SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cochlear Implant System

Device Trade Name: MED-EL Cochlear Implant System

Device Procode: MCM

Applicant's Name and Address: MED-EL Elektromedizinische Geräte GmbH
Fuerstenweg 77a
6020 Innsbruck
Austria

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P000025/S134

Date of FDA Notice of Approval: November 26, 2025

The original PMA (P000025) for the MED-EL Cochlear Implant System was approved on August 20, 2001. The original device was intended to provide the opportunity to detect and recognize auditory information through electrical stimulation of the auditory nerve for bilateral, severe to profound hearing-impaired individuals (ages 18 months and older) who obtain little or no benefit from conventional acoustic amplification in the best-aided condition. (SSED to support the indication is available on the CDRH website: http://www.accessdata.fda.gov/cdrh_docs/pdf/P000025b.pdf) The indications for use were also expanded in P000025/S006 (Age indication expansion from 18 months to 12 months), P000025/S084 (Expanded indication for Combined Electric-Acoustic Stimulation (EAS)) , P000025/S104 (Expanded indications for Single-Sided Deafness (SSD) and Asymmetric Hearing Loss (AHL)), and P000025/S129 (Expanded indications for adults).

The current panel-track supplement was submitted to expand indications for the MED-EL Cochlear Implant System for children aged 7 months to 17 years, 11 months.

II. INDICATIONS FOR USE

The MED-EL Cochlear Implant System is intended to evoke auditory sensations via electrical stimulation of the auditory pathways for individuals with debilitating sensorineural hearing loss (SNHL) who obtain limited benefit from acoustic amplification in the ear(s) to be implanted and is indicated for the following pediatric populations:

Children aged 7 months to 17 years, 11 months must demonstrate a bilateral SNHL as follows.

- Children implanted at 7-11 months of age should demonstrate a profound SNHL, defined by a

3-frequency pure-tone average (PTA3) of ≥ 90 dB HL at 500, 1000, and 2000 Hz.

- Children implanted at 12-71 months of age should demonstrate a moderately-severe to profound SNHL in the low frequencies, defined by a PTA3 ≥ 55dB HL at 500, 1000, and 2000 Hz and a severe to profound SNHL in the high frequencies with thresholds not better than 70 dB HL at 2000-8000 Hz.
- Children implanted at 6 years to 17 years, 11 months of age should demonstrate a moderate to profound SNHL in the low frequencies, defined by a low-frequency PTA (LFPTA) > 40 dB HL at 250, 500, and 1000 Hz with thresholds not better than 65 dB HL at 3000-8000 Hz.
- Children implanted at 7 months to 5 years, 11 months of age must also demonstrate insufficient functional access to sound with appropriately fitted amplification and aural habilitation. Children who lack the requisite language to complete word recognition testing should demonstrate either a lack of progress or plateau on an accepted scale of auditory skill development (e.g., LittlEARS Auditory Questionnaire (LEAQ), Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS)). Children with the requisite language to complete word recognition testing should demonstrate a percent correct score ≤ 40% on a developmentally appropriate test of word recognition (e.g., based on age, cognitive ability, language skills, and clinical judgement).
- Children implanted at 6 years to 17 years, 11 months of age should demonstrate limited benefit from hearing aids, defined by test scores of 50% correct or less in the ear to be implanted and 60% or less in the non-implant ear on recorded tests of monosyllabic word recognition (e.g., Consonant-Nucleus- Consonant [CNC] Words).
- Children implanted under 12 months of age should show repeatable behavioral test results that are consistent with objective/electrophysiological test results.
- MED-EL strongly recommends a hearing aid trial of at least 1-3 months for children without previous hearing aid experience. Risk of ossification or lack of aidable hearing may preclude a hearing aid trial.

III. CONTRAINDICATIONS

An individual must not be implanted:

- if the individual is known to be intolerant of the materials used in the implant (including medical grade silicone, platinum, iridium, titanium, and parylene c);
- if there is an absence of cochlear development;
- if the cause of deafness is non-functionality of the auditory nerve and/or the upper auditory pathway;
- if external or middle ear infections are present or if the tympanic membrane is perforated in the ear to be implanted;
- if there are medical contraindications to surgery of the middle and inner ear and anesthesia as required;
- if an anatomic situation is present that would prevent appropriate placement of the stimulator housing and recessing the pins in the bone of the skull or prevent placement of the chosen electrode array into the cochlea, using the implant shall be carefully considered prior to surgery;
- if the psychological status of the individual is unstable or
- if the individual has unrealistic expectations.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MED-EL Cochlear Implant System labeling.

V. DEVICE DESCRIPTION

MED-EL Cochlear Implant System

No design changes to the approved devices in the MED-EL Cochlear Implant System are required for the new indications.

The MED-EL 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, a reference electrode and an electrically evoked compound action potential reference electrode):
  Mi1250 SYNCHRONY 2 (PIN),
  Mi1260 SONATA 2,
  Mi1210 SYNCHRONY ST,
  Mi1200 SYNCHRONY (PIN),
  Mi1050 CONCERTO 2 (PIN),
  SONATATI100
- Processors (single-unit processor or Behind-The-Ear (BTE); For BTE processors, an external coil containing 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):
  SONNET 3 (EAS)
  SONNET 2 (EAS),
  SONNET (EAS),
  RONDO 3,
  RONDO 2,
  RONDO
- Fitting / Apps:
  MAX Programming Interface
  HearCare MED-EL
  MAESTRO 11 and above
  AudioKey 3 and above

In the MED-EL Cochlear Implant System, the audio processor analyzes the sound signal from the microphone according to the speech coding strategy programmed into the audio processor and transforms it into a coded electrical signal that is sent to the externally worn coil. This coded signal contains information about how the individual electrodes of the implant should be stimulated so sound can be perceived. The coil is magnetically held in place over the implant and sends the coded signal across intact skin to the MED-EL cochlear implant via an inductive link. The energy necessary for stimulation is also sent via the inductive link. The electronics within the MED-EL

cochlear implant decode the signals received by the internal secondary coil and send a corresponding pattern of stimulation pulses to the individual electrodes of the active electrode array. These stimulation pulses excite action potentials that travel along the auditory nerve to the brain, where the brain can categorize the sound and assign meaning. Within the MED-EL Cochlear Implant System, the MAESTRO software together with the MAX Programming Interface and HearCare MED-EL app serves to allow programming of the system components to provide access to speech for the user.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The most common alternative treatment of moderate to profound bilateral high-frequency SNHL is the use of conventional air conduction hearing aids. Conventional air conduction hearing aids are often effective for this population unless speech discrimination becomes significantly compromised. Patients may also choose to forego obtaining a hearing device and pursue rehabilitation via speech reading and/or sign language training. Each of these alternatives has its own advantages and disadvantages. Patients should fully discuss the alternatives with their physician and audiologist in order to select the treatment that best meets their expectations and lifestyle.

VII. MARKETING HISTORY

In all markets other than the United States (US), the indications for use for the MED-EL Cochlear Implant System are defined more broadly for individuals (both adults and children). This supplement now better aligns the indication criteria for individuals 7 months or older in the US with the approvals currently held in over 134 countries globally:

> Albania, Algeria, Argentina, Armenia, Aruba, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Belarus, Belgium, Benin, Bhutan, Bolivia, Bosnia and Herzegovina, Brazil, Bulgaria, Cameroon, Canada, Cayman Islands, Chile, Colombia, Costa Rica, Côte d'Ivoire, Croatia, Cuba, Cyprus, Czechia, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Ethiopia, Finland, France, Gabon, Georgia, Germany, Ghana, Greece, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kazakhstan, Kenya, Korea (the Republic of), Kosovo, Kuwait, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Luxembourg, Macao, Macedonia, Malawi, Malaysia, Mali, Malta, Mexico, Moldova, Mongolia, Montenegro, Morocco, Myanmar, Namibia, Nepal, Netherlands, New Zealand, Nigeria, Norway, Oman, Pakistan, Palestine, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Senegal, Serbia, Singapore, Slovakia, Slovenia, South Africa, South Sudan, Spain, Sri Lanka, Sudan, Sweden, Switzerland, Syrian Arab Republic, Taiwan, Tajikistan, Tanzania, Thailand, Togo, Trinidad and Tobago, Tunisia, Turkey, Uganda, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, Uzbekistan, Venezuela, Vietnam, Yemen, Zimbabwe

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 MED-EL Cochlear Implant System:

- Partial or total loss of residual hearing, either suddenly or over time
- Vertigo, dizziness, or balance problems that did not exist preoperatively or worsened postoperatively
- Facial nerve problems including injury and unintended stimulation
- Meningitis
- Perilymphatic fistulae
- Tinnitus that did not exist preoperatively or worsened postoperatively
- Implant migration/extrusion
- Skin flap problems
- Device-related problems including programming problems and device failure requiring explantation/reimplantation.
- Dura exposure for implanting children at ages < 12 months

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

IX. SUMMARY OF NONCLINICAL STUDIES

The pre-clinical studies that were previously submitted to FDA in the original PMA (P000025) and its supplements continue to support the safety and effectiveness of the commercially available MED-EL Cochlear Implant System. No additional preclinical studies were required to evaluate the safety of the MED-EL Cochlear Implant System for the treatment of expanded pediatric indications. The previously approved supplements which support the device, and its components are listed in Table 1 below.

Table 1. Summary of System/Device Components and Approvals

DEVICE	APPROVAL REFERENCE
Cochlear Implants	
Mi1250 SYNCHRONY 2 (PIN)	P000025/S110
Mi1260 SONATA 2	P000025/S114
Mi1210 SYNCHRONY ST	P000025/S103
Mi1200 SYNCHRONY (PIN)	P000025/S079
Mi1050 CONCERTO 2 (PIN)	P000025/S123
Mi1000 MED-EL CONCERT (PIN)	P000025/S050 & S058
SONATATI100	P000025/S021
Audio Processors	
OPUS 1	P000025/S023
OPUS 2	P000025/S029
RONDO	P000025/S062
RONDO 2	P000025/S099
RONDO 3	P000025/S116
SONNET (EAS)	P000025/S078
SONNET 2 (EAS)	P000025/S117

SONNET 3 (EAS)	P000025/S131
Fitting:	
MAX Programming Interface MAESTRO 10 and above HearCare MED-EL AudioKey 3 and above	P000025/S077 P000025/S131 P000025/S126 P000025/S117

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish reasonable assurance of safety and effectiveness of the MED-EL Cochlear Implant System for children in the US under IDE G180269 (*Expanded Indications in the MED-El Pediatric Cochlear Implant Population*). Children enrolled in IDE G180269 received a MED-EL cochlear implant before 6 years of age. Additional data leveraged from IDE G170111 (*Expanded Indications in the Adult Cochlear Implant Population*) supported the PMA approval decision for children implanted at ages ≥ 6 to < 18 years. The summary below describes the clinical study (G180269) used for the PMA approval decision.

A. Study Design

The clinical study on *Expanded Indications in the MED-EL Pediatric Cochlear Implant Population* (IDE G180269) included a prospective study arm and a retrospective study arm to establish a reasonable assurance of safety and effectiveness of the use of the MED-EL Cochlear Implant System in pediatric subjects aged 7 months – 6 years.

The prospective study arm included children implanted at 7-71 months of age between July 30, 2019, and March 26, 2021. The prospective database included data for 38 children collected through April 22, 2022. There were five prospective study sites.

The retrospective study adopted a prospectively designed, retrospective analysis using 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). The retrospective arm included children implanted under 72 months of age between January 1, 2005, and October 31, 2020. The retrospective database included data for 209 children collected through November 1, 2023. There were seven retrospective study sites.

This was a multicenter, nonrandomized, open-label, study. The study design included within-subject, repeated-measure comparisons, where each subject served as his or her own control. The study endpoint was defined as 12 months after device activation (post-activation).

The primary effectiveness endpoint was defined in terms of clinical success and used to calculate an effective sample size. The hypothesis stated that at least 75% of subjects would demonstrate clinical success by 12 months post-activation. If the observed proportion of subjects achieving clinical success is 90%, an effective sample size of 54 subjects was needed to detect a difference from the performance goal of 75% with 80% power. Testing of the primary effectiveness endpoint used a 0.025 level of significance.

The primary effectiveness endpoint was analyzed by first determining which subjects achieved clinical success by 12 months relative to their baseline measurements. The proportion of subjects achieving clinical success was then calculated, and that proportion was tested against the performance goal of 0.75 (75%). A one-sided, 97.5% lower confidence bound was used to demonstrate that the proportion of subjects achieving clinical success is greater than 75%. The lower confidence bound was constructed using the Clopper-Pearson method (exact binomial).

A sensitivity tipping point analysis was performed for subjects with missing effectiveness endpoint data in the intent-to-treat (ITT) analysis population. The primary effectiveness analysis was repeated, assigning subjects with missing endpoint data all combinations of imputed endpoints for "no clinical success"/"clinical success" at 12 months post-activation.

The primary safety endpoint was a tabulation of adverse device effects (ADEs: adverse events related to the device or procedure) through 12 months post-activation. No formal hypothesis was tested for this endpoint.

Primary endpoints were also analyzed based on subgroups of interest using descriptive statistics. Continuous variables were summarized using mean and standard deviation, or median and interquartile range, depending on the distribution and range. Categorical variables were summarized using counts and percentages.

1. Clinical Inclusion and Exclusion Criteria

Children enrolled in the prospective study arm met the following inclusion criteria.

- 7-71 months of age at the time of implantation
- Bilateral, severe to profound SNHL in the high frequencies (≥ 70 dB HL at 2000 Hz and above) and:
    - For children implanted under 12 months of age: PTA3 ≥ 70 dB HL at 500, 1000 and 2000 Hz
    - For subjects implanted at 12-71 months of age: PTA3 ≥ 25 dB HL at 500, 1000 and 2000 Hz
- Insufficient functional access to sound with appropriately fitted hearing aids and aural habilitation (based on clinic standard of care), defined as:
    - For children who lack the requisite language to complete open-set word recognition testing: LEAQ Total Score below the expected value for children with normal hearing of the same chronological age in the everyday listening condition
    - For children with the requisite language to complete open-set word recognition testing: Monosyllabic word score < 60% on the Multisyllabic Lexical Neighborhood Test (MLNT)/Lexical Neighborhood Test (LNT) at 60 dB Sound Pressure Level (SPL), in the ear(s) to be implanted.
- Objective measures consistent with repeatable unaided audiometric thresholds (optional for children ≥ 12 months of age with reliable, ear-specific, behavioral thresholds). Note: Candidates with Auditory Neuropathy Spectrum Disorder (ANSD) were considered if all other inclusion and exclusion criteria were met.

- Radiographic evidence of the potential for full insertion with one of the included electrode arrays in the ear(s) to be implanted
- Ability to undergo general anesthesia. Subjects implanted under 12 months of age must meet the criteria for American Society of Anesthesiologists (ASA) Class 1 or Class 2.
- At least one parent/guardian who is fluent in one of the available languages of the LEAQ
- Parental commitment to study parameters

Children who met any of the following exclusion criteria could not enroll in the prospective study arm.

- Magnetic Resonance Imaging (MRI) evidence of cochlear nerve aplasia/hypoplasia in the ear(s) to be implanted
- Active middle ear infection
- Permanent conductive hearing loss, defined as a persistent air-bone gap (ABG) of > 10 dB HL at three or more frequencies and diagnosed pathology of the outer or middle ear. Note: Candidates with a pseudo-conductive hearing loss like that seen in Enlarged Vestibular Aqueducts (EVA) and no diagnosed pathology of the outer or middle ear could be considered if all other inclusion and exclusion criteria were met.
- Treatable mixed hearing loss
- Current or history of meningitis
- Common cavity in the ear(s) to be implanted
- Skin or scalp condition precluding use of the external audio processor
- Suspected cognitive impairment, organic brain dysfunction, or syndromic etiology that could affect performance (based on medical history, early intervention services, clinical judgment, and/or developmental milestones)
- ASA Class 3 or higher in subjects implanted under 12 months of age
- History of prior use of a hearing implant
- Unrealistic parental/patient expectations
- Inability to complete developmentally appropriate speech perception testing in English

The retrospective study arm used an all-comer design with broad inclusion criteria and limited exclusion criteria to enroll as many children as possible. Children enrolled in the retrospective study arm received a MED-EL cochlear implant between January 1, 2005, and October 31, 2020, at ages ≤ 71 months and had a surgical/operative note from cochlear implantation in the electronic health record (EHR). The retrospective study arm only excluded children implanted at ages 12-71 months who met the current MED-EL labeling criteria for bilateral, profound SNHL (thresholds ≥ 90 dB HL at 1000 Hz and above in both ears).

2. Follow-up Schedule

Study visits for prospective subjects included baseline, surgery, activation, and 1, 3, 6, and 12 months after activation. Table 2 below shows the schedule of events and outcome measures for each prospective study visit. Adverse events and complications were recorded throughout the study duration.

Table 2. Schedule of Events

		Enrollment/ Baseline	Surgery	Activation	1 month post-activation	3 months post-	6 months post-	12 months post-
	Consent	X						
	Medical assessment	X						
	Surgery		X					
	Tympanometry	X						
	Unaided AC and BC thresholds[a]	X		R	X	R	R	X
	Processor programming			X	X	X	X	X
Individual implant ear(s)	Aided word recognition in quiet[c] (ESP[d], MLNT, LNT, CNC Words)	X				X	X	X
Non-implant ear[b]		X						
Individual implant ear(s)	Aided Pediatric AzBio Sentences in quiet[c]	X				X	X	X
Non-implant ear		X						X
Individual implant ear(s)	Aided Pediatric AzBio Sentences in noise (+10 dB SNR, S0N0)[c]	X				X	X	X
Non-implant ear		X						X
Everyday listening condition[e]	LEAQ	X		X	X	X	X	X
	ASC	X		X	X	X	X	X

Abbreviations: X, required testing; AC; air-conduction; BC, bone-conduction; R, recommended testing; ESP, Early Speech Perception test; MLNT, Multisyllabic Lexical Neighborhood Test; LNT, Lexical Neighborhood Test; CNC, Consonant-Nucleus-Consonant; SNR, signal-to-noise ratio; S0N0, speech and noise at 0º azimuth; LEAQ, LittlEARS Auditory Questionnaire; ASC, Auditory Skills Checklist.

[a] AC pure-tone thresholds at 125-8000 Hz (ear-specific with insert earphones if possible) and BC pure-tone thresholds at 500-4000 Hz (with the bone oscillator on each mastoid if possible)

[b] For children implanted unilaterally (n = 3).

[c] For children with the requisite language skills (n = 2 at baseline), using a decision tree to progress through the speech recognition hierarchy with speech presented at 60 dB SPL and children seated 1 meter from the speaker.

[d] Monosyllable subtest only

[e] Using both ears

Retrospective chart review included similar preoperative data collected up to 180 days before surgery and postoperative data collected up to approximately 12 months after activation (+/- 180 days). Of 209 children with retrospective data, eight were not followed by the implanting center through 12-months post-activation. Four children moved and four children were lost to follow-up before the 12-month visit window.

Retrospective analysis included tests of speech recognition and auditory skill development comparable to the prospective arm that were commonly used in clinical practice between 2005 and 2020. Speech

recognition tests included the following.

- Early Speech Perception (ESP) Test
- Northwestern University-Children's Perception of Speech (NU-CHIPS) Test
- Multisyllabic Lexical Neighborhood Test (MLNT)/Lexical Neighborhood Test (LNT)
- Phonetically Balanced Kindergarten (PBK) Words
- Consonant-Nucleus-Consonant (CNC) Words
- Pediatric AzBio Sentences

Questionnaires included the following.

- Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS)/Meaningful Auditory Integration Scale (MAIS)
- LittlEARS Auditory Skills Questionnaire (LEAQ)
- Auditory Skills Checklist (ASC)

The key timepoints are shown below in the Tables 3-4 summarizing safety and effectiveness.

3. Clinical Endpoints

Table 3 below lists the study objectives and endpoints.

Table 3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and effectiveness of MED-EL cochlear implants for children implanted outside the current FDA-approved indications	Safety: The number and proportion of subjects experiencing an ADE by 12 months post-activation
	Effectiveness: At least 75% of subjects will show clinical success by 12-months post-activation on developmentally appropriate measures of speech recognition or auditory skill development
Secondary (Prospective Arm)	
To compare postoperative outcomes with the MED-EL cochlear implant to preoperative performance with appropriately fitted hearing aids	1. Change from baseline on a hierarchy of developmentally appropriate tests of word and sentence recognition in the implanted ear(s)
	2. Change from baseline in Total Score on the LEAQ and ASC at 12 months post-activation in the everyday listening condition

Regarding safety, ADEs were defined as adverse events related to the device or surgical procedure through 12 months post-activation. Adverse events unrelated to the device and procedure were reported separately to help determine the benefit/risk profile for regulatory decision-making.

Regarding effectiveness, clinical success was based on speech recognition, if available, and used a hierarchy similar to the Pediatric Minimum Speech Test Battery. Clinical success for children without a

preoperative speech recognition score was based on the postoperative LEAQ Total Score, if reported, or similar developmentally appropriate questionnaire.

Regarding success/failure criteria, overall study success was based on the percentage of children who reached pre-defined performance goals for individual clinical success. Study success required at least 75% of children to reach the performance goals for individual clinical success shown in Table 4 by 12 months post-activation.

Table 4. Pre-defined Performance Goals for Clinical Success

Prospective Arm	**Retrospective Arm**
Speech Recognition, if available	
Improvement of ≥ 10 percentage points on MLNT with the cochlear implant by 12 months post-activation, compared to baseline with a hearing aid in the individual implant ear(s) for prospective subjects with preoperative MLNT scores	Improvement of ≥ 10 percentage points on the same developmentally appropriate speech recognition test or progression to a more difficult test in the speech recognition hierarchy with the cochlear implant by 12 months post-activation, compared to preoperative scores with a hearing aid in the individual implant ear(s)
Auditory Skill Development	
LEAQ Total Score ≥ 25 points[a] by 12 months post-activation in the everyday listening condition	LEAQ Total Score ≥ 25 points[a], if reported, or improvement of ≥ 25 percentage points on another developmentally appropriate questionnaire in the everyday listening condition by 12 months post-activation

[a] Mean Total Score expected for children with normal hearing at 12 months of age.

B. Accountability of PMA Cohort

At the time of prospective database lock, 36 of 38 subjects (95%) implanted in the prospective study arm were available for analysis at study completion, the 12-month post-activation visit. Of 209 subjects enrolled in the retrospective study arm, 209 had safety data available for analysis. Of those, 201 subjects (96%) were seen within the estimated 12-month post-activation endpoint window (+/- 180 days), and 92 children have "evaluable data" for effectiveness analysis at study completion. Figure 1 and Figure 2 below show subject disposition in each analysis population.

Figure 1 shows subject disposition in the prospective study arm. The intent-to-treat (ITT) population includes all subjects with a signed and dated consent. Three subjects were terminated before intervention was attempted and considered screen failures. Thirty-eight children received the study device. The per protocol (PP) population includes 36 children with primary effectiveness measured at 12 months post-activation.

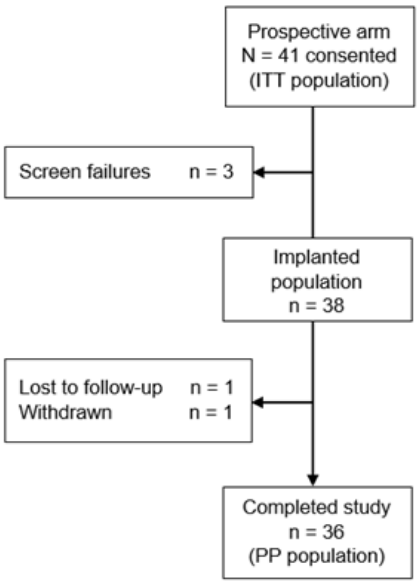

Figure 1. Prospective subject distribution.

Figure 2 shows subject disposition for the retrospective study arm. The retrospective arm used an all-comer approach to enroll 209 children with available safety data (ITT population), and no subjects were withdrawn after enrollment. At a minimum, safety data included a surgical/operative note from cochlear implant surgery in the EHR. However, not all retrospective subjects had effectiveness data available for analysis. The "effectiveness analysis population" includes children with effectiveness outcome measures reported in the EHR (n = 121), while the "evaluable data population" (n = 92) includes children with effectiveness data that could be used to determine clinical success for the primary effectiveness endpoint. Figure 2 shows where subjects fall out of the effectiveness analysis population and evaluable data population.

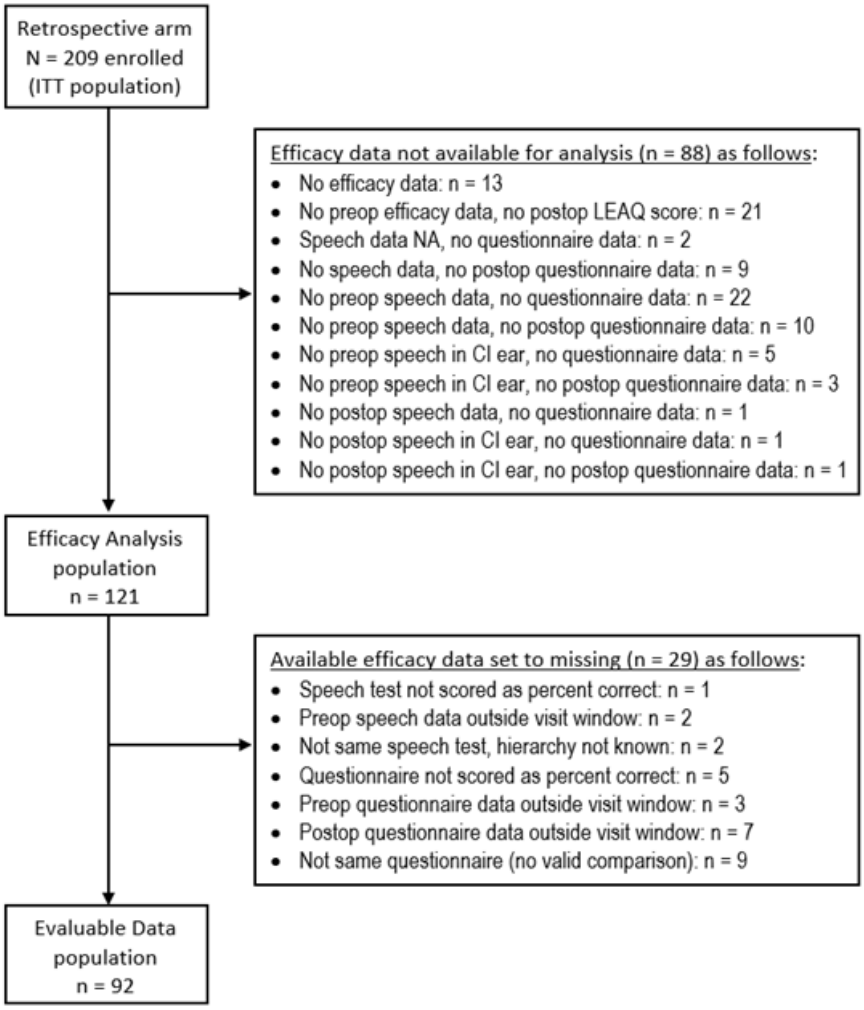

Figure 2. Retrospective subject distribution.

C. Study Population Demographics and Baseline Parameters

Children in this prospective study were implanted under 6 years of age. All subjects had severe to profound SNHL in the high frequencies. Of 38 subjects implanted, 26 (68%) were implanted under 12 months of age with bilateral, severe to profound SNHL. Enrollment of children aged 12-71 months with mild to moderately severe SNHL in the low frequencies posed significant challenges. Investigators reported that children with significant low-frequency residual hearing often do not present for cochlear implant evaluation until they reach school age and struggle in the classroom setting. Enrollment of these children was disproportionately impacted by COVID-19 stay-at-home orders and restrictions. Borderline cochlear implant candidates were not exposed to challenging listening environments during social distancing, resulting in fewer prospective subjects with residual hearing implanted at ages 12-71 months. Poor uptake in this subgroup halted prospective recruitment, and the study shifted to retrospective enrollment during the COVID-19 pandemic. Table 5 below shows prospective subgroup stratification for baseline characteristics.

Table 5. Prospective Baseline Characteristics (Implanted Population, n = 38)

Subgroup	**Subjects**[a]
Age at implantation (months)	**n = 38**
Median (IQR) [range][b]	9.0 (7.8-15.3) [7.0-61.0]
7-11 months	26 (68)
12-24 months	5 (13)
25-71 months	7 (18)
Sex	**n = 38**
Female	20 (53)
Male	18 (47)
Preoperative PTA3 at 500, 1000, 2000 Hz (dB HL)	**n = 41**[c]
Median (IQR) [range]	110 (100-120) [63-125]
PTA3 ≥ 90 dB HL	34 (83)
PTA3 70-89 dB HL	6 (15)
PTA3 25-69 dB HL	1 (2)

Abbreviation: IQR, interquartile range.

[a] Data presented as median (IQR) [range] or n (%).

[b] Data collected in years and months and reported in months to one decimal place.

[c] Preoperative PTA3 differs in right and left ears for three bilateral subjects (38 + 3 = 41).

The retrospective arm is more representative of the intended population, with a greater proportion of children implanted at ages 12-71 months compared to those implanted under 12 months of age. Table 6 shows retrospective subgroup stratification for baseline characteristics. Subjects implanted at ages 25-71 months include children subsequently implanted in the second ear and children with progressive hearing loss, single-sided deafness, or asymmetric hearing loss. Eighty-five of 209 subjects (41%) received bilateral implants and are included in more than one subgroup when subgroup data differ between the two ears.

Table 6. Retrospective Subjects per Subgroup (ITT Population, N = 209)

Subgroup	**Subjects (N = 209)**[a,b]
Age at implantation (months)	**N = 227**[c]
Median (IQR) [range]	22 (11-46) [3-71]
<12 months	70 (31)
12-24 months	49 (22)
25-71 months	108 (48)
Sex	**N = 209**
Female	106 (51)
Male	103 (49)
Preoperative PTA3 at 500, 1000, 2000 Hz dB HL)	**n = 209**[d,e]
Median (IQR) [range]	90 (80-113) [37-125]
PTA3 25-39 dB HL	1 (0)
PTA3 40-69 dB HL	20 (10)

Table 6. Retrospective Subjects per Subgroup (ITT Population, N = 209)

Subgroup	**Subjects (N = 209)**[a,b]
PTA3 70-89 dB HL	72 (34)
PTA3 ≥ 90 dB HL	116 (56)
Preoperative word score (% correct)	**n = 24**[f,g]
Median (IQR) [range]	25 (8-40) [0-83]
0-20% correct	10 (42)
21-40% correct	8 (33)
≥ 41% correct	6 (25)

[a] Data presented as median (IQR) [range] or n (%).
[b] Counts and frequencies exclude subjects without available data in the medical record.
[c] Age subgroup differs in first and second ears for 18 sequential bilateral subjects (209 + 18 = 227).
[d] Data not available for 23 subjects (209 – 23 = 186), and preoperative PTA3 subgroup differs in right and left ears for 23 subjects (186 + 23 = 209).
[e] Subjects without a PTA3 may have preoperative unaided thresholds based on speech awareness thresholds, speech recognition thresholds, and/or Ling 6 sound thresholds.
[f] Data not available for 185 subjects (209 - 185 = 24).
[g] Subjects without available word scores may have completed speech testing that does not yield a word score and/or more than 6 months before surgery (e.g., Ling 6 Sounds, ESP Pattern Perception, Bamford-Kowal-Bench (BKB) Speech In Noise (SIN)).

D. Safety and Effectiveness Results

1. Safety Results

The primary safety endpoint in both study arms includes the number and percentage of subjects experiencing ADEs by 12 months post-activation.

Rates of ADEs and Serious Adverse Device Effect (SADE)

Prospective analysis includes ADEs reported through at least 12 months post-activation and continuing through study completion for 38 prospective subjects in the implanted population. Nine prospective subjects (24%) experienced 11 ADEs, including 2 subjects (5%) with a SADE. Table 7 summarizes all prospective subjects with one or more ADEs.

Table 7. Summary of Prospective ADE Classifications (Implanted Population, n = 38)

Classification of ADE	**Subjects Affected (n = 38)**[a]
Number of subjects with any ADE	9 (24)
Number of subjects with any SADE	2 (5)
Number of subjects with any unanticipated ADE	0 (0)
Number of subjects with any unanticipated, SADE	0 (0)

[a] Data presented as n (%).

The retrospective safety analysis includes ADEs reported through 12 months post-activation in the

evaluable data population (n = 92) and the ITT population (N = 209). Eleven of 92 retrospective subjects (12%) in the evaluable data population experienced 12 ADEs, including four subjects (4%) with a SADE. Thirty three of 209 retrospective subjects (16%) in the ITT population experienced 33 ADEs, including 12 subjects (6%) with a SADE. Overall, the rates of ADEs and SADEs do not differ between the ITT population (n = 209) and the evaluable data population (n = 92). Table 8 and Table 9 show retrospective subjects with one or more ADEs in the evaluable data and the ITT populations, respectively.

Table 8. Summary of Retrospective ADE Classifications (Evaluable Data Population, n = 92)

Classification of ADE	Subjects Affected (n = 92)[a]
Number of subjects with any ADE	11 (12)
Number of subjects with any SADE	4 (4)

[a] Data presented as n (%).

Table 9. Summary of Retrospective ADE Classifications (ITT Population, N = 209)

Classification of ADE	Subjects Affected (N = 209)[a]
Number of subjects with any ADE	33 (16)
Number of subjects with any SADE	12 (6)

[a] Data presented as n (%).

Overall, ADE rates ranged from 12-24% across prospective/retrospective study populations, with SADE rates consistently low at 4-6%.

Types of ADEs and SADEs

The most reported ADE in the prospective arm was abnormal telemetry (n = 3). Two subjects had irregular impedances on two channels that resolved with programming changes. One child had high impedances on seven channels and required surgery to replace the device. The second most common prospective ADE was postoperative symptoms (n = 2) and infection (n = 2). One child with an infection was explanted and reimplanted at a later date. Table 10 lists all ADEs and revision surgeries in the prospective arm.

Table 10. Type and Number of Prospective ADEs (Implanted Population, n = 38)

ADE Type	Number of ADEs	Subjects Affected (n = 38)[a]
Abnormal telemetry[b]	3	3 (8)
Postoperative symptoms[c]	2	2 (5)
Infection	2	1 (3)
CSF leak	1	1 (3)
Loss of residual hearing	1	1 (3)
Overstimulation	1	1 (3)
Suture irritation	1	1 (3)
SADE		

Table 10. Type and Number of Prospective ADEs (Implanted Population, n = 38)

ADE Type	Number of ADEs	Subjects Affected (n = 38)[a]
No	9	9 (24)
Yes	2	2 (5)[d]
Unanticipated ADE		
No	11	9 (24)
Yes	0	0 (0)
Implant replaced		
No		36 (95)
Yes		2 (5)

Abbreviation: CSF, cerebrospinal fluid
[a] Data presented as n (%).
[b] High impedances, short circuit.
[c] Drainage, swelling.
[d] Nine subjects experienced 11 (S)ADEs, including two subjects with one ADE and one SADE.

The most common retrospective ADE in the evaluable data population of the retrospective arm was infection, including cellulitis (n = 2) and mastoiditis (n = 2). The second most common retrospective ADE in this population was postoperative symptoms (n = 3), including one SADE in a child readmitted for pain and swelling. No subjects in the evaluable data population were explanted by the 12-month retrospective endpoint. Table 11 lists all ADEs and revision surgeries in the evaluable data population of the retrospective arm.

Table 11. Type and Number of Retrospective ADEs (Evaluable Data Population, n = 92)

ADE Type	Number of ADEs	Subjects Affected (n = 92)[a]
Infection[b]	4	4 (4)
Postoperative symptoms[c]	3	3 (3)
CSF leak/gusher	2	2 (2)
Skin-related[d]	2	2 (2)
Device migration	1	1 (1)
Serious ADE		
No	8	8 (9)
Yes	4	4 (4)[e]
Implant replaced		
No		92 (100)
Yes		0 (0)

Abbreviation: CSF, cerebrospinal fluid.
[a] Data presented as n (%).
[b] Dizziness, headache, nausea, vomiting, swelling, pain.
[c] Cellulitis, mastoiditis.
[d] Dermatitis, irritation, redness.
[e] Eleven subjects experienced 12 (S)ADEs, including one subject with one ADE and one SADE.

The most common retrospective ADE in the ITT population of the retrospective arm was CSF leak/gusher (n = 10), including one SADE in a child readmitted for surgical repair of a CSF leak. The second most common ADE in this population was postoperative symptoms (n = 10), including one SADE in a child readmitted for pain and swelling. The third most common ADE was infection (n = 7). Five subjects in the ITT population were explanted by the 12-month retrospective endpoint. Table 12 lists all ADEs and revision surgeries in the ITT population of the retrospective arm.

Table 12. Type and Number of Retrospective ADEs (ITT Population, N = 209)

ADE Type	Number of ADEs	Subjects Affected (N = 209)[a]
CSF leak/gusher	10	10 (5)
Postoperative symptoms[b]	10	9 (4)
Infection/suspected infection[c]	7	7 (3)
Skin-related[d]	4	4 (2)
Device/electrode migration	3	3 (1)
Poor telemetry/device failure	2	2 (1)
Other (revision)	1	1 (0)
Serious ADE		
No	23	21 (10)
Yes	12	12 (6)
Implant replaced		
No		204 (98)
Yes		5 (2)

[a] Data presented as n (%).
[b] Bleeding, dizziness, nausea, vomiting, headache, swelling, pain.
[c] Cellulitis, mastoiditis, MSSA, suspected infection.
[d] Dermatitis, irritation, redness, stitch abscess.

Overall, all ADEs were known risks of cochlear implantation, with low device explantation rates at 2-3%.

Surgical/Anesthetic Risks

Additional safety data associated with surgical/anesthetic risks were collected for the prospective and retrospective arms, including total duration under anesthesia, estimated blood loss, readmissions to cochlear implant center/hospital within 30 days post-surgery, temperature regulation issues and/or any instances of arrhythmia, facial nerve injury, exposed dura during drilling, skin flap breakdown or extrusion, CSF leak, and dura abraded, etc.. Table13 and Table 14 list the breakdown of surgical/anesthetic risks by age groups (i.e., 7-8 months, 9-11 months, 12-24 months, and 25-71 months). The breakdown results do not show more risks among children implanted at ages < 12 months than children implanted at ages 12-71 months except for dura exposure and minor skin irritation (highlighted in Tables 13 and 14 below). This is because younger children < 12 months typically have thinner skull thickness and skin flap thickness than older children > 12 months (see "Physical Observations" in Table 15 below). No children in either study arm experienced dural injury or

complications due to dural exposure, and no children experienced skin flap breakdown or device extrusion. Safety data were further broken down for younger children implanted at ages of 7-8 months vs. 9-11 months. The breakdown results do not show more risks (including dura exposure) among children implanted at ages 7-8 months than children implanted at ages 9-11 months (highlighted in tables below).

Table 13. Prospective Surgical and Anesthetic Risks by Age Group (Implanted Population, n = 38)

Characteristic	**7-8 Months (n = 15)**[a]	**9-11 Months (n = 11)**[a]	**12-24 Months (n = 5)**[a]	**25-61 Months (n = 7)**[a]
Anesthesia Time, One Ear (hours)	Not applicable	Not applicable	1.9 (0.0) [1.9 -1.9][b]	2.1 (0.2) [1.9-2.3]
Anesthesia Time, Two Ears (hours)	4.6 (1.1) [3.5-7.0]	4.4 (1.4) [2.2-6.4]	4.9 (1.4) [3.2-6.0]	4.2 (0.6) [3.3-4.8]
Blood Loss (cc)	15 (9) [5-30]	17 (13) [3-50]	10 (4) [5-15]	19 (16) [5-50]
Readmission in 30 Days	1 (4)[c]	0 (0)	0 (0)	0 (0)
Temperature Regulation/Arrythmia	0 (0)	0 (0)	0 (0)	0 (0)
Facial Nerve Injury	0 (0)	0 (0)	0 (0)	0 (0)
Exposed Dura[d]	**1 (7)**	**2 (18)**	0 (0)	1 (14)
Dura Abraded	0 (0)	0 (0)	0 (0)	0 (0)
Skin Flap Breakdown/Device Extrusion	0 (0)	0 (0)	0 (0)	0 (0)
Minor Skin Irritation	**2 (13)**[e]	0 (0)	0 (0)	0 (0)
CSF Leak	1 (7)[f]	0 (0)	0 (0)	0 (0)

[a] Data presented as mean (SD) [range] or n (%).
[b] Includes only one subject.
[c] Unrelated upper respiratory virus.
[d] No complications reported.
[e] Suture reaction (n = 1), incision redness/drainage (n = 1). Both resolved with non-invasive treatment in < 2 weeks.
[f] Treated before closing incision without complications.

Table 14. Retrospective Surgical and Anesthetic Risks by Age Group (ITT Population, N = 209)

Characteristic	**< 9 Months (n = 20)**[a,b]	**9-11 Months (n = 56)**[a,b]	**12-24 Months (n = 49)**[a,b]	**25-61 Months (n = 108)**[a,b]
Anesthesia Time, One Ear (hours)	2.8 (0.9) [2.0-3.9]	3.0 (0.8) [1.7-5.0]	3.2 (0.8) [1.4-5.5]	3.1 (1.0) [1.1-7.2]
Anesthesia Time, Two Ears (hours)	4.9 (0.8) [3.5-6.4]	4.4 (1.1) [2.6-6.5]	5.1 (0.8) [4.4-6.0]	4.5 (1.6) [2.4-6.2]
Blood Loss (cc)	10 (9) [2-30]	9 (6) [0-20]	8 (6) [1-30]	9 (9) [0-50]

Table 14. Retrospective Surgical and Anesthetic Risks by Age Group (ITT Population, N = 209)

Characteristic	< 9 Months (n = 20)[a,b]	9-11 Months (n = 56)[a,b]	12-24 Months (n = 49)[a,b]	25-61 Months (n = 108)[a,b]
Readmission in 30 days	0 (0)	3 (6)[c]	0 (0)	1 (1)
Temperature Regulation/Arrythmia	0 (0)	0 (0)	0 (0)	0 (0)
Facial Nerve Injury	0 (0)	0 (0)	0 (0)	0 (0)
Exposed Dura	**4 (21)[d]**	**9 (16)[d]**	0 (0)	0 (0)
Skin flap breakdown/device extrusion	0 (0)	0 (0)	0 (0)	0 (0)
Minor Skin Irritation	0 (0)	1 (2)[e]	2 (4)	1 (1)
CSF Leak[f]	0 (0)	2 (4)	4 (8)	4 (4)

[a] Data presented as mean (SD) [range] or n (%).
[b] Age subgroup differs in first and second ears for 24 sequential bilateral subjects (20 + 56 + 49 + 108 = 233 – 24 = 209).
[c] Pain (n = 1), unrelated fever (n = 1), surgical repair of CSF leak (n = 1).
[d] Age subgroup differs in first and second ears for three sequential bilateral subjects (4 + 9 = 13 – 3 = 10). All 10 subjects (13 ears) implanted by one surgeon who drilled a deeper implant bed and bony island in surgeries before 2013 with no complications.
[e] Mild skin irritation/redness resolved with weaker magnet.
[f] Nine of 10 subjects (90%) had EVA or other cochlear malformation.

Table 15. Physical Observations – Prospective Arm (Implanted Population, n = 38)

	7-8 Months (n = 15)[a,b]	9-11 Months (n = 11)[a,b]	12-24 Months (n = 5)[a,b]	25-61 Months (n = 7)[a,b]
Skull Thickness	2.8 (0.5) [1.5-3.5]	2.3 (0.4) [2.0-3.0]	3.4 (1.5) [2.0-5.0]	5.0 (2.1) [3.0-9.0]
Skin Flap Thickness	3.6 (1.0) [2.0-6.0]	3.8 (0.9) [3.0-6.0]	4.4 (1.3) [3.0-6.0]	4.7 (1.2) [3.0-6.0]
Abnormal Course of FN	0 (0)	2 (18)	1 (20)	0 (0)

[a] Data presented as mean (SD) [range] or n (%).
[b] Mean skull and skin flap thickness are general estimates based on preoperative imaging or intraoperative observation. Preoperative imaging does not correlate with age at implant, and the duration between imaging and surgery varies across subjects.

2. Effectiveness Results

The analysis of effectiveness was based on 92 retrospective subjects with evaluable data at the 12-month time point (+/- 180 days). Effectiveness was also supported by 36 prospective subjects with effectiveness data at the 12-month endpoint. Table 16 and Table 17 below present key effectiveness outcomes in the retrospective and prospective populations, respectively. In total, 29 of 36 prospective subjects (81%) and 81 of 92 retrospective subjects (88%) reached clinical success by 12 months post-activation. The retrospective primary effectiveness endpoint was met with a 95% confidence interval

of 80% to 94% ($p = 0.002$). While 81% of prospective subjects achieved clinical success, the sample size of 36 subjects is too small to show significance for the primary effectiveness endpoint ($p = 0.2207$).

Table 16. Retrospective Primary Effectiveness Endpoint: Clinical Success by 12 Months Post-Activation (Evaluable Data Population, n = 92)

	Speech (n = 28)	Questionnaire (n = 64)	Total (n = 92)	*P*-value
Clinical Success[a]	27 (96)	54 (84)	81 (88)	$p = 0.002$

[a] Data presented as n (%).

Table 17. Prospective Primary Effectiveness Endpoint: Clinical Success by 12 Months Post-Activation (PP Population, n = 36)

	MLNT (n = 2)	LEAQ (n = 34)	Total (n = 36)	*P*-value
Clinical Success[a]	2 (100)	27 (79)	29 (81)	$p = 0.2207$

[a] Data presented as n (%).

Table 18 and Table 19 below present the number/percentage of subjects implanted at the ages 7-8 months, 9-11 months, and 12 months-6 years who achieved clinical success in the retrospective arm and the prospective arm, respectively. Overall, the percentages of children who achieved clinical success do not differ across age groups of 7-8 months, 9-11 months, and 12 months-6 years.

Table 18. Retrospective subjects implanted at ages 7-8 months, 9-11 months, and 12 months - 6 years: Clinical Success by 12 Months Post-Activation (Evaluable Data Population, n = 92)

	7-8 Months (n = 9)	9-11 Months (n = 28)	12 months – 6 years (n = 55)
Clinical Success[a]	8 (89)	24 (86)	49(89)

[a] Data presented as n (%).

Table 19. Prospective subjects implanted at the age 7-8 months, 9-11 months, and 12 months – 6 years: Clinical Success by 12 Months Post-Activation (PP Population, n = 36)

	7-8 Months (n = 14)	9-11 Months (n = 11)	12 months – 6 years (n = 11)
Clinical Success[a]	13 (93%)	8 (73%)	8 (73%)

[a] Data presented as n (%).

3. Subgroup Analyses

The study was not specifically powered to examine associations among all baseline characteristics. Post-hoc subgroup analyses for both study arms included summary statistics of categorical data stratified by subject demographic and preoperative characteristics. Subgroup analyses for homogeneity across characteristics were assessed using logistic regression. A separate logistic regression model was created for each covariate, with primary effectiveness success as the dependent variable. The strength of

evidence of subgroup heterogeneity was assessed using the significance probability from the Chi-square statistic resulting from the logistic regression analysis.

Prospective subgroup analyses revealed no evidence of heterogeneity across any predefined subgroups or covariates. Among retrospective subgroups, only preoperative comorbidities showed evidence of heterogeneity treatment response. Subjects without preoperative comorbidities demonstrated higher rates of primary effectiveness success. Among the 12 subjects with preoperative comorbidities, 4 (33%) failed to achieve clinical success as defined by the study protocol. All four subjects presented with retrocochlear pathology and multiple comorbidities. The only retrospective covariate significantly associated with primary effectiveness success was baseline performance on questionnaires other than the LEAQ. Lower scores were associated with greater likelihood of success. This association was likely influenced by three outliers with near-ceiling baseline scores (≥ 70%).

4. Pediatric Extrapolation

In this premarket application, existing clinical data were leveraged to support the reasonable assurance of safety and effectiveness of the proposed, expanded, pediatric indications for use in the pediatric sub-population of children aged 6-18 years per the FDA guidance titled "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices", issued on June 21, 2016. The specific details about the leveraged data are included in the Section XI.

E. Data limitation for the Premarket Clinical Study

Real-World Data (RWD) Quality Analyses

The relevance and reliability of RWD collected from the retrospective, multi-centric, longitudinal, clinical analysis were evaluated according to the FDA RWE guidance. The RWD demonstrated sufficient quality to ensure source reliability and validity of analysis findings, supporting the proposed pediatric indication expansion for children aged 7-71 months, with a major data limitation noted below.

Limitations of Premarket Clinical Data

Limitations of premarket clinical data collected under G180269 include: 1) the prospective arm's small sample size (n=36) failed to demonstrate statistical significance for the primary effectiveness endpoint (p = 0.2207), despite achieving an 81% clinical success rate (29/36 subjects); 2) substantial missing data in the retrospective arm RWD collection resulted in only 92 of 209 subjects (44%) having evaluable data for primary effectiveness analysis; and 3) no premarket data were available for the requested pediatric indication expansion for children aged 6-18 years. The premarket regulatory decision relied largely on extrapolation from adult clinical trial data (G170111) per the FDA guidance titled "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices", issued on June 21, 2016 (see Section XI).

XI. 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 41 investigators, none of whom were full-

time or part-time employees of the applicant, and five 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: 5
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interests/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.

XII. PEDIATRIC EXTRAPOLATION

The FDA guidance document "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" was issued on June 21, 2016. The document offers guidance on when extrapolation of available clinical data, such as adult data, is appropriate for use in the pediatric population. The guidance provides a decision tree for use in evaluating the suitability of extrapolation for a particular dataset. This section addresses questions from the pediatric extrapolation decision tree (Figure 1 of the FDA guidance document) to demonstrate that a full extrapolation could be applied to the available clinical data collected in an adult population under clinical trial G170111 (available at the link: P000025-S129 SSED). Data collected under G170111 were used in support of an expansion in cochlear implant criteria to include children aged 6-18 years with bilateral, moderate to profound SNHL with limited benefit from amplification.

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

Yes. Newborn hearing screenings identify permanent hearing loss at a rate of approximately 1.7 per 1,000. Prevalence of hearing loss increases with age and has been estimated as 3.5 per 1,000 to 23 per 1,000 in adolescents. Some cases of hearing loss in children may have a later onset or be progressive in nature, and amplification may only provide benefit for a period of time. Children with ineffectively treated hearing loss may experience difficulty in following or understanding instructions, frustration with communication breakdowns, and feeling exhausted at the end of a school day. Hearing loss that is not adequately aided may cause academic, behavioral, and social difficulties at school. Appropriate intervention is important for ensuring older children and adolescents do not fall behind in the classroom.

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. Speech perception both in quiet and in noise was the primary effectiveness endpoint in the clinical trial conducted in adults, with scores at 6 months post-activation compared to preoperative scores with an appropriately fitted hearing aid. Speech perception in quiet was measured via CNC

word score, which has been demonstrated to be an appropriate test material for children aged 5 years and older. Speech perception in noise was measured via AzBio sentence score. The pediatric version of the AzBio is recommended for children aged 5 years and older. Given that both test materials used are also used in the pediatric population, it is reasonable to expect that effectiveness outcomes from the adult study would directly apply to the pediatric population 6 years and older.

The number and proportion of device-related AEs served as the primary safety outcome in the adult study. The safety profile of the MED-EL cochlear implant system is the same for both adults and children 6 years and older. Because the risks of cochlear implantation are well understood, the AE rate in the adult population is expected to be similar in the pediatric population.

Questions Box C.

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?

The device is implanted but does not differ in location or duration of implantation. The size of the human cochlea is anticipated to be the same in a child 6 years of age and older as it is for an adult, as the cochlea does not grow throughout the lifespan. While the head may be smaller in the pediatric population, the location of the implant is the same. The duration of both the procedure and device use is also anticipated to be the same in adults and children aged 6 years and older.

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. There are no differences in the device or use of the device between the adult and intended pediatric population that could impact safety or effectiveness in a 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 currently approved for children younger than the intended population. The risk profile for cochlear implantation is well understood, and there are no characteristics in children 6 years of age and older that would impact safety or effectiveness in a meaningful way.

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. Both adult and pediatric cochlear implant candidates must demonstrate significant SNHL that cannot be appropriately amplified with a hearing aid. Both populations undergo similar testing to identify hearing loss and demonstrate a variety of etiologies, including genetic causes, infection,

and unknown or idiopathic hearing loss. Children who become cochlear implant candidates at 6 years of age or older may demonstrate underlying pathology more similar to the adult population. Children with low-frequency residual hearing, especially those at risk of progressive hearing loss, need early access to cochlear implants to reach their full potential. Children in this group have demonstrated better performance with cochlear implants compared to hearing aids, which is similar to the adult population, where cochlear implantation is typically recommended when candidacy criteria are met so patients can experience the full benefits of a cochlear implant sooner.

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

No. There are no other identified differences between the adult and intended pediatric population that could impact device effectiveness or safety in a clinically meaningful way.

Conclusions for pediatric data extrapolation

The safety and effectiveness for the requested indication expansion among adults (i.e., bilateral moderate to profound SNHL, defined as a low-frequency PTA greater than 40 dB HL and high frequencies not better than 65 dB HL; limited benefit from amplification with CNC word scores in quiet of 50% or less in the ear to be implanted and 60% or less in the non-implant ear on recorded tests of monosyllabic word recognition) have been demonstrated in the G170111 clinical study, in terms of improved speech perception in quiet and noise, and higher subjective quality of hearing (see Section X 1. of P000025-S129 SSED). Additionally, published studies have also provided evidence to confirm and support the G170111 study findings among pediatric patients for the proposed indications (see Section XII). Together, it is appropriate to leverage the available, clinical, adult data from the G170111 study and literature findings to support extrapolation among pediatric patients aged 6-18 years who meet the following audiometric/speech criteria: 1) a moderate to profound SNHL in the low frequencies, defined by a low-frequency PTA (LFPTA) >40 dB HL at 250, 500, and 1000 Hz with thresholds not better than 65 dB HL at 3000-8000 Hz, and 2) limited benefit from hearing aids, defined by test scores of 50% correct or less in the ear to be implanted and 60% or less in the non-implant ear on recorded tests of monosyllabic word recognition (e.g., CNC Words).

XIII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

In accordance with the required elements for a PMA, the applicant conducted an extensive literature search to collect additional supporting clinical evidence of cochlear implants in expanded pediatric indications.

A. Bibliography of published reports on the indication expansion in the pediatric cochlear implant population - Children younger than 12 months of age with severe-to-profound SNHL.

Literature Search Strategy

Table 20 lists the literature search strategy and PubMed search results for expanded cochlear implant indications in children <12 months of age with severe-to-profound SNHL (reporting period October 31, 2013 –October 31, 2023; reporting period November 1, 2023 - October 31, 2024).

Table 20. Search Step	Search Terms	Number of retrieved publications from October 31, 2013 to October 31, 2023	Number of retrieved publications from November 1, 2023 to October 31, 2024
1	cochlear implant	21, 075	22,294
2	"word recognition" OR "word discrimination" OR "word perception" OR "speech discrimination" OR "speech recognition" OR "speech perception"	40,088	41,877
3	“auditory development” OR “auditory skills” OR “auditory behaviour” OR “auditory behavior” OR “LittlEARS” OR “LEAQ” OR "LittlEARS Auditory Questionnaire" OR “IT-MAIS” OR "Infant-Toddler Meaningful Auditory Integration Scale" OR “MAIS” OR "Meaningful Auditory integration Scale" OR "Parents Evaluation of Aural/Oral Performance" OR “Auditory Skills Checklist” OR "questionnaire" OR "parent questionnaire" OR "functional listing index" OR "meaningful use of speech scale"	554,213	596,444
4	“safety”	899,229	990,360
5	"severe to profound hearing loss" OR "severe-to-profound hearing loss" OR "severe-to-profound sensorineural hearing loss" OR "severe to profound" OR "severe-to-profound" OR "bilateral hearing loss" OR "bilateral sensorineural hearing loss”	5,286	5,563
6	Children OR pediatric OR infant	3,990,189	4,181,037
7	2 OR 3 OR 4	1,464,842	1,596,953
8	1 AND 7	8,025	8,493
9	8 AND 5 AND 6	375	391
10	Limit 9 to *Language*: *English*	361	-
10	Limit 9 to Language: English, and Publication date: 01 November 2023 to 31 October 2024	-	**18**

11	Limit 10 to *Publication date*: 31 October 2013 – 31 October 2023	**223**

Table 21 lists Cochrane Reviews and Cochrane Trials search results for expanded cochlear implant indications in children <12 months of age with severe-to-profound SNHL (October 2013 - October 2024)

Table 21. Search Term	Cochrane Reviews	Cochrane Trials
(((cochlear implant) AND ((("word recognition" OR "word discrimination" OR "word perception" OR "speech discrimination" OR "speech recognition" OR "speech perception") OR ("auditory development" OR "auditory skills" OR "auditory behaviour" OR "auditory behavior" OR "LittlEARS" OR "LEAQ" OR "LittlEARS Auditory Questionnaire" OR "IT-MAIS" OR "Infant-Toddler Meaningful Auditory Integration Scale" OR "MAIS" OR "Meaningful Auditory integration Scale" OR "Parents Evaluation of Aural/Oral Performance" OR "Auditory Skills Checklist" OR "questionnaire" OR "parent questionnaire" OR "functional listing index" OR "meaningful use of speech scale")) OR ("safety"))) AND ("severe to profound hearing loss" OR "severe-to-profound hearing loss" OR "severe-to-profound sensorineural hearing loss" OR "severe to profound" OR "severe-to-profound" OR "bilateral hearing loss" OR "bilateral sensorineural hearing loss")) AND (Children OR pediatric OR infant) with Cochrane Library publication date Between Oct 2013 and Oct 2024 (Word variations have been searched)	**0**	**7**

Table 22 lists inclusion and exclusion criteria for the literature search for expanded cochlear implant indications in children <12 months of age with severe-to-profound SNHL

Table 22. **Inclusion Criteria**	
Population, disease, or condition	**1)** Children under the age of 12 months with severe-to-profound SNHL* with a cochlear implant **2)** Children from 12 months through 17 years with better than profound SNHL* (mild to moderate HL*) with a cochlear implant
Intervention or treatment	Cochlear implant (unilateral, bilateral sequential, or bilateral simultaneous; all models from all manufacturers).
Comparator	N/A
Outcomes	Word recognition scores**, parent questionnaires***

	(only testing materials in English language, unless an officially translated version of a validated test also available in English was used)
Exclusion Criteria	
E1	Not a clinical trial in humans
E2	Not a clinical trial in children within the respective age range (<12 months for search 1; 12 months through 17 years for search 2); à also see inclusion criteria for "Population" above
E3	No relevant outcomes (safety outcomes, word recognition tests or parent questionnaires) addressed
E4	No relevant device used (i.e., no cochlear implant used) [1]
E5	Publication lacking sufficient information (e.g., age range of the study population not clearly defined; indication not clearly defined; age at cochlear implantation not clearly defined; subgroups not separately analyzed in mixed populations; no report of clinical trial available)
E6	Wrong study population (e.g., children with retrocochlear hearing loss, children with cochlear nerve aplasia or hypoplasia, children of wrong age range, different indication, mixed populations without intra-individual follow-up)

Table 23 lists literature appraisal criteria.

Table 23. Level of evidence	Description	Grading System
Level of evidence	What is the source and level of evidence of the included data?	L1 – Clinical practice guidelines or position statements published by medical societies L2 – High level secondary literature (e. g. systematic literature reviews, meta-analyses, recommendations from medical societies) and primary studies of high relevance (e.g. RCTs comparing alternative treatments) L3 – Low level secondary literature (e.g. narrative literature reviews) and large

[1] All models from all cochlear implant manufacturers were considered relevant

		prospective studies or retrospective reviews (>100 patients) L4 – Primary literature/original articles of lower relevance, retrospective reviews (<100 patients) L5 – expert opinions, editorials, case reports and case series	
Data Suitability	Description	Grading System	Score
Appropriate Device	Were the data generated from the device in question?	D1 – Actual device (exclusively MED-EL cochlear implant system or EAS system)	3
		D2 – Comparable device (cochlear implants or EAS systems from other manufacturers, or not specified)	2
		D3 – Other device (e.g., other hearing implants, hearing aids)	1
Appropriate Device Application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A1 – Same use (unilateral, bilateral sequential or bilateral simultaneous cochlear implantation)	3
		A2 – Minor deviation	2
		A3 – Major deviation	1
Appropriate Patient Group	Were the data generated from a patient group that is representative of the treatment population (e.g. age, sex, etc.) and clinical condition (i.e. disease including state and severity) and?	P1 – Applicable (pediatric cochlear implant recipients of the respective age range)	3
		P2 – Limited (representative population with other clinical conditions, or mixed population)	2
		P3 – Different population (e.g. adult cochlear implant recipients, HA users, children >12 months with severe-to-profound SNHL, children <12months with better than profound SNHL, normal hearing participants listening to cochlear implant simulations)	1
Acceptable Report/Data Collation	Did the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1 – High quality	3
		R2 – Minor deficiencies	2
		R3 – Insufficient information (e.g., case report or case series, age group of interest not separately analysed)	1

Data Contribution	Description	Grading System
Data Source Type	Was the design of the study appropriate?	T1 – Yes T2 – No
Outcome Measures	Did the outcome measures reported reflect the safety and intended performance of the device?	O1 – Yes O2 – No
Follow-Up	Was the duration of the follow-up long enough to assess treatment effects and identify complications?	F1 – Yes F2 – No
Statistical Significance	Was a statistical analysis of the data provided and appropriate?	S1 – Yes S2 – No
Clinical Significance	Was the magnitude of the treatment effect observed clinically significant?	C1 – Yes C2 – No

Safety Results

Nineteen publications examined safety outcomes for cochlear implantation in children under 12 months with severe to profound hearing loss (N = 118). Three studies reported no complications, and across all studies, no anesthetic complications, facial nerve palsies, or deaths were reported.[2-4]

Major complications included CSF leak, hemorrhage/transfusion, return to operating room for device repositioning, device failure, meningitis, surgical-site infection with wound breakdown, and mastoiditis.[5-14] Minor complications included imbalance leading to prolonged hospitalization, wound swelling, bleeding or hematoma, seroma, wound infection requiring antibiotic treatment, mild acute otitis media, tip fold-over, and transient facial nerve weakness.[5,7,9,15-19] A single case of postoperative meningitis was identified.[6]

Comparative analyses showed no significant differences in complication rates between children implanted before 12 months (N = 747) and older children (N = 3840).[5,7,9,15-19] A meta-analysis (Sbeih et al., 2021; N=449 children, 626 ears) found major complications in 3.1% of patients and minor complications in 2.4% of patients. Wu et al. (2023) systematic review (N=242 children ≤12 months) reported CSF leak in 2.5%, device failures in 1.2%, and infections in 0.8% of patients. Bruijnzeel et al. (2016) concluded that cochlear implantation before 12 months can be performed safely with no increased anesthetic or surgical risks compared to older children.[20]

Effectiveness Results

Twenty-one studies evaluated auditory performance outcomes in children implanted before 12 months. Overall, the evidence demonstrates that earlier implantation is associated with improved outcomes across multiple domains, though some variability exists in the literature.

Speech Perception: Earlier implantation consistently produced superior outcomes.[9,15,18,21-23] Children achieved higher speech recognition and comprehension scores, reached open-set speech perception earlier, and performed closer to normal-hearing peers. Colletti et al. (2012) and Manrique et al. (2019) found significant long-term advantages for implantation before 12 months. Tajudeen et al. (2010) and Chweya et al. (2021) reported superior word and sentence recognition compared to children implanted between 12-36 months. High mean speech perception scores (>85-90%) were reported in cohorts implanted before 12 months.[10,14,25] Wu et al. (2023b) reported children implanted ≤12 months achieved average CNC word scores of 80%, GASP 71%, IT-MAIS 73%, and LEAQ 84%.[26] However, Bruijnzeel et al. (2016) did not find significant benefit for speech perception <12 months, though some studies suggested faster acquisition of age-appropriate speech and language.[20]

Subjective and Functional Measures of Auditory Performance: Parental questionnaires and developmental assessments showed faster auditory skill acquisition and higher scores within the first year after implantation for children implanted before 12 months than after 12 months.[2,10,14,22,27,28]

Language Development: Children implanted before 12 months demonstrated significantly higher receptive and expressive language scores, faster growth rates, and greater likelihood of oral-only communication compared to later-implanted peers.[3,8,9,14-16,22,24,29-31] Those implanted before 6-9 months frequently achieved age-appropriate language levels equivalent to normal-hearing peers.

Speech Production: Earlier implantation resulted in significantly higher accuracy and intelligibility scores, with performance approaching normal-hearing children by 4 years post-implantation.[15,16,24] Studies reported significantly higher CAP, CAP II, and SIR scores for children implanted before 12 months, with all children achieving intelligible speech within five years.[4,5,15]

Conclusions

Collectively, the evidence from the literature indicates that cochlear implantation in children <12 months of age is not associated with higher peri- or postoperative complication rates compared to older pediatric populations. Cochlear implantation before 12 months of age results in auditory, speech, and language outcomes that are at least equivalent to, and often better than, those achieved with later implantation.

B. Bibliography of published reports on the indication expansion in the pediatric cochlear implant population - Children from one through 17 years of age with better than profound SNHL (especially mild-to-moderate sloping to severe-to-profound SNHL)

Literature Search Strategy

Table 24 lists the literature search strategy and PubMed search results for expanded cochlear implant indications in children from 1 through 17 years of age with better than profound SNHL (reporting period October 31, 2013 - October 31, 2023; reporting period November 1–October 31, 2024).

Table 24. Search Step	Search Terms	Number of retrieved publications from October 31, 2013 to October 31, 2023	Number of retrieved publications from November 1, 2023 to October 31, 2024
1	cochlear implant OR electric acoustic stimulation OR electric-acoustic stimulation OR electro acoustic stimulation OR electroacoustic stimulation OR acoustic electric stimulation OR “EAS” OR electro natural stimulation OR “ENS”	42,986	4,864
2	"word recognition" OR "word discrimination" OR "word perception" OR "speech discrimination" OR "speech recognition" OR "speech perception"	40,088	41,877
3	“auditory development” OR “auditory skills” OR “auditory behaviour” OR “auditory behavior” OR “LittlEARS” OR “LEAQ” OR "LittlEARS Auditory Questionnaire" OR “IT-MAIS” OR "Infant-Toddler Meaningful Auditory Integration Scale" OR “MAIS” OR "Meaningful Auditory integration Scale" OR "Parents Evaluation of Aural/Oral Performance" OR “Auditory Skills Checklist” OR "questionnaire" OR "parent questionnaire" OR "functional listing index" OR "meaningful use of speech scale"	553,575	595,843
4	“severe hearing loss” OR "moderate hearing loss" OR "mild hearing loss" OR “mild-to-moderate hearing loss” OR “mild to moderate hearing loss” OR "residual hearing" OR “partial deafness” OR “partial hearing” OR “high frequency hearing loss” OR “sloping hearing loss” OR “low frequency hearing”	16,034	16,856
5	Children OR pediatric OR adolescents	4,691,748	4,902,814
6	2 OR 3	592 407 [2]	636,370

[2] Note that the numbers given for the found publications in Table 25 are taken directly from the saved PubMed search results from the search conducted on 15 NOV 2023. We noted that search step #6 should result in a total of 593 663 publications (40 088 from search step #3 + 553 575 from search step #3). However, the search results documented a total of 592 407 publications for search step #6, which is reported here for completeness.

7	1 AND 6	8,150	8,650
8	7 AND 4 AND 5	326	335
9	Limit 8 to *Language*: *English*	313	-
10	Limit 9 to *Publication date*: 31 October 2013 - 31 October 2023	**169**	**-**
10(alt)	Limit 8 to Language: English; Publication date: 01 November – 31 October 2024	**-**	**9**

Table 25 lists Cochrane Reviews and Cochrane Trials search results for expanded cochlear implant indications in children from one through 17 years of age with better than profound SNHL (October 2013 - October 2024)

Table 25. Search Term	Cochrane Reviews	Cochrane Trials
(((cochlear implant OR electric acoustic stimulation OR electric-acoustic stimulation OR electro acoustic stimulation OR electroacoustic stimulation OR acoustic electric stimulation OR "EAS" OR electro natural stimulation OR "ENS") AND (("word recognition" OR "word discrimination" OR "word perception" OR "speech discrimination" OR "speech recognition" OR "speech perception") OR ("auditory development" OR "auditory skills" OR "auditory behaviour" "auditory behavior" OR "LittlEARS" OR "LEAQ" OR "LittlEARS Auditory Questionnaire" OR "IT-MAIS" OR "Infant-Toddler Meaningful Auditory Integration Scale" OR "MAIS" OR "Meaningful Auditory integration Scale" OR "Parents Evaluation of Aural/Oral Performance" OR "Auditory Skills Checklist" OR "questionnaire" OR "parent questionnaire" OR "functional listing index" OR "meaningful use of speech scale"))) AND ("severe hearing loss" OR "moderate hearing loss" OR "mild hearing loss" OR "mild-to-moderate hearing loss" OR "mild to moderate hearing loss" OR "residual hearing" OR "partial deafness" OR "partial hearing" OR high frequency hearing loss OR sloping hearing loss OR high-frequency hearing loss OR low frequency hearing)) AND (Children OR pediatric OR adolescents)" with Cochrane Library publication date Between Oct 2013 and Oct 2024, in Cochrane Reviews, Trials (Word variations have been searched)	**2**	**5**

Table 22 details the inclusion and exclusion criteria used for the literature search on expanded cochlear implant indications in children from 1 through 17 years of age with better than profound SNHL. The literature appraisal criteria in Table 22 were used.

Safety Results

Ten studies and one systematic review reported on outcomes related to the safety (complications and hearing preservation outcomes) of cochlear implantation in children 1 through 17 years of age with better than profound SNHL.

Cochlear implantation was generally safe in children with better than profound hearing loss with minimal complications. Two smaller studies reported no surgical complications among 16 pediatric recipients.[32-34] A larger study by Quatre et al. (2020) (N=147) found 5.4% minor and 2.8% major complications. A systematic review of 8 studies (N=424) reported no surgery-related complications or device failures.[35]

Hearing preservation results were mixed. Five studies showed favorable outcomes with 45-96% partial to complete hearing preservation in most children (N=154).[33,36-39] Spitzer et al. (2023) noted moderate PTA declines (≤ 15-25 dB HL over 24 months).[40] However, two studies reported limited preservation (N=33),[41,42] and one systematic review noted 37.2% of children experienced residual hearing loss.[35]

Effectiveness Results

Twenty-eight studies and three systematic reviews reported on outcomes related to performance of cochlear implantation in children 1 through 17 years of age with better than profound SNHL.

Speech Perception: Studies consistently demonstrated improved speech perception following cochlear implantation, including in "borderline" non-traditional candidates. Improvements occurred in word, sentence, and phoneme recognition in both quiet and noisy conditions. Several studies showed significant gains even in children with preoperative speech perception exceeding current candidacy criteria.[34,43-45] Electric-acoustic stimulation (EAS) often yielded superior speech perception scores, particularly in noise.[40,46,47] Three systematic reviews confirmed superior outcomes when hearing preservation or EAS was maintained.[35,41, 46, 48,49]

Subjective Outcomes: Parent-reported measures (CAP, IT-MAIS, SSQ, PEACH, LIFE-R) uniformly showed enhanced auditory functioning and listening ability post-implantation. Children with single-sided deafness reported improvements across all SSQ domains, particularly in speech and spatial hearing.[50] Non-traditional candidates (CAP 5-6 pre-cochlear implant) demonstrated meaningful benefits in daily listening and communication.[33,34,45]

Language Development: Leigh et al. (2016) and Carlson et al. (2015) showed children achieved notable gains in receptive and expressive language, often closing gaps with normal-hearing peers within 2-3 years post-implant.[53,54] Results were less consistent in older children or those with moderate sloping hearing loss.[37] Overall, the evidence suggests that earlier implantation supports more robust language development even in children with better than profound SNHL.

Conclusions

Taken together, the available evidence demonstrates that cochlear implantation in children aged 1 through 17 years with better than profound hearing loss is safe with a low incidence of major complications and is effective, providing significant benefits in speech perception, auditory performance, and language development.

Limitations for the Literature Data

Limitations of the literature data include: 1) very limited individual data are available for effectiveness outcomes, 2) the patients from whom data were collected received cochlear implants of various device models from different manufacturers, 3) reported device effectiveness and study endpoints are not consistent across the reported studies; and 4) most studies were retrospectively designed. That is, data collection and analyses were not prospectively defined in a study protocol. Many details regarding study endpoints, inclusion/exclusion criteria, device selection, adverse event tracking, and statistical analysis plan, etc., are not fully specified in the cited published studies. However, given that subjects in the above articles identified through the literature search largely match the proposed candidacy criteria of the requested indication expansion, the safety and effectiveness data reported in these articles can serve as supporting evidence to confirm the findings captured in the G180269 study according to the FDA guidance document titled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" (issued August 31, 2017).

XIV. 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 (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.

XV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint in this study was pre-specified as at least 75% of subjects demonstrating clinical success by 12-month post-activation on developmentally appropriate measures of speech recognition or auditory skill development. This effectiveness analysis of pediatric cochlear implantation evaluated 92 retrospective and 36 prospective subjects at 12 months post-activation, demonstrating high clinical success rates of 88% and 81%, respectively. The retrospective study met its primary effectiveness endpoint with statistical significance ($p = 0.002$), while the prospective study, despite achieving a similar 81% success rate, did not reach statistical significance due to its smaller sample size ($p = 0.2207$). Clinical success rates were consistently high across all age groups, ranging from 86-89% in the retrospective population and 73-93% in the prospective population, with no significant differences observed between children implanted at 7-8 months compared to those implanted at older ages (9-11 months or 12 months-6 years). Overall, the effectiveness data support that cochlear implantation achieves optimal clinical outcomes in pediatric subjects regardless of implantation age, including in the youngest children as early as 7-8 months of age.

The literature data provide supporting, confirmatory evidence for the effectiveness outcomes from the G180269 clinical study, demonstrating that children who meet the candidacy criteria of the requested expanded indication benefit from a cochlear implant in terms of speech perception, auditory performance, and language development.

B. Safety Conclusions

The risks of expanded indications in the pediatric population are based on data collected in a clinical

study conducted to support PMA approval as described above. The primary safety objective was to report all complications/adverse events (major or minor complications) as the number of subjects experiencing an adverse event. This safety analysis of pediatric cochlear implantation evaluated 38 prospective and 209 retrospective subjects. Overall, ADE rates ranged from 12-24% across prospective/retrospective study populations, with SADEs consistently low at 4-6%. The most common complications included abnormal telemetry requiring programming adjustments or device replacement, postoperative symptoms such as swelling and drainage, infections, and CSF leaks. Device explantation rates were low at 2-3%. All reported ADEs were known risks of cochlear implantation. Surgical and anesthetic risks among the younger children (i.e., 7-12 months) were comparable to those in older pediatric populations (12 months – 6 years) except for dura exposure and minor skin irritation. This is attributed to thinner skull and skin flap thickness among younger children (i.e., 7-12 months) than older children. However, the dura exposure did not result in increased serious complications. The overall safety outcomes in the youngest children (i.e., < 12 months) were comparable to those in older pediatric populations, supporting the acceptable safety profile of cochlear implantation in children as young as 7-8 months of age.

The literature data provide supporting, confirmatory evidence for the safety outcomes from the G180269 clinical study, demonstrating that 1) cochlear implantation in children <12 months of age is not associated with higher peri- or postoperative complication rates compared to older pediatric populations; and 2) cochlear implantation in children aged 1 through 17 years with better than profound hearing loss is safe with a low incidence of major complications.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. This effectiveness data evaluated 36 prospective and 92 retrospective subjects, demonstrating that cochlear implantation achieved high clinical success rates in pediatric subjects, with 81% of prospective subjects (29/36) and 88% of retrospective subjects (81/92) reaching clinical success by 12 months post-activation. The retrospective study met its primary effectiveness endpoint with statistical significance ($p = 0.002$), while the prospective study, despite showing a similar 81% success rate, did not achieve statistical significance due to its smaller sample size of 36 subjects ($p = 0.2207$). The effectiveness data support that cochlear implantation achieves optimal clinical outcomes in pediatric subjects regardless of implantation age, including in the youngest children as early as 7-8 months of age.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. This safety data evaluated 38 prospective and 209 retrospective subjects, demonstrating acceptable safety profiles across all age groups, including children as young as 7-8 months. ADE rates ranged from 12-24% across prospective/retrospective study populations, with SADEs and device explantation rates consistently low at 4-6%, and 2-3%, respectively. All reported ADEs were known risks of cochlear implantation. Surgical and anesthetic risks among the younger children (i.e., <12 months) were comparable to those in older pediatric populations except for dura exposure. The safety data support the safety of cochlear implantation among the requested, expanded pediatric population as young as 7-8 months of age.

The subject PMA supplement is to expand the indications for use of a previously approved

cochlear implant system. While the analysis of clinical study data and the extrapolation described in Section X above have limitations, the FDA agrees that (1) the probable benefits outweigh the probable risks of expanded indications in the MED-EL pediatric cochlear implant population; and (2) the degree of uncertainty is acceptable in the context of the overall benefit-risk profile of implanting children at 7 months to 17 years, 11 months of age.

1. Patient Perspective
   Patient perspectives considered during the review included parent-reported outcomes on accepted scales of auditory skill development. Clinical success on parent questionnaires was defined by an LEAQ Total Score ≥ 25 points or improvement of 25 percentage points on other developmentally appropriate scales of auditory skill development.

   Results showed high success rates with 79% of prospective subjects (27/34) and 84% of retrospective subjects (54/64) meeting clinical success criteria at 12 months post-activation across various assessment tools. The 25-point LEAQ threshold represents a rigorous standard, equivalent to the expected mean for normal-hearing children at 12 months of age. Fifty percent of prospective subjects achieved this benchmark by 6 months post-activation. At 12 months post-activation, median LEAQ scores reached 33 points (prospective subjects) and 32 points (retrospective subjects), approaching the maximum possible score of 35 points and matching expected performance levels for normal-hearing children at 24 months of age. The above results demonstrate that young cochlear implant recipients can achieve auditory development comparable to normal-hearing peers.

In conclusion, given the available information above, the data support that the overall hearing benefits of the device outweigh the risks for children 7 months to 17 years, 11 months of age who do not benefit from traditional hearing aids and meet the criteria specified in the proposed indication.

D. Overall Conclusions

The data in this application from the G180269 clinical study and literature articles, along with analyses based on FDA guidance documents (i.e., RWE and pediatric data extrapolation), demonstrate reasonable assurance of safety and effectiveness of this device when used in accordance with the proposed, expanded, pediatric indications for use. Based on the available clinical data, it is reasonable to expect clinical benefits with use of the MED-EL cochlear implant system in children 7 months to 17 years, 11 months of age. A significant portion of subjects show meaningful improvement in speech perception or auditory performance. Implanting children aged 7-11 months of age with profound SNHL is not associated with higher peri- or postoperative complication rates compared to older pediatric populations. Implanting children aged 1 through 18 years with better than profound SNHL is safe with a low incidence of major complications. The potential benefits of MED-EL cochlear implants in this population are expected to outweigh the residual risk.

XVI. CDRH DECISION

CDRH issued an approval order on November 26, 2025. The final clinical conditions of approval cited in the approval order are described below.

The MED-EL Cochlear Implant Pediatric Post-Approval Study (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 7 months to 18 years. The study will be conducted as a prospective/retrospective, non-controlled, non-randomized, multicenter study at 8 sites. Prospective evaluation for safety and effectiveness up to a minimum of 2 years post-implantation will be conducted among approximately 26 children implanted at ages 7-12 months who were enrolled in the prospective arm of the premarket, prospectively designed, prospective/retrospective study for the extended follow-up study. Retrospective evaluation for safety and effectiveness up to a minimum of 2 years post-implantation will be conducted among a minimum of 80 new subjects implanted at ages 12 months to18 years (30 subjects implanted at ages 1-6 years and 50 subjects implanted at ages 6-18 years) for the new, prospectively designed, retrospective study. The primary safety endpoint is the number and proportion of subjects experiencing device-, procedure-, or otologic-related adverse events up to 24 months post-implantation. The effectiveness endpoints will include the within-subject differences in cochlear implant performance on age-appropriate speech perception from the pre-implantation baseline to the 24-month post-implantation condition.

XVII. 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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