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 Corp.
Fürstenweg 77a
6020 Innsbruck, Austria

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P000025/S104

Date of FDA Notice of Approval: July 19, 2019

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 profoundly hearing-impaired individuals (ages 18 months and older) who obtain little or no benefit from conventional acoustic amplification in the best-aided condition. The SSED to support the indication is available on the CDRH website and is incorporated by reference here (http://www.accessdata.fda.gov/cdrh_docs/pdf/P000025b.pdf). The current supplement was submitted to expand the indication for the MED-EL Cochlear Implant System for patients with single-sided deafness (SSD) or asymmetric hearing loss (AHL).

II. INDICATIONS FOR USE

The MED-EL Cochlear Implant System is indicated for evoking auditory sensations via electrical stimulation of the auditory pathways for individuals ages 5 years and above with single-sided deafness (SSD) or asymmetric hearing loss (AHL), where:

- SSD is defined as profound sensorineural hearing loss in one ear and normal hearing or mild sensorineural hearing loss in the other ear.
- AHL is defined as a profound sensorineural hearing loss in one ear and mild to moderately severe sensorineural hearing loss in the other ear, with a difference of at least 15 dB in pure tone averages (PTAs) between ears.
- Profound hearing loss is defined as having a PTA of 90 dB HL or greater at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Normal hearing is defined as having a PTA of up to 15 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild hearing loss is defined as having a PTA of up to 30 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. Mild to moderately severe hearing loss is defined as having a PTA ranging from 31 to up to 55 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

Individuals with SSD or AHL must obtain limited benefit from an appropriately fitted unilateral hearing aid in the ear to be implanted. For individuals ages 18 years-old and above, limited benefit from unilateral amplification is defined by test scores of five (5) percent correct or less on monosyllabic consonant-nucleus-consonant (CNC) words in quiet when tested in the ear to be implanted alone. For individuals between 5 and 18 years-old, insufficient functional access to sound in the ear to be implanted must be determined by aided speech perception test scores of five (5) percent or less on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone.

Before implantation with a cochlear implant, individuals with SSD or AHL must have at least one (1) month experience wearing a Contra Lateral Routing of Signal (CROS) hearing aid or other relevant device and not show any subjective benefit.

III. CONTRAINDICATIONS

A patient 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 auditory pathways;
- 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 present against surgery of the middle and inner ear and anesthesia as required;
- if anatomic abnormalities are present that would prevent appropriate placement of the stimulator housing in the bone of the skull, or prevent placement of the chosen electrode array into the cochlea. In such cases, using the cochlear implant must be carefully considered prior to surgery;
- if the psychological status of the patient is unstable or
- if the patient has unrealistic expectations.

Additionally for SSD / AHL individuals should not be implanted,

- if individual has had profound hearing loss for over ten years
- if individual has an acoustic neuroma

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 SSD and AHL indications do not apply to the MED-EL EAS System.
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 EAP reference electrode):
  Mi1250 SYNCHRONY 2 (PIN),
  Mi1210 SYNCHRONY ST,
  Mi1200 SYNCHRONY (PIN),
  Mi1000 MED-EL CONCERT (PIN),
  SONATA$_{TI100}$
- 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):
  OPUS 1,
  OPUS 2,
  RONDO,
  RONDO 2,
  SONNET
- Fitting:
  MAX programming interface
  MAESTRO software 7.0 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 that changes in 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 sends a corresponding pattern of stimulation pulses to the individual electrodes of the active electrode array. These stimulation pulses excite action potentials which 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 serves to allow the "fitting" or programming of the system components to the optimal benefit of the individual user.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

VII. MARKETING HISTORY

The MED-EL Cochlear Implant System was first approved for SSD and AHL indications for both children and adults in the EU in March 2013. Subsequently, SSD has been approved in over 120 countries globally (Albania, Algeria, Argentina, Armenia,

Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Belarus, Belgium, Benin, Bolivia, Bosnia-Herzegovina, Brazil, Bulgaria, Cameroon, Canada (18 years and older), Chile, China, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, Estonia, Ethiopia, Finland, France, Gabon, Georgia, Germany, Ghana, Greece, Guatemala, Hungary, Iceland, India, Indonesia, Ireland, Israel, Italy, Ivory Coast, Jordan, Kazakhstan, Kenya, South Korea, Kosovo, Kuwait, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Luxembourg, North Macedonia, Malawi, Malaysia, Mali, Malta, Mexico, Moldova, Mongolia, Montenegro, Morocco, Myanmar, Namibia, Nepal, Netherlands, New Zealand, Nigeria, Norway, Oman, Pakistan, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Senegal, Serbia, Singapore, Slovakia, Slovenia, South Africa, South Sudan, Spain, Sri Lanka, Sudan, Sweden, Switzerland, Syria, Tajikistan, Tanzania, Thailand, Togo, Trinidad & Tobago, Tunisia, Turkey, Uganda, Ukraine, United Arab Emirates, United Kingdom, Uruguay, Uzbekistan, Venezuela, Vietnam, Yemen, Zimbabwe). Approvals of SSD and AHL indications have not been withdrawn from any market for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Sudden losses of residual low-frequency hearing
- Total loss of residual hearing
- 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.

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 (bench and animal) 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 for the proposed indication.

No additional preclinical studies were required to evaluate the safety of MED-EL Cochlear Implant System for the treatment of the new patient populations of SSD and AHL. The previously approved supplements which support the device and its components are listed below in Table 1.

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

Device	Approval Reference
Cochlear Implants:	
Mi1250 SYNCHRONY 2 (PIN) Mi1210 SYNCHRONY ST Mi1200 SYNCHRONY (PIN) Mi1000 MED-EL CONCERT (PIN) SONATATI[100]	P000025/S110 P000025/S103 P000025/S079 P000025/S050 & S058 P000025/S021
Processors:	
OPUS 1 OPUS 2 RONDO RONDO 2 SONNET	P000025/S023 P000025/S029 P000025/S062 P000025/S099 P000025/S078
Fitting:	
MAX Programming Interface MAESTRO 7.0	P000025/S077 P000025/S097

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant conducted a clinical study to establish a reasonable assurance of safety and effectiveness of the MED-EL Cochlear Implant System in SSD/AHL subjects 18 years of age and older in the US under a feasibility study conducted at the University of North Carolina at Chapel Hill (UNC) under IDE # G140050. Data from this study, as well as supporting evidence from a comprehensive literature review, were the basis for the PMA approval decision.

The UNC Feasibility Study

A. Study Design

Patients were treated between 2014 and 2019. The database for this Panel Track Supplement reflected data collected through 2014 and included 38 patients. There was 1 investigational site.

The feasibility study for the MED-EL Cochlear Implant System was conducted under IDE (G140050) to evaluate the safety and effectiveness of the MED-EL Cochlear Implant System in individuals 18 years of age and older with SSD or AHL. The primary study goal was to determine whether subjects with SSD or AHL demonstrated an improvement in speech perception, localization, and quality of life after receiving a cochlear implant. Both objective and subjective performance data were collected, as well as safety data in the form of adverse events. Forty subjects were implanted at the University of North Carolina at Chapel Hill with the MED-EL CONCERT or SYNCHRONY Cochlear Implant System in this prospective, single-site, non-randomized, non-blinded, repeated measures clinical study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in G140050 was limited to patients who met the following inclusion criteria:

- 18 years of age or older at the time of implantation
- Unilateral moderate-to-profound sensorineural hearing loss
    - Unaided residual hearing thresholds measured from 250-8000 Hz (PTA ≥70 dB HL in the ear to be implanted)
    - For SSD: normal to mild residual hearing thresholds from 250-8000 Hz in the contralateral ear (≤35 dB HL at each frequency, 250-8000 Hz)
    - For AHL: mild to moderate hearing thresholds from 250-8000 Hz in the contralateral ear (PTA ≥35 and ≤55 dB HL)
        - Aided word recognition of 80% or more as measured with CNC words (50-word list)
- Duration of moderate-to-profound sensorineural hearing loss less than or equal to 10 years
    - Hearing loss for less than 10 years: study participants were only included if they had used a hearing aid consistently for 5 years
    - Hearing loss for less than 5 years: study participants were only included if they had at least completed a 1-month hearing aid trial
- Previous experience (at least one month) with a current treatment option for SSD, including a conventional hearing aid, bone-conduction device, or CROS/BICROS technology
- Aided word recognition in the ear to be implanted of 60% or less as measured with CNC words (50-word list)
- Realistic expectations
- Willingness to obtain recommended meningitis vaccinations per CDC recommendations
- No reported cognitive issues: pass of the Mini Mental State Examination (MMSE) screener
- Ability and willingness to comply with study requirements, including travel to investigational site and study-related activities

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- Non-native English speaker
- Conductive hearing loss in either ear
- Compromised auditory nerve, including those with a history of vestibular schwannoma
- Ossification
- Inability to participate in follow-up procedures (i.e., unwillingness, geographic location)
- History of meningitis, autoimmune disease, or any medical condition that contraindicate middle or inner ear surgery or anesthesia
- Meniere's disease with intractable vertigo
- Trauma that precludes inner ear surgery
- Case of sudden sensorineural hearing loss that has not been first evaluated by a physician

- Pregnancy
- Tinnitus as the primary purpose for seeking cochlear implantation
- Severe or catastrophic score on the Tinnitus Handicap Inventory

2. Follow-up Schedule

This study involved up to ten visits before and after implantation, for about a one-year period. Candidacy testing included medical and audiological evaluations (e.g., audiograms, speech recognition tests) to determine study eligibility. After confirming eligibility, the subject underwent baseline testing. The device was subsequently implanted based on the subject's candidacy testing. An initial follow-up visit was completed following surgery, and the cochlear implant was activated following a healing period of 2 to 4 weeks.

The baseline and postoperative measurements are summarized under 'Test Conditions' below. All patients were scheduled to return for follow-up examinations at 1, 3, 6, 9, and 12 months postoperatively. Pre-operatively and post-operatively, unaided air conduction thresholds were collected. At all intervals, speech perception in quiet and in noise and localization data was collected. Adverse events and complications were recorded at all visits.

The key timepoints (pre-op baseline and 12-months post-op) are shown below in the tables summarizing safety and effectiveness.

Test Conditions

The test battery was completed at the pre-operative interval and again at 1, 3, 6, 9, and 12 months post-operatively. For soundfield measures (speech perception and localization), a 180° arc with 11 speakers spaced 18° apart was utilized. Post-operative aided soundfield assessment was completed with the subject using the SONNET or OPUS 2 speech processor unless otherwise noted. For the AHL group, soundfield testing was completed with a hearing aid in the contralateral ear. See below for further details on testing conditions.

Subjects participated in two aural rehabilitation sessions with a board-certified speech-language pathologist. One session was completed after the initial activation of the external speech processor. The second session took place in conjunction with the 1-month post-initial activation interval.

- Unaided Diagnostic Assessment
    - Air-conduction thresholds in both ears
    - Assess bone-conduction thresholds if there is a PTA shift of >15 dB as compared to the previous interval
- Tympanometry for each ear
- Sound Field Measures
    - Aided thresholds with the external speech processor on measured using pulsed, warble tones
        - Frequencies assessed: 250-8000 Hz
        - Masking presented to the contralateral ear
    - Speech Perception Measures (recorded materials presented at 60 dB SPL)

        - Speech Perception in Quiet
            - Speech 0° azimuth
            - CNC words
            - AzBio sentences
        - Speech Perception in Noise
            - Speech and noise 0° azimuth
            - Speech 0° azimuth and noise to implanted side
            - Speech 0° azimuth and noise to contralateral ear
            - AzBio sentences
            - If >50% at SNR+10, then SNR+5; if >50% at SNR+5, then SNR0
            - BKB-SIN sentences with adaptive SNR
            - Cochlear implant speech processor off
            - Cochlear implant speech processor on
    - Localization
        - 200-ms speech-shaped noise, presented at 70-dB SPL from one of the 11 speakers (evenly spaced -180 to 180 degrees), selected at random
        - Intensity level for each stimulus presentation randomly varied (10 dB around 70 dB SPL)
        - Cochlear implant speech processor off
        - Cochlear implant speech processor on
- Subjective questionnaires
    - Speech, Spatial and Qualities of Hearing Scale (SSQ)
    - Abbreviated Profile of Hearing Aid Benefit (APHAB)
    - Tinnitus Handicap Inventory (THI)

3. Clinical Endpoints

Measures

Safety Measure: The primary safety measure was the evaluation of all adverse events reported within 12 months. The full profile of adverse events was summarized and considered, with specific attention given to device-related adverse events. The adverse events include anticipated and unanticipated adverse events. The list of anticipated adverse device effects noted in the study protocol are as follows:

- Risks from the SYNCHRONY IFU
    - Loss of residual hearing
    - Increased vertigo
    - Delay of healing of the scar
    - Impairment of the sense of taste
    - Potential for swallowing difficulties
    - Numbness
    - Increased tinnitus
    - Stimulation of the facial nerve
    - Temporary pain and uncomfortable sounds during stimulation
- Additional surgical risks
    - Facial nerve injury

    - Infection
    - Bleeding
    - Cerebrospinal fluid (CSF) leak
    - Pain
    - Scarring
- Additional post-operative risks
    - Swelling around the incision and/or coil site
    - Pain
    - Reduced or loss of pinna sensitivity on the surgical side
    - The cochlear implant may not provide any auditory stimulation
    - The cochlear implant may provide auditory stimulation, but with a sound quality too poor to aid in the perception of speech
    - The cochlear implant may provide auditory stimulation, but with a sound quality too poor to aid in localization
    - Pain associated with the coil and/or placement of the external speech processor on the subject's ear
    - Movement of the internal receiver
    - Discomfort from electric stimulation
    - Facial nerve stimulation
    - Headache
    - Dizziness
    - Altered taste (i.e. reports of metallic tastes on the same side of the tongue as the surgical ear)
    - Fatigue during follow-up assessment (completion of the test battery and/or mapping)
    - The internal device may fail, requiring revision cochlear implantation
    - The sound from the cochlear implant may interfere with the better hearing ear.

Effectiveness Measures: The primary effectiveness measures were the comparisons of speech perception and localization performance between the bilateral, pre-operative, unaided/best-aided (with BCHA) condition and the bilateral, 12-month-post-operative CI + NH (or HA) condition. Aided speech perception performance on word and sentence materials at the post-activation intervals was evaluated to monitor trends over time. Unaided and aided (with BCHA or CI, as applicable) localization performance was also compared pre-operatively and at each of the post-activation intervals. The overall RMS error is reported for localization in each condition. Additionally, subjective report scores were compared pre-operatively and at the 12-month post-activation intervals.

Audiometric Test Methods & Effectiveness Measures

Speech perception and localization measures were recorded in a research lab that featured a 180° arc with 11 speakers spaced 18° apart. Postoperative aided sound field assessment was completed with the study participant listening with the OPUS 2 or SONNET speech processor.

Speech perception in quiet was tested at 0° azimuth, presenting CNC words (Peterson & Lehiste, 1962) or AzBio sentences (Spahr et al., 2012) at 60 dB SPL.

Speech perception in noise was tested in the conditions (1) speech and noise 0° azimuth (S0N0), (2) speech 0° azimuth and noise to the affected ear/implanted side (S0NCI), and (3) speech 0° azimuth and noise to the contralateral ear (S0NContra). AzBio sentences were presented at 0 dB signal-to-noise ratio (SNR) in most cases. BKB-SIN sentences were presented with adaptive SNR.

For the localization task a 200-ms speech-shaped noise was presented at 70-dB SPL from one of the 11 speakers (selected randomly). The intensity level for each stimulus presentation was randomly varied (10 dB around 70 dB SPL). The listener was facing the center speaker during stimulus presentation and the task was to identify the source of the noise. No feedback was provided. In the condition cochlear implant speech processor OFF, study participants were only listening with the contralateral ear. In the condition cochlear implant speech processor ON, sound was perceived both via the cochlear implant and the contralateral ear.

Subjective data was collected via the SSQ and the Abbreviated Profile of Hearing Aid Benefit (APHAB) (Cox & Alexander, 1995). The SSQ can be further divided into three subscales: speech, spatial, and quality. The APHAB consists of four subscales: Ease of Communication (EC), Background Noise (BN), Reverberation (RV), and Aversiveness (AV). The Tinnitus Handicap Inventory (Newman, Jacobson & Spitzer, 1996) was also utilized to collect information on severity of tinnitus pre-operatively as well as at the 12-month interval.

B. Accountability of Study Cohort

In the SSD cohort, 20 subjects were enrolled and completed testing through the 12-month interval. In the AHL cohort, 20 subjects were enrolled and 18 completed testing through the 12-month interval. One subject in the AHL cohort withdrew prior to completion of all test intervals, and one subject was still undergoing follow-up testing at the time of data analysis.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a feasibility study performed in the US. Proportions enrolled are consistent with the age, sex/gender, racial and ethnic prevalence of the SSD and AHL.

1. SSD Cohort

Of the 20 implanted subjects, 12 were female and 8 were male. At the time of implantation, subjects ranged in age from 22 to 66 years of age. The duration of profound hearing loss ranged from 0.1 to 6.6 years. Fifteen subjects experienced sudden hearing loss and five subjects experienced a gradual hearing loss. Hearing loss was reported as unknown in 16 cases, due to Meniere's disease in three subjects, and caused by trauma in one case. Further information on subject demographics and hearing related variables is summarized in Table 2 below.

Table 2. Descriptive statistics for subject variables

Parameter/Category or Statistic	Total (n=20)
Gender	
Male	40% (8/20)
Female	60% (12/20)
Age (years)	50 (20) (22 – 66)
Duration of hearing loss (years)	
Noticeable	4.2 (20) (0.1 – 14.6)
Profound	2.6 (20) (0.1 – 6.6)
Implanted ear	
Left	55% (11/20)
Right	45% (9/20)
Tinnitus Handicap Grade Level	
Slight	35% (7/20)
Mild	40% (8/20)
Moderate	25% (5/20)
*Numbers are % (Count/Sample Size) or Mean (N) (Min – Max)	

2. AHL Cohort

Of the 18 subjects who completed follow-up, 9 were female and 9 were male. At the time of implantation, subjects ranged in age from 52 to 79 years of age. The duration of profound hearing loss ranged from 0.0 to 9.8 years. Ten subjects experienced sudden hearing loss and six subjects experienced a gradual hearing loss, with the remaining two subjects experiencing both a gradual and sudden loss. Hearing loss was reported as unknown in 14 cases, due to Meniere's disease in two subjects, due to noise-induced hearing loss in one subject, and caused by viral infection in one case. Further information on subject demographics and hearing related variables is summarized in Table 3 below.

Table 3. Descriptive statistics for subject variables

Parameter/Category or Statistic	Total (n=18)
Gender	
Male	50% (9/18)
Female	50% (9/18)
Age (years)	70 (18) (52 – 79)
Duration of hearing loss (years)	
Noticeable	11.5 (17) (0.0 – 51.5)
Profound	3.5 (17) (0.0 – 9.8)
Implanted ear	
Left	67% (12/18)
Right	33% (6/18)
Tinnitus Handicap Grade Level	
Slight	55% (10/18)
Mild	28% (5/18)
Moderate	17% (3/18)
*Numbers are % (Count/Sample Size) or Mean (N) (Min – Max)	

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on all patients implanted under G140050 (N=40) up to 12 months post implantation. Table 4 displays the adverse events reported for this study.

Adverse effects that occurred in IDE G140050:

Adverse events were collected for all implanted subjects throughout the duration of the study. Adverse events were classified as anticipated/unanticipated, serious/non-serious, or device-related/unrelated. A total of nine adverse events were reported to be related to the device or procedure. An additional six adverse events were not able to be ruled out as device or procedure-related. No serious, unanticipated, device-related adverse events were reported.

Table 4. Number and percentage of adverse events observed for SSD subjects.

Events Reported as Device- or Procedure-Related	No. of Events	No. of Subjects	% of Subjects
Vertigo/dizziness/imbalance	11	9	22.5%
Unrelated infection	3	3	7.5%
Changes in sound quality/volume	3	2	5%
Depression	3	2	5%
Aural pressure	2	2	5%
Facial stimulation	2	2	5%
Headache	2	2	5%

Events Reported as Device- or Procedure-Related	No. of Events	No. of Subjects	% of Subjects
Atrial fibrillation	1	1	2.5%
Bleeding at surgical site	1	1	2.5%
Electrode contact dislodged	1	1	2.5%
Fall involving bump to the implant	1	1	2.5%
Type C tympanogram	1	1	2.5%
Short circuit	1	1	2.5%
Total	32	21*	52.5%

*Some subjects experienced more than one device-related adverse event

The most frequently observed adverse event was vertigo, dizziness, or imbalance, which was reported a total of 11 times. In four cases, the event was deemed unrelated to the device or procedure. In three cases, it could not be ruled out that the event was related to the device or procedure. In the remaining four cases, it was determined that the event was related to the procedure. Unrelated infection was reported in three cases: two upper respiratory infections and one sinus infection. In all cases, the event was deemed unrelated to the device or procedure. All other events occurred at a rate of 5% or less (2 subjects or fewer), which is consistent with the rate of adverse events observed for the approved indication of bilateral, severe-to-profound, sensorineural hearing loss.

2. Effectiveness Results

The primary effectiveness measures were the comparisons of speech perception and localization performance between the bilateral, pre-operative, unaided/best-aided (with BCHA) condition and the bilateral, 12-month-post-operative CI + NH (or HA) condition among 20 subjects with SSD and 17 subjects with AHL. Additionally, subjective reports from the SSQ and APHAB were also compared pre-operatively and at the 12-month post-operative interval.

Speech Perception in Quiet

SSD Cohort

Speech perception testing in quiet at the 12-month interval demonstrated an improvement in the implant ear alone when tested with the CI-ON, compared to the pre-operative, unaided condition. In the contralateral ear, no change was observed on CNC words from baseline to 12 months. When tested in soundfield with both ears (unaided v. CI-ON), no change was demonstrated on AzBio sentences in quiet across test intervals. The comparison of AzBio sentence score in quiet with a BCHA to scores at 12 months with the CI-ON also demonstrated no change. Table 5 displays the descriptive statistics of the speech perception in quiet scores for the SSD cohort.

Table 5. Speech perception in quiet (SSD Cohort)

SSD speech in quiet	Implant Ear		Contralateral Ear		Soundfield, both ears		
	Baseline, unaided CNC	12-month, CI-ON CNC	Baseline, unaided CNC	12-month, unaided	Baseline, unaided AzBio	Baseline, BCHA AzBio	12-month,

				CNC			CI-ON AzBio
N	20	20	20	20	20	20	20
Mean (SD)	3.5 (6.68)	54.6 (18.15)	99.3 (2.27)	99.8 (0.62)	99.0 (1.56)	99.2 (1.15)	99.5 (1.19)
Min – Max	0 - 22	10 - 84	90- 100	98 - 100	95 - 100	95 – 100	95 - 100

AHL Cohort

For the cohort with asymmetric hearing loss, an improvement was demonstrated for speech perception testing in quiet at the 12-month interval in the implant ear alone when tested with the CI-ON, compared to the pre-operative, unaided condition. No change was observed on CNC words from baseline to 12 months in the contralateral ear. When tested in soundfield with both ears (unaided v. CI-ON), no change was demonstrated on AzBio sentences in quiet between the pre-operative and 12-month intervals. Additionally, no change was demonstrated in the comparison of AzBio sentence score in quiet between BCHA pre-operatively and 12 months with the CI-ON. See Table 6 below for the descriptive statistics of the speech perception in quiet scores.

Table 6. Speech perception in quiet (AHL Cohort)

SSD speech in quiet	Implant Ear		Contralateral Ear		Soundfield, both ears		
	Baseline, unaided CNC	12-month, CI-ON CNC	Baseline, unaided CNC	12-month, unaided CNC	Baseline, unaided AzBio	Baseline, BCHA AzBio	12-month, CI-ON AzBio
N	18	18	18	18	18	18	18
Mean (SD)	6.3 (7.98)	56.2 (18.41)	94.2 (7.06)	92.7 (8.68)	87.4 (13.96)	87.7 (11.01)	94.3 (8.38)
Min – Max	0 - 22	28 - 86	78 – 100	72 - 100	50 - 99	(61 – 99_	72 - 100

Speech Perception in Noise

SSD Cohort

On AzBio sentence testing in noise, subjects in the SSD cohort demonstrated an improvement between the bilateral, baseline, pre-operative, unaided testing and the bilateral, 12-month post-operative, CI + NH testing in the speech front, noise front condition. This same improvement was also noted between the bilateral, baseline, pre-operative, aided (with BCHA) condition and the bilateral, 12-month, post-operative, CI + NH condition. NO differences were found between pre-operative unaided and pre-operative, aided (with BCHA) scores. In the speech front, noise to the CI ear condition, subjects demonstrated no change in score in comparing the pre-operative interval to the CI-ON at 12 months. However, when comparing the pre-operative aided scores to the 12-month scores with CI, an improvement in performance was noted. Better scores were obtained for the pre-operative unaided condition as compared to the pre-operative aided condition.

A significant improvement was noted with the cochlear implant on at 12 months post-operative compared to the pre-operative, unaided interval for the speech front, noise to the contralateral ear condition. This same improvement was also found when comparing CI-ON at the 12-month, post-operative condition to the pre-operative, aided (with BCHA) condition. This improvement demonstrates that when noise presents as a masker to the better hearing ear, the cochlear implant provides benefit in speech understanding. Table 7 provides further details on AzBio sentence in noise scores.

Table 7. Speech perception in noise (SSD Cohort, AzBio)

SSD AzBio	S0N0			S0NCI			S0NContra		
	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON
N	20	20	20	20	20	20	20	20	20
Mean (SD)	37.5 (10.98)	31.5 (16.56)	47.2 (10.72)	83.4 (9.51)	61.25 (27.92)	85.0 (11.04)	16.5 (12.78)	18.3 (13.50)	52.6 (21.43)
Min-Max	20 - 64	0 – 59	29 - 68	59 - 94	0 – 98	60 - 97	0 - 45	0 – 59	8 - 86

A similar pattern was noted for speech in noise testing on the BKB-SIN. No significant changes were found in any comparisons for the speech front, noise front or speech front, noise to the CI ear conditions. However, in the speech front, noise to the contralateral ear condition, it was found that the CI does provide benefit in speech perception, and thus, a significant improvement was found when comparing the 12-month, post-operative CI + NH condition to the pre-operative, unaided condition or to the pre-operative, aided (with BCHA) condition. Table 8 provides the detailed descriptive statistics of the BKB-SIN scores.

Table 8. Speech perception in noise (SSD Cohort, BKB-SIN)

SSD BKB-SIN	S0N0			S0NCI			S0NContra		
	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON
N	20	20	20	20	20	20	20	20	20
Mean (SD)	0.1 (1.42)	0.8 (1.98)	-0.8 (1.74)	-4.8 (1.64)	-2.6 (2.39)	-4.8 (1.66)	1.8 (1.33)	1.8 (2.35)	-1.0 (2.20)
Min-Max	-2.5 – 3.0	-2.5 – 4.5	-3.0 – 4.0	-7.5 – -1.5	-7.0 – 1.0	-7.5 – -2.0	-0.5 – 4.0	-2.5 – 8.0	-5.0 – 5.5

AHL Cohort

For the AHL cohort, the majority of subjects were tested at 0 dB SNR. However, some subjects were tested at +5 or +10 dB SNR according to a decision tree implemented for determining SNR. Pre-operative and post-operative comparisons within subject were done at the same SNR. For this reason, only 17 subjects are included in the AzBio analysis for both the pre-operative unaided/aided (with BCHA) condition and the 12-month post-operative CI + HA condition.

In the speech front, noise front condition, a significant improvement was found on AzBio sentences for the 12-month, post-operative CI + HA condition compared to the pre-operative, unaided condition and compared to the pre-operative, aided (with BCHA) condition. Pre-operative, BCHA scores were worse than pre-operative unaided scores and worse than 12-month, post-operative CI + HA scores in the speech front, noise to the CI ear condition. In the speech front, noise to the contralateral ear condition, a significant improvement was noted for the 12-month, post-operative CI + HA testing compared to both the pre-operative, unaided testing and the pre-operative, aided (with BCHA) testing. Table 9 below displays the descriptive statistics of the AzBio testing for the AHL Cohort.

Table 9. Speech perception in noise (AHL Cohort, AzBio)

AHL AzBio	S0N0			S0NCI			S0NContra		
	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON
N	17	17	17	17	17	17	17	17	17
Mean (SD)	22.7 (13.95)	20.5 (12.86)	33.5 (22.10)	44.2 (17.70)	30.5 (18.23)	44.6 (24.74)	6.3 (9.49)	11.3 (16.69)	29.4 (22.59)
Min-Max	0 – 47	0 – 47	3 – 85	9 – 78	1 – 70	5 – 94	0 – 36	0 – 66	1 – 95

For BKB-SIN testing, no changes were demonstrated in the speech front, noise to the CI ear condition. An improvement was found between the pre-operative, aided (with BCHA) condition and the 12-month, post-operative CI + HA condition in the speech front, noise front condition. Similar to the AzBio test results for the SSD cohort, there was a significant improvement for BKB-SIN in the speech front, noise to the contralateral ear condition when comparing the 12-month, post-operative CI + HA condition to the pre-operative, unaided condition. Table 10 below displays the analyses of BKB-SIN testing in the AHL cohort.

Table 10. Speech perception in noise (AHL Cohort, BKB-SIN)

AHL BKB-SIN	S0N0			S0NCI			S0NContra		
	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON	Baseline, unaided	Baseline, BCHA	12-month, CI-ON
N	18	18	18	18	18	18	18	18	18
Mean (SD)	4.3 (3.62)	5.1 (3.04)	3.7 (3.28)	1.3 (3.89)	2.5 (3.77)	2.6 (3.78)	7.1 (4.14)	5.9 (4.50)	4.6 (4.44)
Min-Max	0.5 – 13.0	0 – 10	-2.0 – 9.5	-6.5 – 8.5	-3.5 – 10.0	-3.5 – 9.0	2.0 – 15.5	0 – 14.5	-1.0 – 15.5

Localization

SSD Cohort

Subjects in the SSD cohort demonstrated a significant improvement in localization performance with the CI at 12 months compared to the baseline, aided (with BCHA) condition. Additionally, results indicated an improvement in performance

between the baseline, unaided condition and the 12-month, postoperative CI + NH condition. Table 11 displays localization performance in RMS error.

Table 11. Localization performance (SSD Cohort)

SSD Localization	Baseline, unaided	Baseline, BCHA	12-month, CI-ON
N	20	20	20
Mean (SD)	66.5 (20.47)	69.6 (18.71)	26.7 (6.32)
Min-Max	42.9 – 109.1	45.3 – 106.1	13.6 – 38.4

AHL Cohort

Similar to the SSD cohort, subjects in the AHL cohort demonstrated improved localization performance with the CI-ON at 12 months compared to the baseline, aided (with BCHA) condition. This improvement was also evident when comparing the 12-month, postoperative CI + HA to the pre-operative, unaided condition. Table 12 displays the analyses of the AHL Cohort's localization data.

Table 12. Localization performance (AHL Cohort)

AHL Localization	Baseline, unaided	Baseline, BCHA	12-month, CI-ON
N	18	18	18
Mean (SD)	76.5 (19.23)	77.2 (18.89)	40.1 (10.65)
Min-Max	43.8 – 105.3	45.6 – 106.5	26.6 – 73.6

Subjective Questionnaire

SSD Cohort

Self-perceived quality of hearing reported on the SSQ improved significantly with the CI on all three scales (speech, spatial, and qualities). Significant changes over time were found in all three scales. See Table 13 below for the descriptive statistics of the SSQ.

Table 13. SSQ (SSD Cohort)

SSD SSQ	Speech Subscale		Spatial Subscale		Qualities Subscale	
	pre	12m	pre	12m	pre	12m
N	20	20	20	20	20	20
Mean	3.7	7.1	2.4	6.5	5.6	7.7
Std. Deviation	1.34	0.99	1.2	1.86	2.09	1.28
Minimum	0.6	5.4	0.5	2.8	0.5	5.6
Maximum	7.2	8.9	4.5	8.9	9.8	9.8

Self-perceived benefit from the CI as reported on the APHAB demonstrated significant improvement on global score and the subscales, except for the aversiveness subscale. Table 14 below provides the detailed APHAB scores at the pre-operative and 12-month intervals.

Table 14. APHAB (SSD Cohort)

SSD APHAB	Global		EC		BN		RV		AV	
	pre	12m	Pre	12m	pre	12m	pre	12m	pre	12m
N	20	20	20	20	20	20	20	20	20	20
Mean	49.8	17.9	31.6	8.7	70.1	25.2	47.5	19.7	43.1	26.7
Std. Deviation	18.65	8.91	21.06	6.15	17.32	11.95	21.96	12.43	28.64	24.83
Minimum	20.3	6.1	2.8	1.0	39.3	10.2	18.7	2.8	1.0	1.0
Maximum	86.3	36.7	81.0	24.8	95.0	56.2	87.0	41.7	93.0	91.0

AHL Cohort

Self-perceived quality of hearing reported on the SSQ improved significantly with the cochlear implant on all three scales (speech, spatial, and qualities). Significant changes over time were found in all three scales. See Table 15 below for detailed information on the SSQ.

Table 15. SSQ (AHL Cohort)

AHL SSQ	Speech Subscale		Spatial Subscale		Qualities Subscale	
	pre	12m	pre	12m	pre	12m
N	18	18	18	18	18	18
Mean	3.2	5.8	2.6	6.0	4.6	6.8
Std. Deviation	1.48	1.50	1.26	1.62	1.77	1.20
Minimum	0.4	3.6	0.3	3.1	0.2	4.4
Maximum	6.0	8.9	4.7	8.5	8.3	8.7

Self-perceived benefit from the cochlear implant as reported on the APHAB demonstrated significant improvement on global score and other subscales over time except the aversiveness subscale. Table 16 below displayed the detailed APHAB scores at the pre-operative and12-month post-operative intervals.

Table 16. APHAB (AHL Cohort)

AHL APHAB	Global		EC		BN		RV		AV	
	pre	12m	pre	12m	pre	12m	Pre	12m	pre	12m
N	18	18	18	18	18	18	18	18	18	18
Mean	54.1	28.1	42.9	16.6	63.5	39.3	56.0	28.3	43.1	42.4
Std. Deviation	16.21	10.49	24.67	13.01	16.84	17.10	18.30	11.96	35.04	29.21
Minimum	20.0	11.3	10.2	1.0	14.5	14.5	14.2	12.0	1.0	1.0
Maximum	92.3	54.1	91.0	54.0	95.0	66.3	97.0	54.2	99.0	97.0

3. Subgroup Analyses

No subgroup analyses were conducted to evaluate the preoperative characteristics (e.g., sex/gender, site, age, race and ethnicity) for potential association with outcomes in the UNC feasibility study.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support the reasonable assurance of safety and effectiveness of the proposed SSD/AHL

indications for use in the pediatric sub-population of individuals aged 5 years and older. The specific details about the leveraged data are included in the section XI.

E. Data limitation for the UNC study

Limitations for the clinical data collected from the UNC study include: 1) it is a single-site feasibility study; 2) it has relatively small sample size (20 subjects with SSD and 18 subjects with AHL); 3) it comprises only adult subjects; and 4) the effectiveness endpoints were not pre-specified to control type-I error and statistical results were based on post-hoc analyses. Given these limitations, the clinical data collected from the UNC study are not sufficient on their own to support the generalization of the clinical outcomes to the proposed, intended adult and pediatric populations, and support the requested SSD/AHL indication expansion.

F. 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 clinical study included 8 investigators of which 0 were full-time or part-time employees of the sponsor and 3 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: 3
- 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 interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

Summary of Real-World Evidence as Supporting Clinical Evidence

Literature Search Strategy

MED-EL conducted an extensive literature search to collect additional supporting clinical evidence of cochlear implants in SSD and/or AHL indications. The search terms they used are listed in Tables 17, 18, and 19, below.

Table 17. Combinations of Search Terms

Search Step	Search Terms	Review Question
1	"hearing loss" OR deaf*	P
2	single sided deafness OR SSD OR unilateral OR UHL OR asymmetric* OR AHL	P
3	cochlear implant* OR hearing aid* OR hearing system OR hearing instrument OR device* OR "no treatment" OR bone conduction OR BCI OR bone anchored OR BAHA OR CROS OR contralateral routing OR BiCROS OR "transcranial CROS" OR in-the-mouth device OR ITM OR soundbite OR bonebridge OR "ad hear"	I & C
4	1 AND 2 AND 3	
5	Limit 4 to *Humans*	
6	Limit 5 to *Language*: English	
7	Limit 6 to *Publication date*: June, 2014 to May, 2017	

Search Step	Search Terms	Review Question
1	(single sided deafness) OR (((((((SSD) OR unilateral) OR UHL) OR asymmetric) OR AHL)) AND (((hearing loss) OR deaf*) OR deafness))	P
2	cochlear implant* OR hearing aid* OR hearing system OR hearing instrument OR device* OR "no treatment"	I & C
3	1 AND 2	
4	Limit 3 to *Humans*	
5	Limit 4 to *Language*: English	
6	Limit 5 to *Publication date*: May 1, 2017 to March 6, 2019	

Note. The different search terms are connected using Boolean logic. Activated filters are displayed in italics. P = Population, disease, or condition; I = Intervention; C = Comparator group or control.
* Wildcard symbol to broaden the search by creating a root word search.

Table 18. Inclusion and Exclusion Criteria for Retrieved Literature

Inclusion Criteria	
Population/Problem	Patients of any age who have single sided deafness
Intervention/Treatment	cochlear implant, any other treatment that makes hearing possible, or no treatment
Outcomes	Safety or performance outcomes (or both) relating to the therapy
Exclusion Criteria	
E1	Not a clinical study in humans
E2	Neither safety nor performance of the therapy addressed
E3	No relevant therapy used
E4	Wrong study population
E5	Devices have been used for purposes outside their indications
E6	Publication lacking sufficient information
E7	Topic not relevant

Inclusion Criteria	
Population/Problem	Patients of any age who have SSD or AHL

Intervention/Treatment	cochlear implant
Outcomes	Safety or performance outcomes (or both) relating to the therapy
Exclusion Criteria	
E1	Not a clinical study in humans
E2	Neither safety nor performance of the therapy addressed
E3	No relevant therapy used
E4	Wrong study population e.g. different type of hearing loss
E5	Devices have been used for purposes outside their indications
E6	Publication lacking sufficient information
E7	Topic not relevant

Table 19. Literature Appraisal Criteria

Data Suitability	Description	Grading System
Appropriate Device	Where the data generated from the device in question?	D1 – Actual device D2 – Comparable device D3 – Other device
Appropriate Device Application	Was the device used for the same intended use (e.g. methods of deployment, application, etc.)?	A1 – Same use A2 – Minor deviation A3 – Major deviation
Appropriate Patient Group	Were the data generated from a patient group that is representative of the intended treatment population (e.g. age, sex, etc.) and clinical condition (i.e. disease including state and severity)?	P1 – Applicable P2 – Limited P3 – Different population
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 R2 – Minor deficiencies R3 – Insufficient information
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 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

Published Literature on Children

The literature search yielded five peer-reviewed papers in SSD and/or AHL children with a candidacy criterion of PTA ≥ 90 dB HL in the ear to be implanted, matching the proposed candidacy criterion for CI in SSD and AHL adults and children aged 5 yrs and older. The papers comprise a total of 26 children with SSD (five of which were reported

to be implanted with MED-EL devices) and a total of nine children with AHL. Tables 17, 18, and 19 above list the detailed literature search criteria and relevant information. The overall benefits of CI in children with SSD and AHL include improved performance in speech perception in quiet and noise, sound localization and subjective measures of quality of life.

Word recognition in quiet:

Beck et al. (2017) reported diverse speech audiometry results. Some of the children showed measurable benefits on speech discrimination. The CAP scores improved for the SSD children (N = 8) with CI compared to preoperative performance. Rahne and Plontke (2016) reported that two SSD children improved with CI over time in number recognition, two SSD children showed no recognition. One child improved over time in word recognition with CI, whereas the other three children showed no recognition.

Word recognition in noise:

Arndt et al. (2015) reported on the speech perception in noise for different speech and noise configuration. Children with SSD demonstrated improved although variable performance on speech perception in spatially-separated conditions. Some children demonstrated improvement in spatially separate speech and noise. Tavora-Vieira and Rajan (2015) showed better and similar speech perception in noise with CI-on compared to CI-off for two SSD children. Gratacap et al. (2015) showed an increase in speech perception in noise in 9 children with AHL after 12 and 24 months of CI use compared to preoperative performance. Rahne and Plontke (2016) reported an improvement in speech reception thresholds in three SSD children when CI-on and CI-off are compared; in one child no measurement was possible.

Sound localization:

Arndt et al. (2015) reported a decreased localization error with CI for most of the children as compared to the pre-operative unaided condition. Tavora-Vieira and Rajan (2015) reported that one child with SSD showed a decreased localization error after 6 and 12 months with the CI-on compared to CI-off condition, whereas the other child with SSD showed the same localization performance in both conditions. Rahne and Plontke (2016) reported an improvement in sound localization in four children with SSD when CI-on and CI-off are compared.

Subjective measures:

Beck et al. (2017) showed that the parents (N = 9) and children (N = 3) with SSD reported an increase score for the SSQ. Arndt et al. (2015) reported an increase the SSQ score in children with SSD with postlingual onset of deafness (N = 9), slight improvement in children with SSD with perilingual onset of deafness (N = 2) and minimal improvement or same performance in children with SSD who are congenitally deaf (N = 2).

Published Literature on Adults

The literature search yielded six peer-reviewed papers in SSD and/or AHL adults with a candidacy criterion of PTA ≥ 90 dB HL in the ear to be implanted, matching the proposed candidacy criterion for CI in SSD and AHL adults. Although the paper by Kitoh et al. (2016) mentioned a study inclusion criterion of PTA > 70 dB HL, all five subjects included in the study had a pre-operative unaided PTA of 92 dB HL or higher. Hence, the results from this study were included in the summary below.

The six papers comprise a total of 58 adults with SSD (N = 50 of which implanted with MED-EL devices) and a total of 52 adults with AHL (N = 37 of which implanted with MED-EL devices). This subject count does not include five SSD nor 16 AHL patients from Skarzynski et al. (2017), as those subjects are part of the larger cohort from the same implant center later reported on by Lorens et al. (2019). Also note that three of the 58 adult SSD subjects might have an unaided PTA close to or below 90 dB HL in the implanted ear, as the paper by Döge et al. (2017) presents PTA data as median and interquartile range only (75%, i.e. N =8 of 11 studied subjects have PTA > 100 dB HL). The overall benefits of CI in SSD and AHL adult patients include improved performance regarding speech perception in quiet and in noise, sound localization and subjective measures regarding quality of life, music enjoyment and tinnitus.

Word recognition in quiet

Döge et al. (2017) showed that with a CI, the mean PTA thresholds of the deaf ear improved from the mean value of 120 dB at unaided condition to below 40 dB in the aided condition in 11 SSD subjects. In addition to the benefit of sound perception, the CI enabled better speech perception in quiet. Skarzynski et al. (2017) compared CI-on vs CI-off condition in 5 SSD and 16 AHL subjects and significantly better speech perception was observed in the CI-on condition. Results with the CI demonstrated a continuous improvement in speech recognition after 12-month of use. Rahne and Plontke (2016) reported a significant improvement in monosyllabic word and multisyllabic number recognition in quiet in comparing the 12-month and 1-month after CI activation in 17 SSD subjects. van Loon et al. (2017) reported that speech recognition scores increased from 74% pre-operatively to 88% at 12-month with bimodal stimulation in 7 AHL cases.

Speech perception in noise

Several studies found that the CI enabled better speech perception in noise. Rahne and Plontke (2016) reported a significant improved speech perception in noise at 3-month of CI activation with CI-on vs CI-off condition, and a continuous improvement occurring at 12-months in 17 SSD subjects. Skarzynski et al. (2017) reported better speech perception in noise at CI-on vs CI-off condition. van Loon et al. (2017) reported that in comparison to the CI-off or CI-only condition, bimodal stimulation resulted in significantly better speech recognition in noise and spatial speech recognition at 3-months, 6-months and 12-months post-activation. Lorens et al. (2019) reported a significant binaural benefit conveyed by CI-on in comparison to the CI-off condition, in 25 SSD and 45 AHL subjects. Kitoh et al. (2016) reported a gradually improved speech perception in noise after 12-months post-activation in comparison to the pre-operative condition. Döge et al. (2017) reported slightly improved speech reception in noise in CI-on vs CI-off condition

in 8 of 11 patients. Three of 11 subjects, however, showed deteriorations at CI-on condition.

Sound localization

Döge et al. (2017) showed a significant decrease of localization error in the CI-on condition in comparison with the CI-off condition in 11 SSD subjects. Skarzynski et al. (2017) observed a significant localization benefit reflected by decrease in RMS angular error at CI-on vs CI-off condition. van Loon et al. (2017) reported a significant improved localization performance in all 7 AHL subjects with bimodal stimulation at 12-month in comparison to the pre-operative condition. Results with the CI demonstrated a continuous improvement in sound localization after 12 months of CI use. Rahne and Plontke (2016) reported that in comparison to CI-off, CI-on significantly improved sound localization, reflected by a decrease in ADE (angular detection error) at 1-month of CI activation. A continuous improvement occurred over time. Kitoh et al. (2016) reported better sound localization in all 5 subjects, with continuous improvement through 12-month.

Subjective measures

van Loon et al. (2017) reported increased frequency and satisfaction of listening to music from 7 AHL CI users. Bimodal stimulation also resulted in better quality, clarity, and appreciation of different music styles. Skarzynski et al. (2017) reported substantial tinnitus suppression in all 15 patients with pre-operative tinnitus and Kitoh et al. (2016) reported decreased disturbance to daily life caused by tinnitus in all 5 SSD cases. Two studies addressed self-evaluation of CI performance in SSD and AHL subjects. Skarzynski et al. (2017) reported a significant improvement in the global score of APHAB, as well as sub-scales including 'Ease of communication', hearing under 'background noise' or under 'reverberation' at 14-months after CI activation in comparison to pre-operative condition. van Loon et al. (2017) reported that except for the 'speech production' subdomain, bimodal stimulation yielded a significant better outcome for all other subdomains of the NCIQ questionnaire. An average appreciation of the cochlear implant was scored 4.3/5, indicating a high satisfaction with the CI.

Limitation for the Literature Data as RWE

Limitations for the literature data as RWE include: 1) very limited individual data are available for effectiveness outcomes, 2) the patients from whom data were collected received CIs 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 all subjects in the above articles identified through the literature search have profound hearing loss (PTA $\geq$ 90 dB HL) in the ear to be implanted and, therefore, match the proposed candidacy criterion for cochlear implantation among individuals aged 5 years and older with SSD or AHL, the safety and effectiveness data reported in these articles can serve as supporting evidence to confirm the findings captured in the UNC feasibility study according to FDA guidance document titled "Use of Real-World

Evidence to Support Regulatory Decision-Making for Medical Devices" (issued August 31, 2017).

Conclusions from Real World Evidence

This clinical evaluation of cochlear implantation for the treatment of SSD and AHL is based on the above literature data sets relevant to the safety, performance, and effectiveness of cochlear implantation as a treatment option for individuals with AHL or SSD.

In this review of Real-World data, the latest clinical data were summarized on SSD and AHL patients from centers both in the US and around the globe that meet the proposed audiometric indication criterion of a profound hearing loss in the ear to be implanted, i.e., a PTA of 90 dB or higher. The clinical populations reported on include both adults and children older than 5 years age.

Taken together, the clinical data from this body of literature show consistent benefits of CI in individuals with SSD or AHL, in terms of improved speech perception in noise, spatial hearing, localization accuracy, and patient-reported subjective outcome measures. Consistent CI use of patients has been shown across literature reports, and notably so in the prospective study by Lorens et al. (2019) in 70 sequentially implanted SSD and AHL CI users (59 of which were implanted with MED-EL devices). These literature data provide Real World Evidence (according to the FDA guidance "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices") in support of the clinical benefits of CI in SSD and AHL recipients, as demonstrated in the UNC study. In this way, these literature reports do serve as supporting evidence which demonstrates a reasonable assurance of device safety and effectiveness and to characterize the benefit/risk profiles for the proposed SSD/AHL indications.

XI. Pediatric Extrapolation

The FDA published a guidance document entitled, "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" (issued on June 21, 2016). The guidance offers detailed recommendations on when and why extrapolation of available clinical data (e.g., adult data) is appropriate for use in pediatric populations. The guidance provides a detailed decision tree to evaluate the suitability of extrapolating data sets. In the following paragraphs, questions from the pediatric extrapolation decision tree as presented in Figure 1 of the FDA guidance document are answered in order to determine whether a full or partial extrapolation can be applied to the available clinical data from the UNC study and literature articles. In the following, the degree of hearing loss in the contralateral ear is not specified and profound unilateral hearing loss can thus include both AHL and SSD.

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

Yes. In the UK, for example, the incidence of sudden unilateral sensorineural hearing loss in adults, aged 16 years or over, was estimated to range between 5 and 20 per 100,000 adults in 2006 (Baguley et al, 2006). Results from the French "Handicap-Santé" survey in 2008 led to an estimated prevalence of single-sided deafness in the total French population of 1.5% (de Kervasdoué & Harmann, 2016). The US Centers for Disease

Control and Prevention (CDC) reported a total of 5,669 children with hearing loss in 2014, 513 of them had severe to profound unilateral sensorineural hearing loss or severe to profound unilateral hearing loss of unknown cause. In school children, incidence rates of 1-5% of unilateral hearing loss have been reported (Bess et al, 1998; Ross et al, 2010). The proportion of cases with severe to profound hearing loss is probably around 30-50% (Boyd, 2015). In neonates, it is estimated that around 1 in 1000 is affected by UHL (Berninger et al, 2011; Prieve et al, 2000; Uus & Bamford, 2006).

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

Yes. The primary effectiveness measures of the clinical study conducted at the UNC (Section X) were the comparisons of speech perception and localization performance between the bilateral, pre-operative, unaided/best-aided (with BCHA) condition and the bilateral, 12-month-post-operative CI + NH (or HA) condition. Additionally, subjective report scores were compared pre-operatively and at the 12-month post-activation intervals. All effectiveness measures collected in the UNC study among adults with SSD and AHL are relevant to the pediatric SSD and AHL population aged 5 years to 21 years, 11 months.

Four studies additionally published outcomes of cochlear implantation in children with SSD and AHL. The studies by Beck et al. (2017), Arndt et al. (2015) and Tavora-Vieira and Rajan (2015) analyzed the speech understanding of SSD children (N = 32). Arndt et al. (2015) and Tavora-Vieira and Rajan (2015) further analyzed the sound localization in SSD children (N = 15). Beck et al. (2017) and Arndt et al. (2015) further reported on the subjective performance in SSD children (N = 22). One objective of the study published by Gratacap et al. (2015) was to review speech discrimination following cochlear implantation in children with residual hearing, including nine children with AHL (Section XI).

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?

No. Neither the location nor duration of the implantation differs between the adult and the intended pediatric population in such a way that either the safety or effectiveness of the device would be impacted. The equipment used is the same as the equipment used for standard CI – there is no change in the device.

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

No. The same device is used for adult and pediatric patient populations. Therefore, there are no differences in device characteristics between pediatric and adult use that could impact either device safety or effectiveness in the pediatric population in a clinically meaningful way.

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

Yes. Cochlear implants are already used for the treatment of children aged 12 months and older with bilateral sensorineural hearing loss. The risk profile of the device is established in the pediatric population and does not change with the requested indication application. However, children younger than 5 years with SSD and AHL have normal or close-to-normal hearing in the contralateral ear and will most likely demonstrate normal hearing/speech/language development. It is impossible to use the questionnaires that capture children's binaural hearing experience in their daily lives (e.g., LEAQ or ASC) to obtain ear-specific information and determine insufficient functional access to sound in the ear to be implanted given the normal hearing or close-normal hearing in the contralateral ear. Therefore, data extrapolation should not be considered for younger children aged less than 5 years with SSD or AHL.

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 patient populations need to fulfill the candidacy criteria for cochlear implantation before treatment. The CI candidacy criteria are detailed in the Intended Use of the MED-EL Cochlear Implant System.

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

No. There are no other differences between adult and pediatric populations that could impact either device effectiveness or safety in the pediatric (sub)population in a clinically meaningful way.

Conclusions for pediatric data extrapolation

The safety profile of cochlear implantation has been well-established and confirmed among children aged 12 months and older with bilateral, profound, sensorineural hearing loss. Device effectiveness for the SSD/AHL indications among adult patients has been demonstrated in the UNC clinical study, in terms of improved speech perception in quiet and noise, improved localization performance, and higher subjective quality of hearing (see Section X). Additionally, published studies have also provided evidence to confirm and support the UNC study findings, among both adult and pediatric patients for the proposed SSD/AHL indications (see Section XI). Together, it is appropriate to leverage the available clinical data from the UNC study and literature findings to support extrapolation use among pediatric patients with SSD/AHL down to 5 years of age who meet the following audiometric criteria: 1) a profound degree of hearing loss (i.e., defined as (PTA4) of 90 dB HL or greater at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz), and 2) less than 5% speech score in the ear to be implanted. For the SSD/AHL indications, data extrapolation is not considered suitable for children younger in age (< 5 years) given that 1) there is uncertainty to obtain ear-specific hearing and amplification related information among them; and 2) the age indication for SSD and AHL (> 5 years) is consistent with

the indication for use for Bone Anchored Hearing Aid (BAHA), a 510(k) device approved for the same patients with SSD.

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Clinical Investigation from the UNC study (IDE G141050) – SSD and AHL

1. Speech understanding in quiet

   Subjects heard better in the ear with profound hearing loss with the cochlear implant on after surgery than they did before surgery. On average subjects in the SSD group scored 4% correct before surgery and 55% correct after surgery on CNC words in quiet. In the AHL group, subjects scored 6% in the profound ear before surgery and 56% after surgery on CNC words in quiet.

2. Speech understanding in noise

   When tested on AzBio sentences in noise, subjects in the SSD group improved from the bilateral, pre-operative, baseline, aided (with BCHA) condition to the bilateral, 12-month post-operative, CI + NH condition when both the speech and the noise were presented from the front and when speech was presented to the front and noise was presented to the ear with normal hearing. The average improvement was 15.7 percentage points with speech and noise from the front, and 34.3 percentage points with speech from the front and noise to the normal hearing ear. No change was demonstrated when speech was presented to the front and noise was presented to the ear with the cochlear implant.

   In the AHL group, subjects demonstrated an improvement on AzBio sentences from the bilateral, pre-operative, baseline, aided (with BCHA) condition to the bilateral, 12-month post-operative, CI + HA condition when speech and noise were presented to the front as well as when speech was presented to the front and noise was presented to the ear with better hearing. Average improvements in this group were 13.0 and 18.1 percentage points, respectively. No differences were seen when subjects were tested with speech the front and noise presented to the ear with the cochlear implant.
   When tested on the BKB-SIN, in the SSD group, no changes were seen when speech was presented to the front and noise was presented to either the front or the ear with the cochlear implant. When speech was presented to the front and noise was presented to the normal hearing ear, an improvement was found. The average change in score was -2.8 dB in this condition.

For the AHL group, on testing with the BKB-SIN, an improvement was demonstrated when speech was presented to the front and noise was presented to the ear with better hearing. The average improvement in this condition was -1.3 dB. No changes were demonstrated when speech and noise were presented to the front or when speech was presented to the front and noise was presented to the CI ear.

3. Localization

Subjects' sound localization performance was also tested. Both groups, SSD and AHL demonstrated an improvement in localization performance from the bilateral, pre-operative, baseline, aided condition to the bilateral, 12-month post-operative, CI + NH (or HA) condition. The SSD group demonstrated an improvement of 42.9 points, while the AHL group demonstrated an average improvement of 37.1 points.

4. Subjective questionnaires

Subjects in both the SSD and AHL groups demonstrated significant improvements over time on the SSQ and APHAB questionnaires. Subscales on the SSQ of Speech, Spatial, and Qualities all showed improvements for both groups. On the APHAB, subscales of Ease of Communication, Background Noise, and Reverberation also all demonstrated improvements over time. The subscale of Aversiveness showed no change over time in both groups.

Literature review

The literature data provide confirmatory evidence for the outcomes from the UNC study, demonstrating that recipients with SSD and AHL benefit from a CI in terms of speech perception, localization, and quality of life. A CI is the only treatment option that has the potential to reinstate binaural hearing in adults with SSD or AHL.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies conducted under prior PMA approvals, as well as data collected in a clinical study conducted to support PMA approval as described above, as well as reported literature. Data from the UNC SSD and AHL study showed the most frequent safety events were related to vertigo, dizziness, or imbalance. Some were attributable to the device, and some not. Unrelated infections were also reported in three cases. All other events occurred at a rate of 5% or less (2 subjects or fewer). This generally matches what is reported in the literature for cochlear implant use in the indication of bilateral, severe-to-profound, sensorineural hearing loss. In all other aspects, the cochlear implant, electrode, audio processor and fitting software are the same for patients who have bilateral severe-to-profound hearing loss, and no other unexpected safety outcomes are reported. According the proposed SSD/AHL indications, patients have a "deaf" ear or a profound degree of hearing loss in the ear to be implanted and there is essentially no residual hearing to lose. Therefore, there are no additional risks associated with implanting SSD/AHL patients when compared to the approved indications for adult and pediatric patients with a bilateral, severe-to-profound or profound, sensorineural hearing loss.

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, as well as data reported in the literature. Expected benefits of cochlear implantation include improved speech perception in quiet and noise, better sound localization, and improved quality of life. The probable risks of the device are based on data collected to support prior PMA approvals, as well as a clinical study conducted to support PMA approval in SSD/AHL indications as described above, and on data reported in the literature. The safety of cochlear implants has been demonstrated in the indication of bilateral, severe-to-profound, sensorineural hearing loss. In the proposed SSD/AHL indications, patients have a "deaf" ear or a profound degree of hearing loss in the ear to be implanted and there is essentially no residual hearing to lose. Therefore, there are no additional risks associated with implanting SSD/AHL patients when compared and the risks are the same as those of the approved indications for patients with bilateral, severe-to-profound (adults) or profound (children) hearing loss.

The subject PMA is to expand the indications for use for a previously approved cochlear implant system. The safety profile of cochlear implants in general is well-understood. Although the clinical data from the study described in Section X and the literature articles described in Section XI are limited, FDA agrees that the degree of uncertainty is acceptable in the context of the overall benefit-risk profile of SSD/AHL patients with a "deaf" ear in the ear to be implanted where the affected ear has essentially no residual hearing to lose, and the patient may gain improved speech perception, better sound localization, and improved quality of life.

1. Patient Perspectives
   Patient perspectives considered during the review included: subjective measures of benefit and satisfaction. The majority of subjects demonstrated improvements in benefit and satisfaction evaluated by both SSQ and APHAB questionnaires regarding the ease of communication, especially in difficult listening conditions, and improvement in quality of life (i.e., social, emotional, physical). The large magnitude of benefit and satisfaction improvement demonstrated through the responses on both SSQ and APHAB (e.g., 31.9% and 26% improvement scores on APHAB for subjects with SSD or AHL, respectively) indicated that patients with SSD or AHL were able to experience the benefit in their daily lives from the MED-EL Cochlear Implant System, compared to their preoperatively used hearing aids.

In conclusion, given the available information above, the data support that the overall hearing benefits of the device outweigh the risks for patients 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 an investigation from the UNC and literature articles, along with analyses based on FDA guidance documents (i.e., Real-World Evidence and pediatric data extrapolation), demonstrate a reasonable assurance of safety and effectiveness of this device when used in accordance with the proposed

SSD/AHL 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 terms of improved speech perception in quiet and noise, better sound localization, and improved quality of life. The risks of cochlear implantation among patients with SSD or AHL are the same as those of the approved indications for patients with bilateral, severe-to-profound (adults) or profound (children) hearing loss.

XIV. CDRH DECISION

CDRH issued an approval order on July 19, 2019. The final conditions of approval cited in the approval order are described below.

The MED-EL New Enrollment SSD/AHL Study is a new enrollment post-approval study that is intended to assess the long-term safety and effectiveness of the MED-EL Cochlear Implant System in treating subjects with SSD and AHL. The study will be conducted as a prospective, non-controlled, non-randomized, multicenter study and will include 65 subjects at 6 sites. Among the 65 subjects, 44 subjects will be 18 years-old and above (10 in the SSD group and 34 in the AHL group). 12 subjects will be between 5 and 12 years of age and 9 subjects will be between 12 and 18 years of age (6 in the SSD group; 6 in the AHL group; 9 in either SSD or AHL group). The primary safety endpoint is the number and proportion of subjects experiencing device-related adverse events throughout the duration of the post-approval study. The effectiveness endpoints include the within subject differences for the improvement on AzBio sentences in noise recognition from the bilateral, pre-operative, best-aided condition to the bilateral, 12 month, post-operative Cochlear Implant (CI) + Normal Hearing (or Hearing Aid) condition for speech and noise presented in S0Ncontra (signal from front, noise from contralateral ear), S0N0 (signal and noise from front), and S0NCI (signal from front, noise from the CI ear) configurations. The stability of perceived hearing benefits over time will be assessed by employing the Speech, Spatial, and Qualities (SSQ) questionnaires. Additionally, localization ability will be evaluated if the sites have facilities to perform the localization test. Subjects will be followed at 3 months, 6 months, 12 months, 24 months, and 36 months post-activation visits.

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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