

# **SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)**

## **I. GENERAL INFORMATION**

Device Generic Name: Cochlear Implant (CI) System

Device Trade Name: Nucleus 24 Cochlear Implant System

Device Procode: MCM

Applicant's Name and Address: Cochlear Americas  
13059 East Peakview Avenue  
Centennial, CO 80111

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P970051/S172

Date of FDA Notice of Approval: March 17, 2020

The original PMA (P970051) for the Nucleus 24 Cochlear Implant System was approved on June 25, 1998. The original device is intended to restore a level of auditory sensation to adults and children via electrical stimulation of the auditory nerve. The current supplement is to seek expansion of the indication for the Nucleus 24 Cochlear Implant System to include patient populations between 9 and 12 months of age.

## **II. INDICATIONS FOR USE**

### Adults

The Nucleus 24 Cochlear Implant System is intended for individuals 18 years of age or older who have bilateral, pre, peri or postlinguistic sensorineural hearing impairment and obtain limited benefit from appropriate binaural hearing aids.

These individuals typically have moderate to profound hearing loss in the low frequencies and profound ( $\geq 90$  dB HL) hearing loss in the mid to high speech frequencies. Limited benefit from amplification is defined by test scores of 50% correct or less in the ear to be implanted (60% or less in the best-aided listening condition) on tape-recorded tests of open set sentence recognition.

### Children

The Nucleus 24 cochlear implant system is intended for use in children 9 to 24 months of age who have bilateral profound sensorineural deafness and demonstrate limited benefit from appropriate binaural hearing aids. Children two years of age or older may demonstrate severe to profound hearing loss bilaterally. In younger children, limited benefit is defined as lack of progress in the development of simple auditory skills in conjunction with appropriate amplification and participation in intensive aural habilitation over a three to six-month period. It is recommended that limited benefit be quantified on a measure such as the Meaningful Auditory Integration Scale or the Early

Speech Perception test. In older children, limited benefit is defined as  $\leq 30\%$  correct on the open set Multisyllabic Lexical Neighborhood Test (MLNT) or Lexical Neighborhood Test (LNT), depending upon the child's cognitive and linguistic skills. A three to six-month hearing aid trial is recommended for children without previous aided experience.

### **III. CONTRAINDICATIONS**

The Nucleus 24 Cochlear Implant System is not indicated for individuals who have the following conditions:

- deafness due to lesions of the acoustic nerve or central auditory pathway
- active middle ear infections
- absence of cochlear development
- tympanic membrane perforation in the presence of active middle ear disease

### **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 age indication expansion.

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
  - Nucleus 24 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 site above the implant by attracting to the magnet inside the implant and a driver for the RF inductive stage):
  - Nucleus 6 Sound Processor
  - Nucleus 7 Sound Processor
  - Kanso Sound Processor
- Fitting Software:
  - Custom Sound 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 electric energy and transmits the pulses via the cochlea. The electric pulses

stimulate the auditory nerve, bypassing the damaged hair cells that cause hearing loss, allowing the brain to perceive sound. Within the Nucleus 24 Cochlear Implant System, Custom Sound software serves to allow the “fitting” or programming of the system components to the optimal benefit of the individual user.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

The alternative for treating profound hearing loss in patients between 9 and 12 months is to fit the child with hearing aids and/or wait until the child is 12 months or older before proceeding with cochlear implantation. Each alternative has its own advantages and disadvantages. Patients’ parents and/or guardians should fully discuss these alternatives with the physician and clinical team to select the method that best meets expectations and lifestyle.

## **VII. MARKETING HISTORY**

The Nucleus 24 Cochlear Implant System was first approved in the United States in June 25, 1998.

The indications for use in countries other than the US do not have identical age or audiometric indications. In some markets, it is the physician’s discretion when a patient is suitable for implantation based on age, which may be less than 12 months (Columbia, Australia, New Zealand, Korea, China, Hong Kong, Taiwan, Malaysia, Singapore, Vietnam, Indonesia, Philippines, Pakistan, Sri Lanka, India, Bangladesh, Lithuania, Estonia, Latvia, Balkans, Czech Republic, Slovakia, Austria, Romania, Poland, Hungary, Ukraine, Belarus, Uzbekistan, Armenia, Russia, South Africa, United Kingdom, Ireland, Denmark, Finland, Norway, Sweden, Benelux, Italy, Azerbaijan, Turkey, France, Portugal, Spain, Switzerland, Israel, and Germany).

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 additional 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 analysis, please see Section X below.

## **IX. SUMMARY OF NONCLINICAL STUDIES**

The preclinical (bench and animal) study findings 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 Nucleus 24 Cochlear Implant System.

No additional preclinical studies were required to evaluate the safety of the Nucleus 24 Cochlear Implant System for the treatment of patient populations between 9-12 months of age. The previously approved supplements which support the device and its components are listed below in Table 1.

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

Device	Approval Reference
<b>Cochlear Implants:</b>	
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
<b>Sound Processors:</b>	
Nucleus 7	P970051/S151
Kanso	P970051/S143
Nucleus 6	P970051/S096
<b>Fitting Software:</b>	
Custom Sound Software	P970051/S038

## X. SUMMARY OF PRIMARY CLINICAL EVIDENCE

The applicant uses Real-World Evidence (RWE) 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 safety and effectiveness of the use of Nucleus 24 Cochlear Implant System in pediatric patients aged 9-12 months.

The applicant performed a prospectively-designed, retrospective analysis from its’ own registry data to establish a reasonable assurance of safety of implantation with the Nucleus 24 Cochlear Implant System for pediatric patients aged 9-12 months. Data from this clinical analysis, as well as supporting safety and effectiveness evidence from the literature review, were the basis for the PMA approval decision. A summary of the clinical analysis is presented below.

### Summary of Pediatric Cochlear Implantation Among Children Aged <12 months: A Prospectively-designed, Retrospective, Clinical Analysis

#### A. Analysis Design

The analysis was a prospectively designed investigation with a retrospective analysis of the collected data. The analysis was conducted under IRB/REB oversight. The primary goal of

the analysis was to gather pre-determined data points used to show safety of the surgical procedure in the pediatric population between 9 and 12 months of age.

Subjects included children aged between 9 and 12 months who were implanted between January 1, 2012 and December 31, 2017. Data were collected through March 2019 and included 84 subjects. Below are the 5 investigational sites geographically distributed across the United States and Canada:

- The Hospital for Sick Children, Toronto, ON, CA
- New York University Langone's Cochlear Implant Center, New York, NY, US
- The Children's Cochlear Implant Center at UNC, Durham, NC, US
- Hearts for Hearing, Oklahoma City, OK, US
- The Children's Hearing Center at Lucile Packard Children's Hospital Stanford, Palo Alto, CA, US

### 1. Clinical Inclusion and Exclusion Measures

Inclusion in the retrospective analysis was limited to pediatric patients who met the following inclusion measures:

- Male or female between 9 and 12 months of age at the time of cochlear implantation
- Cochlear implantation with a Nucleus device between January 1, 2012 and December 31, 2017
- Record of at least one of the specified reportable measures on file
  - Total duration under anesthesia
  - Estimated blood loss
  - Total duration in recovery
  - Readmissions to CI center/hospital within 30 days post-surgery
  - Amount of pain medication administered in hospital
  - Temperature regulation issues and/or any instances of arrhythmia
  - Facial nerve injury
  - Exposed dura during drilling
  - Skin flap breakdown or extrusion
  - Device malfunctions
  - Other (any other significant complications noted on the operative record, Adverse Events, or anything that would be MDR reportable)

Patients were not included in the retrospective analysis if none of the specified reportable criterion were identified on file.

### 2. Analysis Procedures

The analysis procedures were limited to review of existing medical records for demographic information, comorbidities, and hospital re-admissions. Surgical information was extracted from the operative note and the anesthesia report. The surgeon's notes and the audiologist's notes were reviewed for post-operative complications, skin-flap breakdowns, or device malfunctions that were reported within the six months after the surgery. A relevant history preceding the initial surgery was also included.

### 3. Clinical Endpoints

*Safety Outcome:* The primary safety outcomes was the evaluation of reportable measures collected from clinician notes. The list of reportable measures as noted in the analysis protocol are as follows:

- Total duration under anesthesia
- Estimated blood loss
- Total duration in recovery
- Readmissions to CI center/hospital within 30 days post-surgery
- Amount of pain medication administered in hospital
- Temperature regulation issues and/or any instances of arrhythmia
- Facial nerve injury
- Exposed dura during drilling
- Skin flap breakdown or extrusion
- Device malfunctions
- Other (any other significant complications noted on the operative record, Adverse Events, or anything that would be MDR reportable)

**B. Accountability of Study Cohort**

A search of the Cochlear database returned 84 registered recipients at the selected sites who met the inclusion measures for date of birth and date of surgery.

**C. Analysis Population Demographics and Baseline Parameters**

The demographics of the analysis population are typical for a single-arm study performed in the US. Information on subject demographics and safety related variables is summarized in Table 2 below.

Table 2. Descriptive statistics (mean, range) for subject variables

<b>Parameter/Category or Statistic</b>	<b>Total (n=84)</b>
<b>Patient Gender</b>	
Male	n=42
Female	n=42
<b>Patient Age</b>	
	Average: 10 mo 15 days (9 mo and 0 days – 11 mo 29 days)
<b>Surgery Type</b>	
Unilateral	n=23
Bilateral (simultaneous)	n=61
<b>Patient Weight</b>	
Unilateral (n=17)	9.4kg (8.26-11.8)
Bilateral (n=60)	9.1kg (6.9-11.7)
<b>Time under anesthesia</b>	
Unilateral (n=21)	2hrs 34min (1:22 – 4:48)
Bilateral (n=61)	4hrs 15min (2:14 – 6:19)
<b>Estimated blood loss (EBL)</b>	
Unilateral n = 19*	10.75 cc (2-25)
Bilateral n = 24**	19.88 cc (2-100)

Time in recovery	
Unilateral n = 19	2hr 18min (0:26 – 9:10)
Bilateral n = 60	1hr 59min (0:35 – 9:04)

\*An additional 2 cases reported EBL as minimal

\*\*An additional 14 cases reported EBL as minimal, 1 case reported no significant blood loss, 1 case reported EBL<50cc

#### D. **Safety Results**

##### *Summary of Reported Adverse Events*

Adverse events that were documented in patient notes were collected for analysis. Adverse events were classified as anticipated/unanticipated, serious/non-serious, or device-related/unrelated. 24 patients experienced 28 medical/surgical complications and 26 of the complications were resolved without major surgical or medical intervention. Device-related complications (i.e. electrode faults) were not captured in this analysis.

Table 3. Number and percentage of adverse events observed

Events Reported as Device- or Procedure-Related	No. of Events	No. of Subjects	% of Subjects
Cerebral Spinal Fluid leak	3	2	2.4%
Facial weakness	2	2	2.4%
Infection	3	2	2.4%
Minor post-operative complication	6	6	7.1%
Minor skin irritation	3	3	3.6%
Otitis Media	3	3	3.6%
Seroma	2	2	2.4%
Temperature regulation during procedure	6	6	7.1%

Six patients experienced minor post-operative complications, four of which were resolved without medical intervention. Two patients experienced cerebral spinal fluid leakage peri-operatively. These were repaired during the cochlear implant surgery, and one required a revision surgery with reimplantation. Two patients experienced post-operative infections including mastoiditis, post-auricular abscess, and surgical site infection. All the infections were medically managed and resolved. Two patients developed seromas and one of these patients was reimplanted. Two patients experienced temporary facial weakness, which resolved with steroid administration. There were no reports of post-operative meningitis.

No device failures, device extrusions, or other serious device malfunctions were reported. Three patients experienced mild skin irritations. One of the irritations were resolved by decreasing the magnet strength and two resolved on their own. Electrode faults that were resolved with programming were not captured in this analysis, and there were no reports of untoward medical events or serious device malfunctions related to electrode faults.

Overall, the above adverse events are typical surgical/procedure/device events observed in children implanted in relatively young age.

#### E. **Real-World Data (RWD) quality analyses**

The relevance and reliability of RWD (collected from the above prospectively-designed, retrospective, clinical analysis) source and analysis were evaluated according to the FDA RWE guidance document. Overall, the RWD are of sufficient quality to ensure the reliability of the RWD source and the validity of the analysis finding to support the reasonable assurance of device safety for cochlear implantation in children aged 9-12 months, with some major data limitations noted in the section below.

**F. Data limitations for the RWD**

Limitations for the clinical data collected from the prospectively-designed, retrospective, clinical analysis include: 1) analysis sites were not randomly selected to meet the required minimum sample size of 100 children aged 9-12 months and to provide variety among clinic type and location; 2) data were limited to review of existing medical records for demographic information, comorbidities, and hospital re-admissions; 3) the success criterion for primary safety endpoint was not pre-specified in the analysis protocol, and the safety data were only descriptively analyzed, and 4) long-term adverse events associated with implanting children before 12 months of age (e.g., device failure, skin flap breakdown, device extrusion due to infection, migration of device due to skull growth, open electrode circuits, and cholesteatoma formation, etc.) were not fully captured or absent in the retrospective analysis due to the limited 6-month post-operative follow-up period.

4. Pediatric Extrapolation

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

**Summary of Literature Reports as Supporting Clinical Evidence**

**A. Literature Search Strategy**

The applicant conducted an extensive literature search across two major databases to provide additional supporting clinical evidence of cochlear implantation in children less than 12 months of age, using the PRISMA guidelines (Moher et al., 2009). Although it is not feasible to identify a specific subset of children implanted at the age between 9 and 12 months in the literature articles, the candidacy criterion for cochlear implantation of children < 12 month matches the proposed candidacy criterion for cochlear implantation of children between 9-12 months of age and, therefore, literature data could be used as confirmatory clinical evidence. The search terms and inclusion and exclusion measures used are listed in Table 4 and Table 5 below, respectively.

Table 4. Combinations of Search Terms used

Search Step	PubMed Database Search Terms	Review Question
1	“Cochlear implants in infants”	P & I
2	Limit 1 to <i>Language</i> : English	
3	Limit 2 to <i>Human studies</i>	
4	Limit 3 to <i>Publication date</i> : Jan 1 2009 to Oct 19 2019	
5	Limit 4 to <i>Ages</i> : birth to 23 months	P

Search Step	PubMed Database Search Terms	Review Question
1	“Pediatric age cochlear implantation”	P & I
2	Limit 1 to <i>Language</i> : English	
3	Limit 2 to <i>Human studies</i>	
4	Limit 3 to <i>Publication date</i> : January 1, 2009 to October, 19 2019	
5	Limit 4 to <i>Ages</i> : birth to 23 months	P
Search Step	EMBASE Database Search Terms	Review Question
1	('cochlear'/exp OR cochlear) AND ('implantation'/exp OR implantation) AND [article]	P & I
2	Limit 1 to <i>Language</i> : English	
3	Limit 2 to <i>Ages</i> : infant 0 to 12 months	P
4	Limit 3 to <i>Human studies</i>	
5	Limit 4 to abstract available	
6	Limit 5 to EMBASE	
7	Limit 6 to <i>Publication date</i> : 2009 to 2020	
Search Step	EMBASE Database Search Term	Review Question
1	('cochlea prosthesis'/exp OR 'cochlea prosthesis') AND [article]	P & I
2	Limit 1 to <i>Language</i> : English	
3	Limit 2 to <i>Age</i> : infant 0 to 12 months	P
4	Limit 3 to <i>Human studies</i>	
5	Limit 4 to abstract available	
6	Limit 5 to EMBASE	
7	Limit 6 to <i>Publication date</i> : 2009 to 2020	
Search Step	EMBASE Database Search Term	Review Question
1	('cochlear'/exp OR cochlear) AND ('implant'/exp OR implant) AND [article]	P & I
2	Limit 1 to <i>Language</i> : English	
3	Limit 2 to <i>Age</i> : infant 0 to 12 months	P
4	Limit 3 to <i>Human studies</i>	
5	Limit 4 to abstract available	
6	Limit 5 to EMBASE	
7	Limit 6 to <i>Publication date</i> : 2009 to 2020	

Note: The different search terms were selected to be broad enough to capture all relevant literature on the review questions and are connected using Boolean logic. Activated filters used to narrow the search are displayed in italics. P = Population, disease, or condition; I = Intervention.

Table 5. Inclusion and Exclusion Measures for Retrieved Literature

Inclusion Measures	
Population	Patients between 9 and 12 months old at time of implant surgery
Intervention	Some or all patients confirmed to or reasonably assumed to have Cochlear Nucleus cochlear implant models

Outcomes	Safety and/or performance outcomes reported related to intervention
Exclusion Measures	
E1	Wrong study population or specific ages of subjects not specified
E2	Data not differentiated for subjects less than 12 months old versus those implanted at older ages
E3	Publication did not supply safety or effectiveness data
E4	Data had previously been published in another article by same author(s)
E5	Topic not relevant

The literature search yielded 49 peer-reviewed articles that reported data regarding safety and/or effectiveness of implantation prior to 12 months of age. These articles comprise data on more than 750 children (Note: It is unclear if these children are all distinct individuals and the actual number of children may be less than 750 due to potential overlapping reporting in the literature.) that were implanted prior to turning 12 months of age. The safety and effectiveness results are listed in Tables 6 and 7 below. The full references for the articles in the table are included in the references section at the end of this document.

### Safety

Safety studies across both reviews that included children implanted at younger than 12 months of age covered a broad range of topics from surgical complications including anesthesia and blood loss, to postoperative pain and dizziness, wound healing problems, and infections.

Table 6. Safety studies identified from PubMed and EMBASE searches

Study	Key Results
Birman 2009	4 had otitis media with effusion (OME) at time of CI; 3 had post-op OME 12-38 months post-op but successfully treated with oral antibiotics. No anesthetic complications, no facial nerve injury; Bone marrow ooze most pronounced in children aged $\leq 6$ months; No post-op wound infection nor meningitis.
Dauids et al 2009	7 soft tissue complications (1.51% complication rate) in infants to 5 years of age: 5 majors (4 resulting in loss of device fixation and 3 resulting in explantation) including 2 soft tissue infections, 1 extrusion, and 2 major seromas leading to device migration. 2 minors: 1 minor seroma and 1 post-op hematoma. Of the 7 complications, only one was an infant implanted $< 12$ months of age. That infant was approx. 7 ½ months at implantation and 3 years later developed a major extrusion following head trauma from a fall. The device was repositioned and re-fixated.
Roland et al 2009	All had full insertions of the electrode array. There were 8 complications post-op in 7 patients: 3 major (6%): 1 cerebrospinal fluid (CSF) leak/re-implantation within a few days, 1 device failure repaired at 9 months, 1 infection/re-implant at 3 months post-surgery; and five minor complications (10%) including hematoma, cellulitis and skin flap erythema all occurring before 10 months post-op: There were no peri-operative anesthetic

Loundon et al 2010	9.9% (43 patients) experienced complications: Of these, 65% were delayed (mean 2 years; range to 8 years); 5.5% were major complications (severe cutaneous infection, meningitis, magnet displacement, cholesteatoma, CSF leak, electrode displacement) and 4.4% had minor complications (vertigo, soft-tissue infection, facial palsy, persistent otitis media); Trauma to mastoid area and inner ear malformations correlated to major delayed complications and early minor complications. Young implantation age not correlated with any complication.
Das Purkayastha et al 2011	There was 1 minor complication (child implanted at 8 months) of skin infection around implant 14 days later, successfully treated with antibiotics. There were no major complications.
Lescanne et al 2011	18 children experienced complications: 8 re-implantations, 3 other revision surgeries, and 7 medical treatment; The youngest child experiencing complications was 18 months old at implantation. Excluding device failures, the complications rate was 9.2%. The major cause (N=10) was postoperative infections. There was no increase in complications for younger compared to older children.
Yeh et al 2011	8 patients had 9 anesthesia-related complications (6.5% complication rate): 5 cases of post-op wheezing/stridor, 3 cases of laryngospasm, 1 case of emesis during inhalation induction. Divided by age group, complications were: 1 in child implanted < 12 months (8.8%) 1 in child implanted 12-24 months (5.6%) 1 in child implanted 2-5 years (3%) 5 in children implanted 5-12 (13%).
<b>Study</b>	<b>Key Results</b>
Broomfield et al 2013	Major complication rate 1.6% (0.95 excluding device failure); similar across bilateral and unilateral CI; Major complications: 2 CSF leaks, 1 hemorrhage, 1 immediate return to surgery for electrode reposition, 6 device failures, 2 wound infections requiring explantation, 1 case meningitis, 1 surgery for infection drainage, 1 surgery on scalp flap. 6.5% minor complications including 12 cases imbalance leading to prolonged post-op hospital stay, 2 cases temporary facial nerve weakness.
Holman et al 2013	No major surgical or anesthetic complication. 1 major complication: device failure 18 months post-op treated with reimplantation (age of patient not specified); 5 minor complications: 2 channel anomalies treated with map exclusion, 1 hematoma, 1 mastoiditis, 1 traumatic dehiscence (device undamaged, wound closed).
Tarkin et al 2013	43 patients (9%) had complications: 21 major complications (4.4%) – 10 device failure, 4 flap necrosis, 2 meningitis, 2 electrode shifting, 2 hematoma, 1 magnet migration. Complications led to re-implantation in 13 and revision surgery in 7. Only one complication was in a child under 12 months at implant: a flap necrosis in a 10 months old; 22 (4.6%) minor complications – 5 otitis media, 4 skin lesion due to pressure on contra ear during surgery, 3 flap swelling, 3 wound infections, 2 transient facial paralysis, 2 transient vertigo, 1 hematoma, 1 facial stimulation, 1 subcutaneous emphysema. Only one complication was in a

Birman et al 2015	At 1-week post-op: 8% had slight dizziness; 4 had large vestibular aqueducts, 2 of whom had slight unsteadiness. None had marked dizziness or unsteadiness. 19 required no analgesic use after hospital discharge (23 hours post-op); Those that did (paracetamol) took it 1.9 avg days post-op but longer for bilat CIs (3.3 days), and infants $\leq$ 12 months old (3.2 days).
Kalejaiye et al 2016	21 complication occurrences (1.55% complication rate) across all subjects: 18 soft tissue complications including superficial surgical site infection, 1 flap failure, 1 pneumonia, 1 bleeding requiring transfusion. 13 children required unplanned re-operation and 39 required re-admission. When comparing patients implanted <12 months to those implanted older, there were no significant differences in complication rate, postoperative length of stay, or reoperation rate. The 2 complications that occurred in the young age-at-implant group were both superficial surgical site infections. However, patients implanted <12 months were more likely to be readmitted (6.9%) versus those implanted older (2.7%) and had longer mean operative times (191 minutes vs.
O'Connell et al 2016	Operative and anesthetic time, and postoperative admission time did not differ significantly between the age-at-implant groups (similar results found in national data); Rate of occurrence of 30-day post-operative complication: 3.6% for younger implanted subjects and 3.2% for older implanted subjects in the national data. For longer-term follow-up in the university data, the complication incidence in younger-implanted group was 13.5% (without device failures, was 8.1%) and older implanted group was not significantly different at 12.7%.
<b>Study</b>	<b>Key Results</b>
Kim et al 2017	Total operative time, length of stay, and readmissions for those implanted at <12 months were significantly greater compared to those >12 months old at the time of surgery; However, there were no significant differences in general surgical complications (superficial incisional surgical site infections, organ/space surgical site infections, and unplanned reoperations) in the 2 age
Hoff et al 2019	Few surgical complications occurred, with no difference by age group. No major anesthetic morbidity occurred, with no critical events requiring intervention in the younger-implanted group, while 4 older-implanted children experienced desaturations or bradycardia/hypotension.
Ajallouyeen et al. 2011	Minor complications occurred in 8.7% of cases across all age groups; Most common was temporary facial weakness. Others were magnet or flap wounds/infection, keloid formation, and otitis media. Major complications occurred in 0.4% of cases across age groups: One case each of electrode movement, vertigo, laryngospasm, and meningitis. Specifically, for implantation < age 1, 5 complications were identified. The complication rate appeared to go down somewhat by age group: 29% for less than 12 months, compared with 22% for 1-2 years old (N=62), 25% for 2-3 years old (N=60), 17% for 3-4 years old (N=66), and 11% for aged 4-6 at implantation (N=57). However, sample sizes were much larger for the older groups, and only one child under age 1 had a major complication (laryngospasm). The small numbers of serious complications precluded statistical comparison.

Anagiotos and Beutner 2013	13 of the 14 subjects showed some decrease in hemoglobin levels due to blood loss during surgery; However, all the children except for one 2 months old (fitted with a competitor's device and well outside the age range of 9-12 months requested by Cochlear) had a normal surgical course with no complications.
Cohen et al. 2014	This surgical technique shortened surgical time and reduced risks of exposing dura; There was one device hard failure at 32 months with the later-recalled CI512 device, but it was successfully replaced with a Freedom model.; There were no postoperative wound complications, and no evidence of device migration was noted in any patient as of the last follow-up appointment
Bruijnzeel et al. 2015	Patients operated by technique B were typically younger than those by technique A; Most complications were minor and occurred early postoperatively; More overall complications occurred with technique B than A (61.5% vs. 20.6%; P < .001) and were mainly infectious. Younger cohort patients (6 – 12 months and 18 – 24 months age groups) most often developed complications; However, logistic regression showed that the surgical rather than the age at implantation was responsible for the documented complications; that is, there was no difference across age groups in complications within a given technique.
Miyamoto et al. 2017	There were no anesthetic or surgical complications, no pulmonary complications, no instances of flap breakdown overlying the implant package, and no facial nerve injuries. A redundant loop of electrode was left in the
Study	Key Results
	mastoid at the time of surgery to allow for later skull growth and at the time of publication no growth-related problems had been encountered.
Karltorp et al. 2020	There were no significant associations between complications after surgery and the age when children had their first implant (p=0.47 for 5-11 months compared with 12-29 months). No severe anesthesia or surgical complications were reported in the cohort, including meningitis or wound infections. Post-operative problems were rare and only occurred in 8 of 103 patients. They included transient seroma on the implant housing and pain or wounds at the surgical sites.

### Effectiveness

The overall benefits of implantation prior to 12 months old include a broad range of topics: auditory and speech perception, language development, localization ability, cognitive functioning, social maturity, and maturation of auditory evoked potentials.

Table 7. Effectiveness studies identified from PubMed and EMBASE searches

Study	Key Results
Ching et al 2009	Results demonstrated that children implanted at <12 months old develop normal language skills over time and at a rate comparable to normal hearing children; while those implanted >12 months perform at 2 SDs below the

Colletti 2009	On CAP, all did well but the youngest implanted group reached top performance faster; On PPVT, only youngest implanted group overlapped with performance of normal hearing children; On TROG, 100% of youngest group reached 77 <sup>th</sup> -100 <sup>th</sup> percentile, but only 38% of middle group and 20% of oldest implanted group did; SIR also best for younger implanted.
Nott et al 2009	Hearing-impaired children required a longer period to reach the first 50 and 100 words and to produce word combinations than the normal hearing group, but the size of the single-word lexicon did not differ between groups; Children in the early implanted group were closer to the results of normal-hearing peers than those later implanted for some outcomes.
Roland et al 2009	LNT/PBK (n=18) mean=93%. Similar scores on MLNT (n=5); GASP (n=8) mean =57%; IT-MAIS scores (n=8) 32 out of 40.
Habib et al 2010	Age <24 months at implantation had a positive, statistically significant impact on BIT scores (achieving mean 93% for implantation younger vs only 80% for older implanted children). There was no significant group difference between 8-12 months and 12<24 months age at implantation; however, 2 of the 3 children whose scores were above normal averages were implanted between 8 and 12 months old
<b>Study</b>	<b>Key Results</b>
Houston and Miyamoto 2010	No difference on speech scores between the groups at 2 years (GAEL-P, PSI) or 4 years (LNT); However, the early-implanted group performed significantly better than the late-implanted group on PPVT at both 2 and 4 years post
Tajudeen et al 2010	Children implanted earliest had an advantage over those implanted in the middle group and especially over those implanted latest, even after accounting for bilateral use and residual hearing; When speech scores were expressed as “hearing age” (time after implant), there was no difference.
Van Deun et al 2010	63% of children were able to localize this signal significantly better than chance level. Parent perception corresponded with performance; Best scores (near normal) were from those who obtained their first CI at the youngest ages.
Wie 2010	Earlier implanted had higher LittLEARS scores than those older implanted and caught up with normal peers sooner; On MSEL and the inventory, those implanted at <12 months showed significantly higher scores at all time points compared to those implanted at 12-18 months old.
Colletti et al 2011	Children implanted in the youngest group did significantly better on CAP and had higher IT-MAIS scores than either older group; Children implanted <12 months performed same as normal-hearing children on PPVT but older implanted-children never reached that level; On TROG and SIR, younger implanted children did better at 5- and 10-years post-implantation. On some cognitive tests, children in the youngest group did better than children implanted older.
Houston et al 2012	CI subjects implanted younger and those with better hearing pre-implant learned the IPLP task, but later implanted profoundly deaf children did not; Performance on IPLP correlated with later vocabulary size and showed a non-significant trend with speech perception. For those with profound loss pre-CI, children implanted <12 months old performed similarly to normal hearing peers, but those implanted at 14-21 months old did not.

May-Mederake 2012	Children implanted at < 2 years score as well as normal-hearing peers on speech & grammar development, & word comprehension, but poorer on phonological working memory for nonsense words; Those implanted <12 months old did better than those implanted at older ages up to age 2.
Szagan and Stumper 2012	Trend toward younger groups having better vocabulary and language skills, but not statistically significant; Different trajectories, with younger groups making gains earlier; When treated as a continuous variable, younger age at implantation was associated with better linguistic skills, but the correlation didn't reach statistical significance.
Ching et al 2013	Some of the variation in scores could be attributed to age at which received CI: Delaying implantation from 10 to 24 months old was associated with a substantial decrement in scores at 3 years old.
Holman et al 2013	Earlier implanted group master auditory skills (reach age-appropriate norms) by 6 months post-implant so have a longer auditory learning period; Earlier implanted group also performs significantly better on speech and language skills than later implanted group.
Leigh et al 2013	Children implanted before 12 months old showed language comprehension growth rates equivalent to their normal-hearing peers and achieved age-
Study	Key Results
	receptive language scores 3 years later; while those implanted at 13-24 months showed a significant language delay. Younger implanted also had better speech production, but there was no difference between groups for speech perception.
Nicholas and Geers 2013	Although there was individual variability, mean receptive vocabulary and language, and expressive language were significantly better in young-implanted vs old-implanted; Also, higher percentages of early-implanted children showed normal levels of performance. Regression analysis revealed a linear relationship between age at implantation & language outcomes
Rinaldi et al 2013	No significant difference between the age-at-implant groups in vocabulary skills or early grammar;
Tobey et al 2013	For the whole sample, 50% of the children were in the normal range for lexical production and use of sentences, but only 25% were in the normal range for pragmatic skills.
Cuda et al 2014	On average, younger implanted children performed better on expressive vocabulary and syntax, and pragmatic judgments; However, there was individual variability. Mean data trajectories show the best CASL scores can be expected from those implanted at <12 months old.
Murri et al 2015	Significant effect of age-at-implant on all performance outcomes; with better performance the earlier implanted.
Dettman et al 2016	Significant effect of age-at-implant for all outcomes: Open-set speech perception scores for Groups 1, 2, and 3 were higher than Groups 4 and 5. Language scores for Group 1 were higher than Groups 2, 3, 4, and 5. Speech production for Group 1 was significantly higher than Groups 2, 3, and 4 combined. Greater percentage of Group 1 had normative range language performance by school entry.
Guerzoni et al 2016	Significant impact of age at implantation, with highest scores for the children implanted at 8-12 months, and poorer for those implanted at 15 months and older; Both assertiveness and responsiveness were higher for younger versus older implanted subjects

Nicholas and Geers 2018	At both test periods, expressive language was delayed equally; Younger age-at-implant and better pre-implant aided hearing were both independently associated with better performance; Between 63%–78% of children implanted at 6–11 months old scored close to normal hearing peers by age 4.5, a level achieved by fewer than 25% of those implanted at 19 months old or older.
Hoff et al 2019	Those implanted at <12 months old developed measurable open-set speech scores earlier (3.3 years vs 4.3 years,) than those implanted at 12 months or older, and were more likely to develop oral-only communication (88.2% vs
Mitchell et al 2019	Children implanted at <12 months had significantly better PLS scores than those implanted at <12 months old.
Silva et al. 2014	All implanted children including the child implanted at 9 months old showed a decrease in CAEP P1 latency after 3-months implant use compared to before - - this decreased latency indicates better auditory system functioning; CAEP latencies for CI subjects approached those of the normal hearing controls, but were still longer at 3 months.
<b>Study</b>	<b>Key Results</b>
Ching et al. 2017	Children who received CIs at ≥12 months old had poorer language ability at age 5 than those implanted at <12 months of age, with benefit progressively increasing down to 6 mos. of age at time of activation.
Miyamoto et al. 2017	Some of the early implanted children achieved normal range of PPVT scores by 3 years old, and all 11 who were tested at 6 years old (the other 6 were lost to follow-up or not yet age 6) showed scores close to those of normal hearing children.
Yang et al. 2017	Preoperative DQ scores suggested that developmental delay was greater the older the CI candidate was; Gesell adaptability score correlated best with outcome; Older age at CI had a negative impact on outcome with the CI; the youngest implanted group showed the most improvement in scores pre- to post-CI surgery.
Lyu et al. 2019	SIR mean scores were significantly better for children implanted ≤11 months old compared to those implanted >11 months old for measurements at 6, 12, and 18 months. post-CI, but then plateaued and showed no difference at 24 months and later. The CAP trend was similar.; Further, the younger implanted children achieved significantly better scores than the older implanted (p < 0,05).
Karltorp et al. 2020	Children implanted at <12 months old reached age-equivalent level of language understanding and better vocabulary sooner than groups implanted later. Children who had surgery at 12-29 months demonstrated more atypical and delayed language abilities over time.
Li et al. 2020	Age at implantation was significantly correlated with the patients' scores on the S-M scale (p=0.011)., while duration of implant use, maternal age, and etiology of loss did not significantly correlate with social maturity; This suggests that timeliness of intervention is the key factor in a positive outcome.

## **B. Summary for the Literature Data as RWE**

The research literature on surgical and post-operative outcomes reported specific to the population under the age of 12 months at implantation did not identify an elevated incidence of complications. The study findings support that the safety profile for cochlear implantation in pediatric patients who are implanted between 9 and 12 months of age is comparable to that of the currently approved population of age 12 months and older. Regarding the

effectiveness outcomes, the literature data using both PubMed and EMBASE databases support that implantation before 12 months of age supports pediatric CI recipients' improved speech and language development. Together, the literature data provide evidence supporting device safety and effectiveness of cochlear implantation in pediatric patients aged 9-12 months.

### **C. Limitation for the Literature Data as RWE**

Some observed limitations for the literature data as RWE are listed below: 1) across published studies a variety of outcome measurements and test parameters were used. This makes challenging to summarize findings across studies, and precludes statistical meta-analyses on the literature data, 2) in some studies the number of implants that were Cochlear Nucleus devices (may be of different models) versus devices from other manufacturers was not specified, 3) a number of studies were retrospectively designed; that is, data collection and analyses were not prospectively defined in the study protocol, and 4) complete details regarding study endpoints, inclusion/exclusion measures, adverse event tracking, and statistical analysis plan etc., are often not fully specified in the cited published studies. However, the data from the articles identified through the literature search differentiates implantation prior to 12 months of age and, therefore, matches the proposed candidacy criterion for cochlear implantation of individuals between 9-12 months of age. Therefore, the safety and effectiveness data reported in these studies can serve as confirmatory evidence for the safety outcomes from the prospectively-designed, retrospective, clinical analysis and as supporting evidence for the safety and effectiveness of cochlear implantation in children aged 9-12 months according to the FDA Guidance document titled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" (issued August 31, 2017).

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the ENT Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

#### Literature Review

The compilation of outcomes from the literature studies found in the systematic review using both PubMed and EMBASE databases provide supporting evidence that children implanted between 9 and 12 months of age obtain significant device benefit in terms of speech and language development.

### **B. Safety Conclusions**

The risks of the device are based on nonclinical laboratory and/or animal studies conducted under prior PMA approvals, as well as data collected in a prospectively-

designed, retrospective, clinical analysis conducted to support PMA approval as described above, as well as the reported literature.

### Pediatric Cochlear Implantation: A Prospectively-designed, Retrospective, Clinical Analysis

Average surgical parameters and reportable safety events associated with implantation in a pediatric population were collected from the prospectively-designed, retrospective, clinical analysis in five North American clinics. There were 84 patients aged 9-12 months implanted with a Nucleus 24 Cochlear Implant System between January 1, 2012 and December 31, 2017. Any and all untoward medical occurrences were collected and analyzed. 24 patients experienced 28 medical/surgical complications and 26 of the complications were resolved without major surgical or medical intervention. Device-related complications (i.e. electrode faults) were not captured in this analysis.

#### Literature review

The literature supports safety of cochlear implantation in pediatric patients between 9 and 12 months of age. The associated risks are shown to be comparable between patients in this age group and the currently approved population of greater than 12 months of age.

### **C. Benefit-Risk Determination**

The probable benefits of the device for age indication expansion from 12 months to 9 months are based on literature data from the systematic review using both PubMed and EMBASE databases to support PMA approval as described above. Children implanted between 9 and 12 months of age are expected to obtain significant benefit in terms of improved speech and language development.

The probable risks of the device are based on data collected from the prospectively-designed, retrospective, clinical analysis and data reported in the literature to support PMA approval as described above. The safety of cochlear implantation in pediatric patients between 9 and 12 months of age, and the associated risks have been shown to be comparable between patients in this age group and the currently approved population of greater than 12 months of age.

The subject PMA supplement is to expand the indications for use for a previously approved cochlear implant system. Although the clinical data from the prospectively-designed, retrospective, clinical analysis and the literature data described in Section X have limitations, FDA agrees that (1) the probable benefits outweigh the probable risks for cochlear implantation among children between 9 and 12 months of age with the Nucleus 24 Cochlear Implant System; and (2) the degree of uncertainty is acceptable in the context of the overall benefit-risk profile of implanting pediatric patients between 9 and 12 months of age.

#### 1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for implanting children aged 9-12 months the probable benefits outweigh the probable risks.

#### **D. Overall Conclusions**

The data in this application collected from the prospectively-designed, retrospective, clinical analysis and literature articles, along with analyses based on the FDA RWE guidance document, demonstrate a reasonable assurance of safety and effectiveness of this device when used in accordance with the proposed age indication expansion from 12 months to 9 months. Based on the available clinical and literature data, it is reasonable to expect that children implanted between 9 and 12 months of age with the Nucleus 24 Cochlear Implant System can obtain significant benefit in terms of improved speech and language development. The risks of implanting children between 9 and 12 months of age are considered comparable to those of the currently approved population.

#### **XIV. CDRH DECISION**

CDRH issued an approval order on March 17, 2020. The final conditions of approval cited in the approval order are described below.

***Nucleus 24 Cochlear Implant Pediatric Post Approval Study (PAS)***: This PAS combines an extended follow-up study and a new, prospectively-designed, retrospective study to assess long-term safety and effectiveness of cochlear implantation in children aged 9-12 months. The study will be conducted as a retrospective, non-controlled, non-randomized, multicenter study at the 5 sites. Retrospective evaluation for safety and effectiveness up to a minimum of 2 years post-implantation will be conducted among all available 84 subjects who were enrolled in the pre-market, prospectively-designed, retrospective study for the extended follow-up study and a minimum of 50 subjects implanted at age of 9-12 months for the new, prospectively-designed, retrospective study. The primary safety endpoint is the number and proportion of subjects experiencing device-/procedure/otologic-related adverse events up to 24 months post-implantation. The effectiveness endpoints will include the within-subject differences for the performance of the cochlear implant on parental questionnaires from the pre-implantation baseline to the 24-month, post-implantation condition. Additionally, the performance of the cochlear implant on pre-to-post-implantation, audiometric thresholds and age-appropriate speech perception tests will also be collected if available.

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.

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