exclusion criteria used are listed in Table 8 and Table 9 below, respectively.

Table 6. Combinations of Search Terms used

DATABASE	SEARCH QUERY	FILTERS
	ADULTS	
Pubmed	((((("hearing loss") OR "hearing impairment") OR "deaf") OR "deafness") AND ((("single-sided deafness") OR “SSD”) OR "unilateral hearing loss") OR "UHL") AND ((((((((((((((((("cochlear implant") OR "hearing aid") OR "hearing system") OR "hearing instrument") OR "hearing device") OR "no treatment") OR “bone conduction”) OR “bone anchored”) OR “BCI”) OR “Baha”) OR "CROS") OR "contralateral routing") OR "BICROS") OR "transcranial CROS") OR "in-the mouth device") OR "ITM") OR "soundbite") OR "bonebridge") OR "ad hear”)	Humans, English, Adolescent: 13-18 years, Adult: 19+ years
Embase	((('hearing loss' OR 'hearing impairment' OR 'deaf' OR 'deafness') AND ('single-sided deafness' OR ‘SSD” OR 'unilateral hearing loss' OR 'uhl') AND ('cochlear implant' OR 'hearing aid' OR 'hearing system' OR 'hearing instrument' OR	NA

DATABASE	SEARCH QUERY	FILTERS
	'hearing device' OR 'no treatment' OR 'bone conduction' OR 'bone anchored' OR 'bci' OR 'baha' OR 'cros' OR 'contralateral routing' OR 'bicros' OR 'transcranial cros' OR 'in-the mouth device' OR 'itm' OR 'soundbite' OR 'bonebridge' OR 'ad hear')) AND 'human'/de AND [english]/lim) AND (2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py) AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim)	
CHILDREN		
Pubmed	((((("hearing loss") OR "hearing impairment") OR "deaf") OR "deafness") AND ((("single-sided deafness") OR "SSD") OR "unilateral hearing loss") OR "UHL") AND ((((((((((((((((("cochlear implant") OR "hearing aid") OR "hearing system") OR "hearing instrument") OR "hearing device") OR "no treatment") OR "bone conduction") OR "bone anchored") OR "BCI") OR "Baha") OR "CROS") OR "contralateral routing") OR "BICROS") OR "transcranial CROS") OR "in-the mouth device") OR "ITM") OR "soundbite") OR "bonebridge") OR "ad hear")	Humans, English, Adolescent: 13-18 years, Child 6-12 months, Preschool child 2-5 years
Embase	((('hearing loss' OR 'hearing impairment' OR 'deaf' OR 'deafness') AND ('single-sided deafness' OR 'SSD' OR 'unilateral hearing loss' OR 'uhl') AND ('cochlear implant' OR 'hearing aid' OR 'hearing system' OR 'hearing instrument' OR 'hearing device' OR 'no treatment' OR 'bone conduction' OR 'bone anchored' OR 'bci' OR 'baha' OR 'cros' OR 'contralateral routing' OR 'bicros' OR 'transcranial cros' OR 'in-the mouth device' OR 'itm' OR 'soundbite' OR 'bonebridge' OR 'ad hear')) AND 'human'/de AND [english]/lim) AND[2015-2021]/py) AND ([adolescent]/lim OR [preschool]/lim OR [school]/lim) AND [english]/lim	

Table 7. Inclusion and Exclusion Criteria for Retrieved Literature

BOTH ADULTS AND CHILDREN
All articles identified as relevant for this review after the final search process met the following five-point eligibility criteria: • The article was available in the English language and published in a scientific peer-reviewed journal. Articles published in trade journals were not included. • The article presented the results of a research study pertaining to the questions regarding efficacy and/or safety. Articles that were identified as relevant to the topic but that were only reviews, editorial/opinion pieces, poster presentations or survey results, were not included in the literature review; however, the reference lists of these articles were used as additional sources in the search for relevant research studies. All types of evaluative study designs were eligible for inclusion.

BOTH ADULTS AND CHILDREN
• Some or all the implanted subjects received Nucleus 24 cochlear implant models, or the models were not specified, but a reasonable assumption could be made that some Nucleus devices may have been included. • The article was published between January 1, 2015 to September 3, 2021 in either final print or e-form. Although there was also research on this topic published prior to 2015 (which also showed positive results for implantation in individuals with SSD), the rationale for using this time frame is that the past 5 years can be considered most representative of the quality and quality of research in CI and SSD. In addition, the last 5 years has seen an increase in such reports, and the later studies include often included previously reported subjects. The last search for this systematic review was completed on September 3, 2021 to give adequate time to obtain full-text articles and complete the report.
ADULTS
• Research subjects were adult recipients with single-sided deafness, with a pure tone average (PTA) > 80 dB HL in the ear to be implanted and normal hearing ear or near normal (PTA 500, 1000, 2000 and 4000 Hz) in the contralateral ear.
CHILDREN
• Research subjects were recipients under 18yrs old with single-sided deafness, who had a pure tone average (PTA) > 80 dB HL in the ear to be implanted and normal hearing ear or near normal (PTA 500, 1000, 2000 and 4000 Hz) in the contralateral ear.

Adults

The systematic literature review yielded 17 peer reviewed articles reporting on the effectiveness of CI in SSD patients who have a PTA ≥70 dB HL in the ear to be implanted and a normal or near normal hearing ear in the contralateral ear.

Across the seventeen studies identified as relevant to the review question, data from a total of 296 adults with SSD were reviewed. A summary of the literature is provided in Table 10 below.

Table 8. Effectiveness of cochlear implantation in adults with SSD identified from PubMed and EMBASE searches

Study	Key Results
Härkönen, et al. (2015)	Speech in Noise: Evaluated 7 patients. Speech understanding in noise was significantly better with the CI at -5 dB SNR at 12 months (85% words correct) compared to preoperatively 70% words correct (p=0.027). Localization: Evaluated 7 patients. Found that the Error Index score was 0.94 without the CI, and at 6 months after activation the score had decreased to 0.41 (p=0.017) and after 12 months to 0.31 (p=0.018).
Rahne & Plontke (2016)	Speech in Noise: Evaluated 17 patients. In S_0N_0 condition SRT improved from -1.95 dB (CI off, SD: 2.7 dB) to - 4.0 dB after 3months (SD: 1.3 dB, p<0.05), -3.8 after 6 months (SD: 2.0 dB, p<0.05), and -4.4 dB after 12 months (SD: 1.4 dB, p<0.05). For the more difficult hearing condition $S_{CI}N_{NH}$, SRT

Study	Key Results
	significantly improved from 4.7 dB (CI off, SD: 5.2 dB) to -1.3 dB after 1 month (SD, 3.5 dB, $p<0.05$) and to -2.8 dB after 3 months (SD: 3.4 dB, $p<0.05$). There was no further significant improvement after 6 and 12 months. Localization: Evaluated 17 patients. The RMS angle detection error (ADE) improved with CI usage at every time point ($p<0.001$) for all CI users. Mean ADE without CI usage was 92 degrees (SD, 21degrees) and 52 degrees (SD: 19 degrees) after 1 month of CI usage $p<0.05$). 46 degrees (SD: 16 degrees) after 3 months, 39 degrees (SD, 16 degrees) after 6 months, and 32 degrees (SD: 16 degrees) after 12 months. Speech Perception with CI alone: Evaluated 17 patients. Significant improvement in monosyllabic word and multisyllabic number recognition in quiet in comparing the 12-month and 1-month after CI activation
Friedman et al. (2016)	Speech in Noise: Evaluated 10 patients. Postoperative data at 12 months was available for 8 patients, and showed significant improvement in the S_0N_{NH} condition, preoperative SRT was -0.3 (SD. 3.1) and at 12 months the SRT improved to -2.5 (SD. 2.0), $p=0.005$ There was also a significant improvement in the S_0N_{CI}, preoperative SRT was -2.4 (SD2.7) and it improved at 12 months to -6.6 (SD. 2.5), $p=0.047$. There was no significant improvement in the S_0N_0 condition. Localization: Evaluated 4 patients. They did not find a significant improvement, preoperatively the RMS was 42.5 (SD. 7.7) and at 12 months post-activation, it was 47.2 (SD. 9.4).
Bernstein et al. (2017)	Speech in Noise: Evaluated 6 patients. The results showed the largest effect was the head-shadow where the speech was presented to the CI ear and noise to the NH ear 5.2 dB ($p<0.005$). They also found a significant 1.8 dB ($p<0.05$) squelch benefit where speech was presented from the front and female talkers as interferers on each side. No significant benefit was found in other listening conditions.
Louza et al., 2017	Assessed quality of life and perceived subjective benefit in 10 patients with SSD. Most of the subjects demonstrated benefits on the Nijmegen Cochlear Implant Questionnaire (NCIQ) and on the SSQ questionnaire.
Arndt et al. (2017)	Speech in Noise: Evaluated 45 patients. There was a significant improvement after 12months CI use for $S_{CI}N_{NH}$ and S_0N_0 compared to preop $p<0.001$, <0.01, respectively. There was no significant improvement or decrement in $S_{NH}N_{CI}$ condition which suggests when noise presented to CI side it does not impair comprehension in the NH ear. Localization: Evaluated 45 patients. Localization ability was significantly better with a CI at 12m vs monaural condition ($p=0.04$) with a reduction in angle error of 22.7^0 and CI was better than BCI (p-0.03) there was however no difference between CI and CROS hearing aid. Speech Perception with CI alone: Evaluated 45 patients. At 12 months, the monosyllabic word score was 48% (SD. 25%).
Legris et al. (2018)	Speech in Noise: Evaluated 9 patients. Results showed speech understanding in noise significantly improved after 12 months of experience with the CI. Mean SRT was improved by 3.9 dB at 12 m ($p=0.002$) in the $S_{NH}N_{CI}$ spatial

Study	Key Results
	configuration and by 7.6 dB (p=0.01) in the S_{CI} N_{NH} spatial configuration. There was no significant improvement in the S_ON_O spatial condition.
Dorbeau et al. (2018)	Speech in Noise: Evaluated 10 patients. SRT in noise was significantly lower with CI on at 12m, (p<.0001) in the $S_{CI}N_{NH}$-condition, and there was no significant difference in the S_ON_O condition. Localization: Evaluated 10 patients. Localization ability was significantly better with CI on versus off, p=0.005.
Dirks et al. (2019)	Speech in Noise: Evaluated 8 patients. Found a significant binaural benefit when the masker was two-talker babble in the S_0N_{NH} configuration (p=0,02). In the other 2 noise configurations (S_ON_O and S_ON_{CI}) there was no significant difference between CI on versus off. Localization: Evaluated 5 patients. Binaural localization errors were smaller than unilateral (acoustic-hearing ear only) localization errors when high-frequency information was present. The addition of the CI did not improve performance under conditions relying on low-frequency temporal fine structure, and no further improvement was found for either the low- or high-frequency stimuli when temporal-envelope ITD information was added via amplitude.
Litovsky, et al. (2019)	Speech in Noise: Evaluated 6 patients. 4 of the 6 patients scored similarly with and without the CI on and two subjects scores were poorer when the CI was added. Localization: Evaluated 9 patients. 8 of the 9 subjects showed an improvement (lower RMS errors) when the CI was added to the acoustic ear, the average mean improvement in RMS error was 27° compared to the acoustic only condition.
Lorens et al. (2019)	Speech in Noise: Evaluated 25 patients. The head shadow effect in the spatial configuration $S_{CI}N_{NH}$, with the CI off the mean score was 46.6% and with the CI on it was 66.2% (p≤0.01). A significant binaural redundancy effect (S_0N_0) was also found with a mean CI off score of 47.8% and a CI on score of 61.6% (p≤0.01). A significant squelch effect was also demonstrated (S_0N_{CI}), with a mean CI off score of 49.6% and a CI on score of 59.4% (p≤0.01).
Peter et al. (2019)	Speech in Noise: Evaluated 10 patients. Use of the CI resulted in an average squelch effect of 1.5 dB (SD1.0), improvement in head shadow effect of 1.5 dB (SD1.6) and spatial release from masking of 3.0 dB (SD 1.9). There was no difference pre to 3, 6 12m for the S_ON_O spatial configuration. Localization: Evaluated 10 patients. Localization improved with a mean improvement in localization error 10.2^0 (p=0.03) and RMSE by 12.2^0 (p=0.03) 12 m after CI.
Haubler et al. (2019)	Speech in Noise: Evaluated 21 patients. There was a significant improvement in speech and noise in the spatial configuration $S_{CI}N_{NH}$, the preop SRT was -0.92 dB (SD 2.37) and improved to -3.4 dB (SD 3.03) (p<0.05) at 6 months.
Sullivan et al. (2019)	Speech in Noise: Evaluated 60 patients. Found a significant in the S_ON_{CI} condition (p<0.001) suggesting a significant improvement in head shadow effect. There were no significant changes in the other two spatial configurations.

Study	Key Results
	Localization: Evaluated 60 patients. Did not find a significant improvement in localization at 3 months postoperatively compared to preoperative assessment. There was steady improvement reported overtime, but it was not reported to be significant. Speech Perception with CI alone: Evaluated 60 patients. A significant improvement was observed 3 months postoperatively, ($p < 0.001$) but there was no major change comparing further follow-up intervals.
Williges et al., 2019	Speech in Noise: Evaluated 8 patients. Speech understanding was evaluated in the NH alone, CI alone and binaural conditions. Three different speaker configurations were used, noise from -900, 00 and +900. Results showed that subjects employed a selective better ear listening strategy which was dependent on the direction of the noise. For the SSD group there was a significant improvement in the CI+NH condition when noise was presented to the NH ($p<.001$). This result suggests an improvement in the head shadow effect. There was no benefit of binaural summation.
Speck et al. 2020	Speech in Noise: Evaluated 13 patients. In the spatial configuration $S_{CI}N_{NH}$, speech recognition improved significantly from an average of -0.6 ±1.9 dB SPL in the preoperative unaided condition to an average of -6.9 dB ±3.2 dB SPL ($p<0.001$) The spatial configurations S_ON_O and $S_{NH}N_{CI}$ there were no significant differences. Localization: Evaluated 17 patients. The localization ability improved from an angle error of 33.4^0 to 11.3^0, ($p=<0.001$)
Mülleret al., 2021	Speech in Noise: Evaluated 11 patients in noise in 3 speaker configurations 1) S0N0, 2) S_0N_{NH} and 3) S_0N_{CI} using 3 different maskers: 1) noise masker, 2) male masker and 3) female masker. Results revealed that informational masking influenced speech understanding in noise. Better speech recognition scores were achieved in the presence of the noise masker for both NH alone and CI+NH conditions. Results showed a significant increase in speech recognition with CI+NH vs. NH alone when the masker was male and in the S0NNH, p=.004. Results suggest that the amount of informational masking may influence speech understanding in noise.

In this literature review, the latest clinical data were summarized on SSD patients from centers in the US and across the globe that met an audiometric criterion of severe or worse hearing loss in the ear to be implanted. Collectively, these reported studies consistently show benefits of a CI in individuals with SSD. Notably, improved speech perception in noise, localization ability corroborated by improved patient reported outcomes, specifically communicating in difficulty listening situations and in spatial hearing.

Children

The systematic literature review yielded 10 peer reviewed articles reporting on the effectiveness of CI in children with SSD who have a PTA > 80 dB HL in the ear to be implanted and a normal or near normal hearing ear in the contralateral ear. The 10 articles

comprise a total of 105 children with SSD. A summary of the literature is provided in Table 11 below.

Table 9. Effectiveness of cochlear implantation in children with SSD identified from PubMed and EMBASE searches

Study	Key Results
Arndt et al. (2015)	Speech in Noise: Evaluated 9 patients. Found a statistically significant improvement in the $S_{CI}N_{NH}$ condition for those with postlingually acquired SSD (N=9, p = 0.007). Localization: Evaluated 9 patients. There was a significant improvement with the CI on (p=0076).
Deep et al. (2021)	Speech in Noise: Evaluated 5 patients. All subjects performed as well or better on percent correct for HINT sentences at 60 dB with the noise at +10dB signal-to-noise ratio with CI on vs CI off in all 3 listening conditions. Significant differences could not be detected due to the ceiling effect from the excellent performance in the normal hearing ear. Speech Perception in Quiet: Evaluated 8 patients. The average word recognition score in CI ear alone was 56% (SD 32, range: 3-88%), which was an improvement of 49.3 percentage points compared to preoperative scores. In the bimodal condition (CI +NH), performance was at ceiling at both preoperatively (94%) and postoperatively (97%), importantly there was no decrement in speech performance in quiet with the addition of a cochlear implant.
Friedmann et al. (2016)	Evaluated 3 patients. Varying degrees of post-operative speech perception are shown in three cases. Performance may be impacted by duration of deafness and device use.
Greaver et al. (2017)	Evaluated 5 patients. Improvement observed in Early Speech Perception, Pediatric, Phonetically Balanced Kindergarten, and/or CNC tests.
Rahne & Plontke (2016)	Speech in Noise: Evaluated 3 patients. Sentence perception in noise significantly improved with CI use ($p<0.05$) in $S_{CI}N_{NH}$ and S0N0. Localization: Evaluated 4 patients. Showed an improvement in their ability to localize after cochlear implantation at each time point (1month, 3 months, 6 and 12 months). No significant differences were observed between the time points. Mean RMS angle detection error (ADE) without CI was 92 degrees and at 6 months it was 32 degrees (SD 16 degrees), $p<0.05$. There was no correlation between word recognition score in quiet and ADE improvement, suggesting that children with limited word recognition may still experience an improvement in sound localization. Speech Perception in Quiet: Evaluated 4 patients. For 2 children there was an improvement for both understanding multisyllabic numbers (both scored 100% at 12 months) in CI alone and for monosyllabic words both children scored 65% at 12 months
Ramos Macías et al (2016)	Speech in Noise: Evaluated 2 patients. Mean scores were reported for disyllabic tests in noise (46% at 6 months and 67.5% at 12 months).

Study	Key Results
Ramos Macías et al. (2018)	Localization: Evaluated 4 patients with congenital SSD and 19 patients with acquired SSD. Following implantation all showed positive results at most angles, 2/4 did not improve in the 45^0 condition suggesting some ability to lateralize the sound source accurately. Prior to implantation the lateralization tests at all angles was negative. Likewise, the 19 children with acquired SSD, all children showed positive results on the lateralization tests. Speech Perception with CI alone: Evaluated 17 patients. Twelve-month CI alone was 61.2% and 98.1% in the binaural condition (CI +NH). There was no reported decrement in performance in the binaural condition.
Rauch et al. (2020)	Reported outcomes: Showed long term benefit all three subcategories of the SSQ as reported on the parent assessment (N=9) and for the speech and spatial subcategories on the child self-assessment (N=5). Speech Perception in Quiet: Evaluated 11 children. The youngest age group (age 1.8 – 3.2 years n=4) showed the most benefit in speech understanding, Middle age range children showed some benefit although not as great as the youngest children and the oldest children showed the least amount of benefit.
Thomas et al. (2017)	Speech in Noise: Found a significant improvement with the CI than without it in three listening conditions. A benefit of greater than or equal to 1.5 dB SNR was found in five subjects (36%) in $S_{NH}N_{CI}$, in seven subjects (50%) in $S_{CI}N_{NH}$, and in three subjects (21%) in S0N0. Localization: Evaluated 14 patients. Results showed that in the CI aided condition was significantly better than in the unaided condition when stimuli were presented from the CI side ($p<0.001$) and from the normal hearing side ($p<0.001$) but not when presented from the front
Zeitler et al. (2019)	Speech in Noise: Evaluated 3 patients. The results demonstrated a mean 1.9 dB advantage (range 1–3.5) in the device-on condition, compared to the device-off condition using an environment simulation system. Speech Perception in Quiet: Evaluated 6 patients. Improvement in word recognition was found in all children. Word recognition score improved from 17.8% (SD 11.3%) to 69.5% (SD18.2%). Speech understanding in quiet was also evaluated using sentences.

In this literature review, the latest published clinical data were summarized on pediatric SSD/UHL patients from centers in the US and across the globe that met an audiometric criterion of severe or worse hearing loss in the ear to be implanted. Collectively, these reported studies show clinical benefit of cochlear implantation in children with SSD.

Literature Search Strategy (Safety of Cochlear Implantation)

Cochlear implantation is considered a reliable and safe procedure to restore auditory input in patients with bilateral moderate-to-profound sensorineural hearing loss. The safety of the device is well established as has been previously reported in PMA 970051. For patients with SSD/UHL the surgical procedure and the Nucleus Cochlear Implant System is the same for patients who have bilateral moderate-to-profound hearing loss

(and down to 9 months of age for children with severe to profound hearing loss). Therefore, the safety outcomes are expected to be similar in the SSD/UHL population.

In support of this application, the applicant completed a systematic review of the literature for the safety of cochlear implantation in children and adults.

The search terms and inclusion and exclusion criteria used are listed in Table 12 and Table 13 below, respectively.

Table 10. Combinations of Search Terms used (Safety of Cochlear Implantation)

DATABASE	SEARCH QUERY	FILTERS
	ADULTS AND CHILDREN	
Pubmed	((((("complication" AND (("cochlear implant") OR "adverse events" AND (("cochlear implant") OR "safety" AND (("cochlear implant")OR "failure" AND (("cochlear implant"))	Humans, English Preschool Child 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Adult 19+ years 2015 – Dec 10, 2021
Embase	(('complication'/exp/mj OR complication OR adverse) AND event OR 'safety'/exp/mj OR safety OR 'failure'/exp/mj OR failure) AND ('cochlea'/exp/mj OR cochlea) AND ('implant'/exp/mj OR implant) AND ([article]/lim OR [article in press]/lim) AND [english]/lim AND ([preschool]/lim OR [school]/lim OR [adolescent]/lim OR [adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim) AND [2015-2022]/py AND [medline]/lim	NA

Table 11. Inclusion and Exclusion Criteria for Retrieved Literature (Safety of Cochlear Implantation)

BOTH ADULTS AND CHILDREN
All articles identified as relevant for this review after the final search process met the following five-point eligibility criteria: • The article was available in the English language and published in a scientific peer-reviewed journal. Articles published in trade journals were not included. • The article presented the results of a research study pertaining to the questions regarding safety. Articles that were identified as relevant to the topic but that were only reviews, editorial/opinion pieces, poster presentations or survey results, were not included in the literature review; however, the reference lists of these articles were used as additional sources in the search for relevant research studies. All types of evaluative study designs were eligible for inclusion. • Nucleus cochlear implant model(s) were not specified. • The article was published between January 1, 2015 to December 10, 2021 in either final print or e-form. Although there was also research on this topic published prior to 2015, the rationale for using this time frame is that the past 6 years can be considered most representative of the quality research in CI. In addition, the last 6 years has seen an increase in such reports, and the later studies include often included previously reported subjects. The last search for this systematic review was completed on December 10, 2021 to give adequate time to obtain full-text articles and complete the report. • Reports of safety of cochlear implantation in recipients age 5 years and older (articles were included even if younger children within dataset) with unilateral and/or bilateral cochlear implants with bilateral sensorineural hearing loss

The systematic literature review yielded 930 peer-reviewed articles of which 282 were duplicates. This resulted in 648 references retained for screening of the study titles and abstracts against the inclusion criteria to determine eligibility for inclusion in the review. A final tally of 24 articles remained relevant to the safety data. Twenty articles are summarized within Table 14 below (the additional 4 articles data are included in the Carlson et al., 2020 summary therefore not summarized separately). Studies were excluded if subjects were < age of 5 years; if device manufacturer did not include Nucleus® cochlear implants; article focus was on revision data only not initial implantation data and single case data.

Table 12. Safety of cochlear implantation in adults and pediatric patients (aged 5 years and older) identified from PubMed and EMBASE searches

Study	Key Results
Aljazeeri et al., 2021 Saudia Arabia	Alijazeeri et al., (2021) conducted a retrospective, descriptive chart review of adult data (≥18 years) "Cochlear implantation in post-lingual adults. A 25-year experience at King Abdullah Ear Specialist Center, Riyadh, Saudi Arabia" between September 1994 – March 2020. There were 176 implantations in 144 patients. Alijzeeri et al., reported on

	surgical outcomes, complication rates and audiological parameters. Overall, intraoperative complications occurred in 6% (11/176) surgeries. Major postoperative complications occurred in three patients (1.7%) with one undergoing explantation due to severe pain with no identifiable reason (AB device) and two other patients being explanted due to device malfunctioning (1=CI512). Minor adverse events that were device or procedure related included: • Vertigo in 6% of subjects • Redness/pain at implant site in 5% of subjects • Facial twitching/paresis in 4% of subjects • Dizziness and tinnitus in 2% of subjects • Taste disturbance in 1% of subjects
Buchman et al., 2020 USA	Buchman et al., (2020) published the 6-month outcomes of a multicenter clinical trial sponsored by Cochlear "Clinical Evaluation of the Cochlear Nucleus® CI532 Cochlear Implant in Adults. There were 100 subjects enrolled in the study. The median age at implantation was 71 years (range 23-91 years). All subjects were implanted with CI532 cochlear implant. Buchman et al., (2020) reported on the adverse events captured at the 6-month interval of the study. Three serious adverse events (AEs) were considered device related or procedure related and required revision surgery to resolve. There were two electrode tip foldovers (2%) identified after surgery that were revised with subsequent surgery and one subject was reimplanted because of aversive, nonauditory stimulation with sound processor use this eventually resolved after revision surgery. Of the remaining AEs, all were classified as minor. The AEs reported that were device or procedure related included: • Swelling/irritation/bleeding/pain in 35% of subjects • Nausea/dizziness/vertigo in 28% of subjects • Sound quality/stimulation issues in 20% of subjects • Skin irritation from speech processor 18% of subjects • Tinnitus in 9% of the subjects • Post-anesthesia issues (non-ear related) in 4% of subjects • Neck pain in 2% of subjects • Migraine in 1% of subjects
Binnetoglu et al., 2020 USA/Turkey	Binnetoglu et al., (2020) conducted a retrospective review of 2597 patients who underwent cochlear implant procedures from 1995-2016. The overall rate of complications was 3.7% (n=97), including 78 cases (3.0%) that developed minor complications and only 19 cases (0.7%) that developed major complications. The most common minor complication was vertigo observed in 28 patients (1.1%) followed by: • Tinnitus 12 patients (0.4%) • Early and late wound infections in 3 (1%) and 7 (0.27%) patients, respectively • Temporary taste dysfunction in 9 (0.35%) patients • Acute otitis media in 6 patients (.0.23%)

	• Transient facial palsy in 6 patients (0.23%) • Hematoma in 1 patient (0.03%) • Wound infection in 15 patients (0.57%) • CSF leak in 6 patients (0.23%)
Carlson, 2020 USA	Carlson (2020) estimated the prevalence of complications associated with cochlear implantation compiled from 10 large, published studies. The studies included were: (Halawani et al., 2019; Black, 2011; Jiang et al., 2017; Petersen et al., 2018; Theunisse et al., 2018; Brito et al., 2012; Ding et al., 2009; Hansen et al., 2010; Kim et al., 2008; Venail et al., 2008). All studies cited included Nucleus devices. The overall complication rate was 12.8% (964/7513), 2.7% (207/7542) were classified as major and 8.4% (482/5771) were classified as minor. The following surgical or medical complications were reported: • Facial nerve paralysis 0.5% (41/7513), • Permanent facial nerve paralysis 0.1% (5/8779), • Meningitis 0.1% (5/7167), • Postop CSF leak 0.2% (9/5985), • Postop infection 1.9% (104/5556), • Mastoiditis 0.5% (26/5757), • Skin flap breakdown 0.3% (30/8779), • Hematoma 1.1% (85/7513), • Taste disturbance 1.6% (74/4509), • Persistent pain 1.7% (49/2889), • Vertigo or unsteadiness 2.2% (102/4664), and • Tinnitus 0.3% (11/3439) Carlson (2020), also estimated device-related complications which included: • Device failure 1.9% (125/6461) • Device migration 0.5% (16/3378) • Electrode misplacement 0.4% (28/6700) • Electrode migration 0.4% (18/4730)
Dazert et al., 2020 Germany	Dazert (2020) and colleagues published a review based on pertinent publications from PubMed, in addition to cochlear implant (CI) guidelines and the CI "white book" of the German Society of Otolaryngology and Head and Neck Surgery for "Cochlear Implantation." Within the review, Dazert et al., reported on complications and summarized the following: • Rates between 5.7% - 12.8% are reported • Most common- implant defects (1.9-3.4%) • Dizziness (2.2-3.9%) • Wound infections (1.9%) • Facial Paralysis (0.1 - 0.6%) • Meningitis (0.1%)

Fakurnejad et al., 2020 USA	Fakurnejad et al., (2020) performed an analysis of claims data of CI cases from a US commercial insurance database (Optum) between 2003-2016. A total of 4154 CI cases (n=3420 patients) were included in the analysis, which looked at both 30-day and 1-year complications. 5 cohorts were included in the results (0-18 yrs; 19-39 yrs, 40-59 yrs, 60-79 yrs, and 80+ yrs). At 30-days, complications across all cohorts included: • CSF leak (17/4154, 0.4%) • Device problems (41/4154, 1.0%) • Facial weakness (84/4154, 2.0%) • Local infection (28/4154, 0.7%) • Meningitis (3/4154, 0.1%) • Myocardial infarction (7/4154, 0.2%) • Stroke (8/4154, 0.2%) • Venous thromboembolism (2/4154, 0.05%) At 1-year, complications across all cohorts included: • Device complications (67/4154, 1.6%) • Local infection (104/4154, 2.5%) At 30 days post-op, complications in the <18 yr group included: • CSF leak (6/1189, 0.5%) • Encephalitis (0/1189, 0.0%) • Facial weakness (20/1189, 1.7%) • Local infection (11/1189, 0.9%) • Meningitis (2/1189, 0.2%) At 1-year, complications in the <18 yr group included: • Local infection (41/1189, 3.4%)
Parent et al., 2020 France	Parent and colleagues (2020) evaluated peri – and post-operative complications related to cochlear implantation retrospectively between January 2012-December 2016 registered through the EPIIC database system. The analyzed data set included 3483 adults (29% of CIs >29 years of age) and 2245 children (35% of CIs performed <10 years of age). Complications were categorized as either intraoperative or post-operative and sub-grouped within each (a. device related b. local c. cochleo-vestibular or d. related to lesions of adjacent structures). Major and minor complications were also evaluated with major defined as adverse events causing one or more undesirable events: need for surgery, hospitalization, permanent disability or severe symptoms. Minor complications were those treated medically or minor surgical intervention. Overall, the rate of complication was not significantly different between the adult and pediatric population (6.9% vs. 6.7% respectively). The authors concluded there was no effect of age groups on the occurrence of complication rates. The major postoperative complications reported in adults were dizziness and scarring (32%) of postoperative reports. In children, infection (18%) and device breakdown (17%) were most commonly reported. The rate of

	major postoperative complications was 2.51%; minor was 2.88%. Minor complications were significantly more common in the adult group (3.47% vs 1.96%) of which 39% were local and 35% were cochleovestibular. Among the major complications, only device-related complications were significantly more frequent in the pediatric group (1.74% vs. 0.60%) compared to the adult group. Overall complication rate of cochlear implantation for the study was 6.84% with no age effect regarding risk of complications supporting the safety of the procedure. Intraoperative: Adults – Intraoperative (n=3483) • CSF Leaks n=11 (0.32%) • Neurovegetative disorders n=9 (0.26%) • Major bleeding n=4 (0.11%) • Neurological complications n=2 (0.06%) Adults – Postoperative • Hematoma n=9 (0.26%) - Local • Pain n=18 (0.52%) - Local • Infections n=26 (0.75%) - Local • Scar disorders n=30 (0.75%) _ Local • Facial paralysis n=26 (0.75%) - Linked to adjacent structures • Tympanic perforation n=3 (0.09%) - Linked to adjacent structures • Dizziness n=47 (1.38%) - Cochleovestibular • Tinnitus n=12 (0.34) - Cochleovestibular • Electrode displacements n=14 (0.40%) - Device-linked • Magnet displacement n=1 (0.03%) - Device-linked • Breakdowns n=1 (0.03%) - Device-linked Children – Intraoperative (n=5728) • CSF Leaks n=23 (0.40%) • Neurovegetative disorders n=9 (0.16%) • Major bleeding n=6 (0.10%) • Neurological complications n=3 (0.06%) Children – Postoperative • Hematoma n=15 (0.26%) - Local • Pain n=23 (0.40%) - Local • Infections n=53 (0.93%) - Local • Scar disorders n=52 (0.91%) _ Local • Facial paralysis n=33 (0.58%) - Linked to adjacent structures • Tympanic perforation n=4 (0.07%) - Linked to adjacent structures • Dizziness n=57 (1.00%) - Cochleovestibular • Tinnitus n=12 (0.34) - Cochleovestibular • Electrode displacements n=28 (0.49%) - Device-linked • Magnet displacement n=1 (0.03%) - Device-linked

	• Breakdowns n=27 (0.47%) - Device-linked
Karamert et al., 2019 Turkey	Karamert et al. (2019) performed a retrospective chart review of complications in cochlear implant patients from July 2002-March 2018. A total of 802 patients were included (924 implantations), of which 695 (75.2%) were younger than 18 years of age. Charts were evaluated according to European Consensus Statement on CI Failure and Explantation. Soft failures and inner ear malformations were not included. n=722 implantations were unilateral while n=49 were bilateral sequential, and n=31 were bilateral simultaneous implantations. 41.8% of devices implanted were Cochlear Americas. Complications among Cochlear devices included: • Device failures (n=10, 2.5%) • Flap related problems (n=6, 1.6%) • Migration (n=9, 2.3%) • Hematoma (n=4, 1%) • CSF leakage (n=3, 0.8%) • Misinsertion (n=1, 0.3%) Overall, the CI survival rate exceeded 90% in a 10-year period and remains stable.
Wijaya et al., 2019 Ireland	Wijaya et al. (2019) performed a retrospective study on a national cochlear implant unit database to report on the long-term experience on revision cochlear implantation between 1995-2016. During that time, N=1207 devices were implanted of which 60 (n=58 patients) required revision implantation. Of those who underwent revision, n=37 were children and n=21 were adults. Reasons for revision CI included: • Device failure (n=25 peds, n=13 adults) • Migration/extrusion (n=2 (5.1%) peds, n=1 (4.8%) adults) • Electrode array migration (n=1 (2.5%) peds, n=2 (9.5%) adults) • Partial insertion (n=2 (5.1%) peds n=2 (9.5 %) adults) • Wound infection (n=4 (10.3%) peds, n=2 (9.5%) adults) • Cholesteatoma (n=2 (5.1%) peds) • Other (behavioral meningitis, cochlear sclerosis pediatric group) (n=3 (7.7%) peds, n=1 (4.8%) adults)
Gardner et al., 2018 USA	Gardner et al. (2018) performed a retrospective chart review of all cochlear implants performed in patients 17 years and younger (n=579). Gardner et al. identified a 4.7% device failure rate, a 0.3% extrusion rate, 0.3% infection rate in this cohort. Revision surgery occurred in n=27 patients, 4 of which were bilateral. Post-revision complications included nausea (n=7, 22.6%), emesis (n=5, 16%), dizziness (n=3, 9.7%) and imbalance (n=1, 1%)
Celerier et al., 2017 France	Celerier et al. 2017 conducted a retrospective review of implanted pediatric ENT patients from 1998 – 2015 who reported complaints of aytpical pain in the area of device implantation. Manufacturer devices in study were Cochlear (Sydney, Australia), (n=16), Advanced Bionics

	(Valencia, CA), (n=2), Neurelec (Vallauris, France, (n=1), MedEl (Innsbruck, Austria, (n=1). Exclusion criteria were: local skin infection, magnet displacement and hard failure according to the International Consensus Statement on Cochlear Failure Expectations. 1448 implantation cases were reviewed, of which 20/1448 reported unusual pain around magnet and/or implant (20 pain cases (1.3%) for 18 patients; 2 patients experienced pain after two reimplantations on the same side each considered an independent case). Of the pain cases, 2 main groups were identified, those with pain only (n=11) and those with pain associated with swelling around implant (n=9). A total of 10 explantations were performed. First line medical treatment was successful in 8 cases (40%); of the 12 patients who failed medical treatment and required surgery, two had resolution with magnet change.
Vila et al., 2017 USA	Vila and colleagues retrospectively analyzed data from Aug 1999-Oct 2013 from 421 pediatric patients (568 implanted ears); median age first implant = 3.6 yrs (range 7 mo-21 yrs); second ear median age 4.6 yrs (range 7 mo - 20 yrs) to assess whether recurrent otitis media is a contraindication for CI. Device manufacturers were Cochlear, MedEl and Advanced Bionics. Findings revealed middle ear infections were the most common postoperative infection (n=210 infections in 103 ears) and 18% of ears experience otitis media at least once after implantation. Median interval from the time of implantation to the first episode was 6 months (range 1 week-65 months). The next most common infection was otitis externa (n=26, 4.6%). Infection of the internal device (n=22, 3.8%); 16 of these infections originating from otitis media with one case resulting in device removal. Overall, otitis media is commonplace and usually resolves with treatment without affecting the device; importance is proactive and aggressive management.
Chiesa Estomba et al., 2017 Spain	Chiesa Estomba et al., (2017), reported on 57 patients who had been implanted at a single site. All patients received a Nucleus cochlear implant. Minor complications were reported in 14 patients (24.6%) and included vertigo seen in 8.8% (5) patients, tinnitus 10.5% (6). There was 1 case (1.8%) of suture dehiscence due to head trauma during the healing process, 1 patient (1.8%) developed a hematoma that resolved spontaneously after 10 days and 1 case of dysgeusia (1.8%). Major complications were reported to occur in 10 patients (17.5%). These included: 1 (1.8%) case of skin flap breakdown, 2 cases (3.6%) of facial palsy, 2 (3.6%) cases of implant extrusion, 1 case (1.8%) of electrode migration and 4 (7%) device failures.
Sivam et al., 2017 USA	Sivam et al., 2017 reported from 2004 to 2014 in a retrospective chart review of immediate post-operative complications in children unilaterally and bilaterally implanted 17 years and younger. A total of 579 implants were placed (Cochlear, MedEl and Advanced Bionics devices used). The overall complication rate was reported to be 23% with nausea/vomiting or imbalance/dizziness comprising 50% and 32% of the total rate, respectively. The odds ratio of developing complications in the group

	ages 1-3 versus all other age patients was found to be statistically significant. The odds ratio of developing a complication after bilateral implantation compared to unilateral implantation was statistically significant. It is important to note that the study included patients with abnormal anatomy (11 cases with Mondini malformations (4 of which had CSF leaks); 2 cases of labyrinthitis ossificans;1 case with an abnormal facial nerve course and 37 cases with enlarged vestibular aqueduct. The authors stated though the proportion of immediate postoperative complications in all pediatric age groups was substantial, the nature of the complications was brief and did not require escalation of treatment; only 1% (6/579) required unplanned medical attention following the procedure. Less common complications observed in study were: • Epistaxis 1/579 (.2%) • Facial swelling 2/579 (.3%) • Aspiration pneumonia 3/579 (.5%) • Eye swelling 1/579 (.2%) • Bloody otorrhea 1/579 (.2%) • Corneal abrasion 1/579 (.2%) • Urinary retention 1/579 (.2%)
Alcas et al., 2016 Peru	Alcas and colleagues reported major and minor complication outcomes of cochlear implantation using retrospective data on 108 patients (96 children and 12 adults). Of the original 108 patients, 107 entered the study, one was excluded who had less than 3 months follow-up. All patients had either Cochlear or MedEl devices. Age range 1-65 years. Major complications occurred in 3.7% (4/107) cases. Minor complications occurred in 14.9% (16/107) cases were reported as follows: • Tinnitus 6 subjects (5.6%) • Dizziness 3 subjects (2.8%) • Infection or wound dehiscence 2 subjects (1.9%) • Facial paralysis with recovery 2 subjects (1.9%) • Tympanic membrane perforation 2 subjects (1.9%) • Taste changes 1 subject (0.9%)
Gawęcki et al., 2016 Poland	Gawecki et al., (2016) at a single site reviewed the medical records of 1076 cochlear implant patients implanted with a Nucleus cochlear implant. They identified that major skin flap complications in 2.06% of children and 1.35% of adults. When a long “C” shaped incision was used the incidence was 2.43% and 1.28% with a short retroauricular incision. They concluded that major skin flap complications are rare and that risk factors include head trauma, acute otitis media, poor hygiene in children and general comorbidities in adults.
Googe et al., 2016 USA	Googe et al. (2016) performed a retrospective chart review to assess complications of cochlear implantation in patients aged 19 and younger between 2003 and 2014. A total of N=248 implantations (156 patients)

	were included in the analysis. Cochlear Nucleus were implanted in n=233 cases (94%). Major complications included: • Device failure (5.2%) • Wound infection (1.2%) • Cholesteatoma (0.4%) • Electrode malposition (0.4%) • Pain requiring explantation (0.4%) Minor complications included: • Acute Otitis Media (2.8%) • Wound infection (2.8%) • Magnetitis (1.6%) • Seroma (0.8%) • Altered mental status (0.4%) • Dysgeusia (0.4%) • Fever (0.4%) • Keloid (0.4%) • Pressure ulcer (0.4%) • Sebaceous gland infection (0.4%) • Delayed transient facial weakness (0.4%) • Transient vertigo (0.4%)
Dietz et al., 2016 Finland	Dietz et al., (2016) performed a retrospective chart review which aimed to determine the prevalence of CI electrode migration. 18/162 patients registered in an institutional CI database met inclusion criteria (increased impedance values or non-auditory stimulation of basal electrodes). Cone-beam computed tomography (CBCT) was used to determine electrode placement, and n=12 patients were found to have a partially migrated array.
Dankuc et al., 2015 Serbia	Dankuc et al., (2015) report on a cohort of 99 patients using Nucleus cochlear implants with a range in age from1-61 years old. The complications were reported in 11 patients, i.e. in 10.5% of 105 surgical procedures. The majority of procedures (89.5%) were not accompanied by any post-surgical complications. Unsuccessful implantation in a single-step procedure (4.04%) and transient facial nerve paralysis was most commonly reported, whereas cochlear ossification (1.01%) and transient ataxia (2.02%) occurred rarely. Stimulation of the facial nerve (1.01%), intraoperative perilymph liquid gusher (1.01%), device failure and late infections (1.01%) were reported infrequently.
Wong et al., 2016 Australia	In a retrospective study between 2001 – 2010, Wong and colleagues assessed outcomes of cochlear implantation (CI) in 150 patients (unilateral and bilateral recipients) who received their devices above the age of 75 years. The investigators stratified patients into 3 groups: 75-79 years (n=56); 80-84 years (n=55) and 85 years and older (n=39). It was reported that 4/39 in the 85+; 2/55 from the 80+ group and 3/56 from the 75+ group did not consistently use his/her device. Postoperative major

	and minor complications were reported. In total, 13 major complications in 7 (4.7%) recipients and 28 minor complications in 25 patients (16.7%) were reported. The investigators made note within the report of the five device failures, all classified as hard failures, found to have failure of the hermeticity of the device (CI512). Prolonged dizziness lasting over 30 days was observed (between 3.6-7.7%) across the age groups). Major Complications: By Group ≥85 yr old n=39 • Intrinsic device failure n=2 (5.1%) • Extracochlear insertion n=1 (2.6%) • Device migration n=1 (2.6%) • Electrode tip fold-over n=1 (2.6%) • Wound infection n=1 (2.6%) • Wound breakdown n=1 (2.6%) 80-84 yr old n=55 • Intrinsic device failure n=2 (3.6%) • Extracochlear insertion • Device migration • Electrode tip fold-over n=0 • Wound infection n=0 • Wound breakdown n=0 75-79 yr old n=56 • Intrinsic device failure n=1 (1.8%) • Extracochlear insertion n=0 • Device migration n=1 (3.6%) • Electrode tip fold-over n=0 • Wound infection n=1 (1.8%) • Wound breakdown n=0) Minor Complications: By Group ≥85 yr old n=39 • Taste disturbance n=3 (7.7%) • Tinnitus n=2 (5.1%) • Transient facial palsy n=0 • Dizziness duration >30 days n=3 (7.7%) 80-84 yr old n=55 • Taste disturbance n=2 (3.6%) • Tinnitus n=3 (5.5%) • Transient facial palsy n=1 (1.8%) • Dizziness duration >30 days n=2 (3.6%) 75-79 yr old n=56 • Taste disturbance n=2 (3.6%) • Tinnitus n=5 (8.9%) • Transient facial palsy n=0

	• Dizziness duration >30 days n=4 (7.1%)

In this literature review, the latest data on the safety of cochlear implants were summarized from centers within the United States and globally. Based on the overall reported complication rates, both major and minor, these studies support cochlear implantation to be a safe procedure for children and adults. In general, there are low incidence and prevalence rates of complications in cochlear implant surgeries across the age spectrum, presenting minimal risk for this procedure which has been established for patients with bilateral sensorineural hearing loss. It is expected that the adverse event rates are comparable between the currently approved indications for patients with bilateral SNHL and for patients with SSD as the surgical procedure does not differ between these indications.

Limitation for the Literature Data as RWE

Adults (SSD)

There are some inherent limitations with the research literature data collectively which included:

- Very limited individual data was reported in the studies.
- While the aims of most of the studies were similar the study endpoints differed. Quantifying the benefit with the addition of a CI (e.g., binaural with CI condition) compared to the NH ear alone was assessed in two ways: a) relative to preoperative unaided performance (which effectively measures the NH ear alone, and b) relative to NH ear alone performance during postoperative testing (e.g., testing with the CI off). Additionally, some studies also included the comparison of the CI+NH condition to the best everyday listening condition preoperatively which may have included some form of amplification such as a CROS hearing aid or a BCD on the poorer ear.
- The studies did not report any safety data; this is not surprising as there is no reason to think that adverse events would be any different than what is seen in cochlear implantation in patients with bilateral sensorineural hearing loss.

Despite these limitations, this systematic literature review provides supporting evidence for the treatment of SSD with cochlear implantation.

Children (SSD)

There are some inherent limitations with the research literature data collectively which included:

- Small study cohorts
- Heterogeneity of the pediatric population including etiology of deafness, duration of hearing loss, and age at implantation
- Not all studies provided individual data

- Majority of the studies were retrospective nature which often times resulted in missing data
- The studies did not report any safety data, this is not surprising as there is no reason to think that adverse events would be any different than what is seen in cochlear implantation in patients with bilateral sensorineural hearing loss.

Despite these limitations, this systematic literature review provides positive support for benefits of a cochlear implant to treat children with SSD.

Adults (Safety of Cochlear Implantation)
There are some inherent limitations with the research literature data collectively which included:

- Heterogeneity in the classification of major and minor complications across the studies
- Some studies did not include cochlear implant manufacturer or the age range of the reported complications

Children (Safety of Cochlear Implantation)
There are some inherent limitations with the research literature data collectively which included:

- In most studies pediatric and adult safety data was reported collectively
- Heterogeneity in the classification of major and minor complications across the studies
- Most pediatric studies focused on the safety of cochlear implantation in a very young age

Conclusions from Systematic Literature Review

Adults (SSD/UHL)

The latest clinical data were summarized in Table 10 on SSD/UHL patients from centers in the US and across the globe that met an audiometric criterion of severe or worse hearing loss in the ear to be implanted. Collectively, these studies showed clinical benefit in individuals with SSD/UHL. Notably, improved speech perception in noise and localization ability was corroborated by improved patient reported outcomes, specifically communicating in difficulty listening situations and in spatial hearing.

Children (SSD/UHL)

Collectively, the studies reported in Table 11 showed clinical benefit for cochlear implantation in children with SSD/UHL. Notably, improved speech perception in noise and localization ability was corroborated by improved patient reported outcomes, specifically communicating in difficulty listening situations and in spatial hearing.

Adults (Safety of Cochlear Implantation)

Collectively, the latest safety data of cochlear implants summarized in Table 14 reports complication rates, both major and minor, to be acceptably low and supports the safety of cochlear of cochlear implantation in adults in with bilateral sensorineural hearing loss. For adults with SSD/UHL, the surgical procedure and the Nucleus Cochlear Implant System is the same for patients who have bilateral moderate-to-profound hearing loss. By default, safety of cochlear implantation for individuals with SSD/UHL is not expected to differ from patients with a bilateral moderate to profound sensorineural hearing loss.

Children (Safety of Cochlear Implantation)

The latest safety data summarized in Table 14 consistently report that complication rates, both major and minor to be acceptably low, supporting the safety of cochlear implantation in children with bilateral sensorineural hearing loss. For children with SSD/UHL the surgical procedure and the Nucleus Cochlear Implant System is the same as for patients who have bilateral moderate-to-profound hearing loss. Consequently the safety outcomes of cochlear implantation are expected to be similar.

Conclusion

These literature data provide Real World Evidence (according to the FDA guidance "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices") in support of the clinical benefits of CI in adult SSD/UHL patients and pediatric SSD/UHL patients. When considered with the data presented in Section X, the literature serves as supporting evidence to demonstrate the safety and effectiveness of cochlear implantation in children 5 years and older and adults who meet the proposed indications.

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 Ear, Nose, and Throat Devices Panel, 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

A. Effectiveness Conclusions

Adults

1. Speech Understanding in Noise

Subjects showed post-operative clinical benefit with the cochlear implant in one ear and one normal hearing ear compared to pre-operative best-aided listening condition. On average, subjects had a 2.8 dB improvement in speech in noise when noise was directed to the normal-hearing ear and the signal was directed

to the front of the subject. When the CI + NH condition was compared to a condition where the CI was turned off, an average improvement of 1.5 dB was found in the bimodal condition (compared to CI turned off). These are considered clinically significant improvement in speech perception with the HINT or BKB-SIN speech in noise tests. Both co-primary endpoints were successfully met.

2. Localization

   Localization scores (RMS error) were significantly improved by 18.8^0 in the bimodal condition compared to the condition where the CI was turned off.

3. Subjective Questionnaires

   Subjects showed an improvement on all scales of the Speech, Spatial, and Qualities of Speech Questionnaire (SSQ). All subscales for the SSQ showed post-operative improvement for subjects compared to the pre-operative condition.

4. Systematic Literature Review

   The literature data provide confirmatory evidence for the outcomes from the feasibility + RWE data, demonstrating that recipients with SSD/UHL benefit from a CI in terms of speech perception, localization, and quality of life. A CI is the only treatment option that has the potential to improve binaural hearing in adults with SSD/UHL.

Children

Full extrapolation of the adult SSD/UHL data and supporting literature can be used to consider approval for the pediatrics (aged 5 and older) who meet the proposed SSD/UHL indication, with additional supporting evidence from the literature review.

B. Safety Conclusions

There was one anticipated adverse event in the feasibility + RWE data (ventilation restriction upon induction of anesthesia). A literature search was conducted to provide supporting safety data for the proposed SSD/UHL indication expansion. This literature review summarized the most recent safety data on cochlear implantation. Based on the overall complication rates, cochlear implantation remains a safe procedure for children and adults. As the surgical procedure is not impacted by whether the candidate has SSD/UHL or bilateral sensorineural hearing loss, this literature safety analysis serves as appropriate evidence of the safety of cochlear implantation.

C. Benefit-Risk Determination

The probable benefits of the Nucleus 24 Cochlear Implant System for the currently proposed SSD/UHL indication are based on data collected in a clinical study conducted

and RWD leveraged to support PMA approval as described above. The clinical study results combined with the RWD data for both primary and secondary endpoints demonstrated a statistically and clinically significant benefit from the use at the post-operative intervals in speech recognition performance in noise over the pre-operative, best-aided performance. For the first co-primary endpoint, 78% (18/23) of subjects showed better speech understanding in noise in bimodal listening condition at the 12-month time interval, and 13% (3/23) showed similar scores to their pre-operative performance. However, 9% (2/23) performed more poorly post-operatively. For the secondary co-primary endpoint, 66% (25/38) of subjects showed better speech understanding in noise in the bimodal listening condition with normal-hearing ear alone (CI off), and 30% (11/38) scored equally to their pre-operative performance. 5% (2/38) performed more poorly on this endpoint post-operatively. Overall, these data show cochlear implantation in adults with SSD/UHL is expected to improve speech recognition in noise and localization for the majority of the indicated population.

For this SSD/UHL indication, the audiometric criteria will be expanded to a 4PTA of > 80 dB HL from the currently approved 90 dB HL. The feasibility study findings had 10 subjects with post-operative data between 80-90 dB HL, with 4 with pre-operative data available (out of 23 subjects; or 17% of evaluable data). These four subjects had clinical benefit post-operatively for the primary endpoint. Further, literature sources provided 3 adult subjects and 3 pediatric subjects with pre-operative PTAs between 80-90 dB HL with post-operative clinical benefit, thus supporting the feasibility study findings. Therefore, these data may serve as supporting evidence for the PTA audiometric expansion to 80 dB HL and has increased our confidence in the effectiveness of the modified SSD/UHL indication expansion in premarket cohort.

The probable risks are also based on data collected in a clinical study conducted and combined with the RWD data to support PMA approval as described above. The safety data from the feasibility study and a literature search suggest that cochlear implant recipients tolerate the anticipated risks well, especially as the majority of adverse events that are device/procedure related to cochlear implantation surgery and resolved postoperatively. Other observed adverse events in the literature were consistent with those typically reported with approved cochlear implant systems and indications for use.

Additional considerations for the expanded indication for cochlear implantation in adults and children with SSD/UHL included:

1. Patient Perspective

   Patient perspectives considered during the review included:
   - The Speech, Spatial, and Quality Questionnaire (SSQ-49)
     - 80% (8/10) subjects showed perceived benefit on the Speech subscale in the bimodal listening condition
     - 70% (7/10) subjects showed perceived benefit on the Spatial subscale in the bimodal listening condition
     - 60% (7/10) subjects showed perceived benefit on the Sound Quality subscale in the bimodal listening condition

- Iowa Tinnitus Handicap Questionnaire
    - At 6 months post-activation, 67% (6/9) of subjects reported an improvement in their tinnitus.
    - At 12 months, 70% (7/10) of subjects reported an improvement in their tinnitus.

In conclusion, given the available information above, the data support that implantation with a Nucleus 24 Cochlear Implant System in patients who meet the proposed indications, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The provided preclinical testing was acceptable. Based on the combined analysis of feasibility clinical study data and RWD, it is reasonable to expect clinical benefits with cochlear implantation in individuals with single-sided deafness. In the clinical analysis, both co-primary and secondary endpoints were met, showing statistically significant and clinical benefit in speech in noise and localization in the bimodal (NH + CI) and bimodal (NH only, CI off) listening conditions. The risks associated with implanting the Nucleus 24 Cochlear Implant System in individuals with single-sided deafness are comparable to those seen with approved cochlear implant systems. FDA believes the available data demonstrate that the benefits outweigh the risks in the clinical study and RWD population, particularly since the device provided benefit for most of these subjects.

XIV. CDRH DECISION

CDRH issued an approval order on January 10, 2022. The final clinical conditions of approval cited in the approval order are described below.

The Cochlear New Enrollment SSD/UHL Study is a new enrollment post-approval study that is intended to assess the long-term safety and effectiveness of the Nucleus 24 Cochlear Implant System in treating children and adults with SSD/UHL. The study will be conducted as a prospective, non-controlled, non-randomized, multicenter study and will include 60 subjects at 15 sites. Among the 60 subjects, 30 subjects will be 18 years-old and above. Twenty subjects will be between 5 and 12 years of age and ten subjects will be between 12 and 18 years old. The primary safety endpoint is the number and proportion of subjects experiencing device-related adverse events throughout the duration of the post-approval study. The effectiveness endpoints include the within subject differences for BKB-SIN sentences in noise and CNC word recognition in in quiet from the bilateral, pre-operative, best-aided condition to the bilateral, 12-month, post-operative Cochlear Implant (CI) + Normal Hearing (or Hearing Aid) condition for speech and noise presented in S_0N_{NH} (signal from front, noise to normal ear), S_0N_0 (signal and noise from front), and S_0N_{CI} (signal from front, noise to the CI ear) configurations. The Preschool

Language Scale (PLS -5) and the Lexical Neighborhood Test (LNT) will be administered to pediatric subjects that fall within the appropriate age range for these tests. The stability of perceived hearing benefits over time will be assessed in adults by employing the Speech, Spatial, and Qualities (SSQ), Cochlear Implant Quality of Life (CIQOL-35), The Tinnitus Handicap Inventory (THI), and the Client Oriented Scale of Improvement (COSI) questionnaires. For children, the SSQ, the Pediatric Health-Related Quality of Life Instrument (Peds QoL), and the HEAR-QL will be administered. Finally, a cognitive screener will be used for subjects aged 55-85 at the time of enrollment and at 12 months post-activation. Subjects will be followed at 3 months, 6 months, 12 months, 24 months, and 36 months post-activation visits.

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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