

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: PGQ

Applicant's Name and Address: MED-EL Corporation
Fürstenweg 77a
6020 Innsbruck, Austria

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P000025/S084

Date of FDA Notice of Approval: September 15, 2016

The original PMA (P000025) for the MED-EL Cochlear Implant System was approved on August 20, 2001 and is intended to provide the opportunity to detect and recognize auditory information through electrical stimulation of the auditory nerve for severe to profoundly hearing-impaired individuals (children aged 18 months and older; adults aged 18 years 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 to include the MED-EL EAS System, consisting of:

- MED-EL implant variant (SONATA_{TI100} +FLEX₂₄, Mi1000 MED-EL CONCERT (PIN) +FLEX₂₄, Mi1200 SYNCHRONY (PIN) +FLEX₂₄, SONATA_{TI100} +FLEX₂₀, Mi1000 MED-EL CONCERT (PIN) +FLEX₂₀, Mi1200 SYNCHRONY (PIN) +FLEX₂₀)
- SONNET EAS Audio Processor, DUET 2 Audio Processor
- MAESTRO 6.0.1 programming software

II. INDICATIONS FOR USE

The MED-EL EAS System is intended to provide electrical stimulation to the mid- to high-frequency region of the cochlea and acoustic amplification to the low-frequency regions, for candidates with residual low frequency hearing sensitivity.

The MED-EL EAS System is indicated for partially deaf individuals aged 18 years and older who have residual hearing sensitivity in the low frequencies sloping to a

severe/profound sensorineural hearing loss in the mid to high frequencies, and who obtain minimal benefit from conventional acoustic amplification. Typical preoperative hearing of candidates ranges from normal hearing to moderate sensorineural hearing loss in the low frequencies (thresholds no poorer than 65 dB HL up to and including 500 Hz) with severe to profound mid- to high-frequency hearing loss (no better than 70 dB HL at 2000 Hz and above) in the ear to be implanted. For the non-implanted ear, thresholds may be worse than the criteria for the implanted ear, but may not be better. The CNC word recognition score in quiet in the best-aided condition will be 60% or less, in the ear to be implanted and in the contralateral ear. Prospective candidates should go through a suitable hearing aid trial, unless already appropriately fit with hearing aids.

III. CONTRAINDICATIONS

The device is contraindicated for individuals as follows:

- If the individual is known to be intolerant of the materials used in the implant (medical grade silicone, platinum, platinum iridium).
- 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.

Furthermore, the MED-EL EAS System is contra-indicated for partially deaf individuals with unstable progressive hearing loss, who are unable to use amplification devices, and / or have cochlear malformations.

IV. WARNINGS AND PRECAUTIONS

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

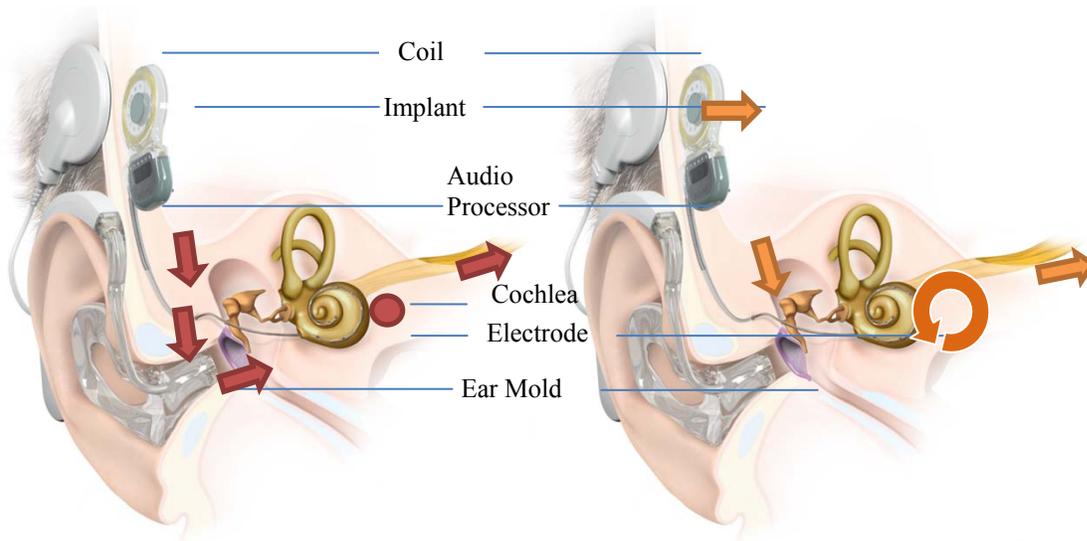
V. DEVICE DESCRIPTION

A. General Description

The “MED-EL EAS System” is an electric-acoustic stimulation (EAS) cochlear implant system. The MED-EL EAS System provides an electric stimulation in the high frequency region of the cochlea and an acoustic stimulation via acoustic amplification in the low

frequency region of the cochlea where patients have normal hearing to a moderate sensorineural hearing loss. The system consists of both internal and external components, as illustrated in Figure 1.

Figure 1 – EAS Principle of Operation



*1a) Acoustic Stimulation
(To cover the low frequencies)*

*1b) Electric Stimulation
(To cover the higher frequencies)*

Note: EAS is the use of a hearing aid and a cochlear implant in the same ear. Complete cochlear coverage (i.e. stimulation of the entire cochlea) is achieved by combined electric and acoustic stimulation. (2) The illustration above indicates Mi1200 SYNCHRONY PIN (implant) and SONNET EAS (audio processor). The operation principles are the same for the other relevant implant and audio processor variants.

Acoustic amplification (Figure 1a)

- (1) Low-frequency sounds are picked up by the microphone of the audio processor and are digitally processed and separated via a dedicated EAS circuitry.
- (2) These sounds are acoustically amplified by the loudspeaker located in the ear hook and relayed via the earmold to the ear canal.
- (3) Sounds reach the undamaged areas of the cochlea responsible for processing low frequency sound.
- (4) The auditory nerve relays the signals to the brain.

Electric stimulation (Figure 1b)

- (1) High frequency sounds are picked up by the microphone of the audio processor and transforms it into coded signals.

- (2) This coded electrical signal is sent to the coil and transmitted across the intact skin via the inductive link.
- (3) The electronics within the implant interprets the coded signals and sends a corresponding pattern of stimulation pulses to the individual electrode contacts of the active electrode array within the cochlea.
- (4) 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.

Complete cochlear coverage (i.e. stimulation of the entire cochlea) is therefore achieved by the combined electric and acoustic stimulation.

B. Implants and Electrodes

i. SONATA_{TI}¹⁰⁰ +FLEX24, Mi1000 MED-EL CONCERT (PIN) +FLEX24 and Mi1200 SYNCHRONY (PIN) +FLEX24 (to extend the indication for EAS)

All the implant types (i.e., receiver-stimulators) and the +FLEX24 electrode array have been previously approved for the conventional cochlear implant indication. Through the current PMA supplement, these implant types and the +FLEX24 electrode array are also approved for the EAS indication.

ii. +FLEX20 electrode array

The +FLEX20 electrode array is a shorter version (approximately 20 mm of the electrode insertion depth) of the existing FLEX electrode variants. The +FLEX20 electrode array is intended to be used for the EAS indication and is compatible with the SONATA_{TI}¹⁰⁰, Mi1000 MED-EL CONCERT (PIN), and Mi1200 SYNCHRONY (PIN) implants. The design of the +FLEX20 electrode array is based on the approved +FLEX24 electrode array. The main differences include the length of the active electrode array (20 mm for the +FLEX20 vs. 24 mm for the +FLEX24), electrode contact spacing (1.4 mm for the +FLEX20 vs. 1.9 mm for the +FLEX24) and the electrode lead length (88 mm for the +FLEX20 vs. 102.2 mm for the +FLEX24).

Figure 2: An example of one of the ten implant variants approved for EAS, the Mi1200 SYNCHRONY Implant



C. Audio Processors

i. DUET2 audio processor

As shown in Figure 3, the DUET2 audio processor includes an antenna coil and its cable, control unit (typically called as the sound processor), acoustic unit (AU) ear hook and ear mold, and battery pack. The DUET2 audio processor uses the OPUS2 control unit which is the same control unit for the approved OPUS2 audio processor. The DUET2 audio processor also uses accessories that are the same with those used for the approved OPUS2 audio processor including a remote control (FineTuner), programming cable, audio adapter cables, sound processor test device, electrical drying kit and desiccants, clean brush, and etc. The DUET2 audio processor is designed to provide electric-acoustic stimulation. For the acoustic stimulation, the DUET2 audio processor needs to be configured and used with an ear mold. For the electric cochlear implant stimulation, the DUET2 audio processor needs to be used in combination with an internal device.

ii. SONNET EAS Audio Processor

As shown in Figure 3, the SONNET EAS audio processor includes SONNET EAS Control Unit including an audio receiver, SONNET Battery Pack, coil and coil cable, and EAS earhook. The SONNET EAS audio processor uses the same design as the approved SONNET for cochlear implant electric stimulation, but the SONNET EAS audio processor provides additional hearing aid functionality for amplification of low frequency sound. The SONNET EAS audio processor also uses accessories that are the same with those used for the approved SONNET audio processor including a remote control (FineTuner), MAX programming

cable, microphone covers, audio adapter cables, sound processor test device, electrical drying kit and desiccants, clean brush, and etc.

The main differences between the SONNET audio processor and the SONNET EAS audio processor include the SONNET EAS Control Unit and the EAS earhook. The DUET2 or SONNET EAS user accessible audio processor functions are accessed via the existing approved and unchanged FineTuner remote control which communicates with the audio processor via a radio frequency (RF) link. In addition, due to the integrated front-end hearing aid audio processor firmware in the SONNET EAS, the volume of the acoustic amplification is adjustable together with the electric stimulation via the same volume control on the FineTuner. For the DUET2 processor, the volume for acoustic amplification is only adjustable manually via the trimmer on the device.

Figure 3. EAS Processors: DUET 2 (left), FineTuner remote control (center), SONNET EAS (right)



iii. Fitting Software and Accessories

The fitting or programming of SONNET EAS and DUET2 audio processors requires the MAESTRO System Software 6.0.1 (and higher) with the MAX Programming Interface for both the cochlear implant signal processing and the acoustic signal processing. There are no trimmers on the SONNET EAS for manual adjustment of acoustic amplification.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The most common alternative treatment of severe to profound bilateral high-frequency sensorineural hearing loss with residual low-frequency hearing is the use of conventional air conduction hearing aids or, in some cases, frequency transposition hearing aids. Patients may also choose to forego obtaining a hearing device and pursue rehabilitation via speechreading and/or sign language training. Each of these alternatives has its own advantages and disadvantages. A patient should fully discuss the alternatives with his/her physician and audiologist in order to select the treatment that best meets his/her expectations and lifestyle.

VII. MARKETING HISTORY

The MED-EL EAS system has been marketed for use in adults and children in over 110 countries, including Albania, Algeria, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Belarus, Belgium, Benin, Bolivia, Bosnia, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, Egypt, Estonia, Finland, France, Georgia, Germany, Greece, Guatemala, Hong Kong, Hungary, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Ivory Coast, Japan, Jordan, Kazakhstan, Korea, Kosovo, Kuwait, Latvia, Lebanon, Libya, Lithuania, Luxembourg, Macedonia, Malawi, Malaysia, Malta, Mexico, Moldavia, Mongolia, Montenegro, Morocco, Nepal, Netherlands, New Zealand, Nigeria, Norway, Oman, Pakistan, Panama, Peru, Phillipines, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Senegal, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sri Lanka, Sudan, Sweden, Switzerland, Syria, Tajikistan, Taiwan, Thailand, Turkey, U. Arab Emirates, UK, Ukraine, Uruguay, Venezuela, Vietnam, Yemen.

Since market introduction, over 4600 implants with +FLEX20 and +FLEX24 electrode variants have been implanted worldwide and over 5000 DUET, DUET 2 and SONNET EAS processors have been sold worldwide.

The MED-EL EAS system has 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/complications associated with the implantation and use of the MED-EL EAS 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

A. Laboratory Studies

i. SONATA_{TI}¹⁰⁰ +FLEX24, Mi1000 MED-EL CONCERT (PIN) +FLEX24 and Mi1200 SYNCHRONY (PIN) +FLEX24 (to extend the indication for EAS)

The +FLEX24 electrode array was previously approved to be used with the SONATA and CONCERT (PIN) implants (P000025/S057 and S058) and SYNCHRONY (PIN) implant (P000025/S079) for the conventional cochlear implant indications. There are no device changes in the +FLEX24 electrode array associated with the EAS indication. Through the review and approval of the +FLEX24 electrodes, Verification and Validation (V&V) activities were reviewed as part of the review and approval of MED-EL's PMA supplements listed in Table 1. Therefore, no additional V&V tests were needed to approve the +FLEX24 electrode arrays for the EAS indication.

Table 1. PMA supplements relevant to the approval of the +FLEX24 electrode array for the conventional cochlear implant indication

Description	Relevant PMA /IDE number	Date of Approval
SONATA _{TI} ¹⁰⁰	P000025/S022	2007 June
SONATA _{TI} ¹⁰⁰ FLEX _{eas} (FLEX ²⁴)	G040002/S008, S009	2008 January
Mi1000 MED-EL CONCERT	P000025/S050	2011 July
New electrode variants including FLEX ²⁴ and +FLEX ²⁴	P000025/S057	2012 April
Mi1000 MED-EL CONCERT (PIN)	P000025/S058	2012 November
Mi1200 SYNCHRONY (PIN), including SYNCHRONY +FLEX ²⁴	P000025/S079	2015 January

ii. +FLEX20 electrode array

Table 2 summarizes the nonclinical testing conducted for the +FLEX20 electrode array and lead, including information about the test, purpose, acceptance criteria and results.

Table 2. The +FLEX20 electrode array and lead testing

Test	Purpose	Acceptance Criteria	Results
Physical dimensions	To verify the physical dimensions	The length of the array must be verified as part	All test requirements

and performance characteristics	and electrical properties	of the electrode assembly verification; all other physical dimensions of the implant have been verified during previous tests.	are fulfilled.
Tensile tests	To demonstrate that the electrode withstands tensile forces that might occur during or after implantation, without fracture of any conductor or deterioration to any functional electrical insulation	Two tests were performed according to ISO 14708-7(23.3), 1) Sustained tensile force of min 1.05N for at least one minute. 2) All insulation impedances > 100kΩ direct current resistance of each active electrode wire ≤ 100Ω	No short circuits after the pull test and elongations are all between 4 -6 mm. Insulation impedance were measured as planned. All acceptance criteria were fulfilled.
Multiple insertion test	To demonstrate sufficient robustness of the electrode to withstand the forces exerted during implantation	The array is to withstand 4 times partial insertions into an obstructed scala tympani model and 2 times full insertions into an open scala tympani model without any open and/or short circuits.	At the completion of the insertion test, the final electrical properties were tested and no open or short circuits were found. The test requirements were fulfilled.
Flex test (Drop test)	To demonstrate that the electrode withstands the flexural stresses that might occur during implantation as required	Per ISO 14708-7 sec 23.5, Test 1, no open or short circuit after five times of stimulator drop must be shown, while the lead is clamped close to the most proximal electrode contact.	All test requirements were fulfilled. The results are valid for CONCERT (PIN) and SYNCHRONY (PIN).
Sterilization evaluation	To perform the sterilization validation via product adoption	Adoption evaluation should be performed according to TIR28:2009, sec 3.4 and assessment of ISO 11135-1:2007 Sec	The candidate product may be adopted into the product's sterilization validation of

		C12.3.2	the SONATA.
Temporal Bone test	To assess the insertion trauma caused by the electrode	Electrodes were inserted into scala tympani with the same procedures via the round window (RW). Various evaluations were performed to verify that the insertion properties of the electrode are acceptable for human implantation.	Smooth and atraumatic insertion can be expected. No tissue damages were observed.

Preclinical Safety Analysis:

Charge density calculations were performed to specify safe stimulus current levels for the +FLEX20 electrode array. Taking into account the area and periphery of the smallest electrode surface, charge density calculations were completed to assure safe current stimulation by electrodes in the cochlea. All temporal bone tests demonstrated consistent results, indicating that the +FLEX20 electrode can be smoothly and fully inserted into the scala tympani without significant intra-cochlear trauma. This is consistent with the findings of insertion tests performed on the other FLEX electrodes, including +FLEX24.

Biocompatibility:

There has been no change associated with the processed materials, manufacturing processes, packaging and sterilization methods for the +FLEX20 electrode array compared to the previously approved electrode variants through P000025-S021, S050, and S057. Therefore, the biocompatibility of the +FLEX20 electrode array is equivalent to the approved electrode variants.

iii. DUET2 audio processor

Like the SONNET EAS audio processor, the DUET2 audio processor also provides electric-acoustic stimulation. The DUET2 audio processor utilizes the approved OPUS2 control unit, FineTuner and COMT+ P coil, of which verification and validation activities are reviewed and approved through P000025/S029. Table 3 summarizes the nonclinical testing conducted for the acoustic unit of the DUET2 audio processor.

Table 3. Nonclinical laboratory tests for the DUET2 audio processor

Test	Purpose	Acceptance Criteria	Results
Acoustic Output Verification	To verify that the hearing aid of DUET 2 fulfills design requirements and hearing aid standards. Tests were further repeated to verify the extended frequency range (125 – 1700Hz).	The acoustic attributes of the DUET 2 with OPUS 2 were tested to the hearing aid standards (ANSI S3 22-2003 and IEC 60118.1994) ANSI S3.22, IEC60118-0, IEC60118-0-2 + A1+A2	All acceptance criteria were met. The design requirements are fulfilled.
Audio input verification	To verify the audio input with mixed microphone and FM system mode for both acoustic amplification and electric stimulation	The acoustic attributes of the DUET 2 with OPUS 2 were tested to the hearing aid standards (ANSI S3 22-2003 and IEC 60118.1994)	All acceptance criteria were met. The design requirements are fulfilled.
Telecoil verification	To verify the telecoil function	ANSI standard S3.22 2003 (section 5.8.1); IEC standard EN 60118-1 (section 5.8.1) The DUET2 can be fitted to user needs either with help of SW-programming and/or with help of 4 trimmers.	All acceptance criteria were met.
Current consumption verification	To verify that the battery life is not unacceptably shortened by the addition of the acoustic amplification.	Current consumption was to IEC60118-0, IEC60118-0-2 + A1+A2, including 1. The DUET2 is powered by 3 zinc-air batteries (or equivalent), size 675, connected in series. Each battery has a nominal voltage of 1.4 V. Supply voltage ranges from 3.1V to 6.0 VDC. 2. The current consumption of the	All acceptance criteria were met. The design requirements are fulfilled.

		<p>DUET2 Battery Pack and AU Ear Hook depends on the acoustic output of the AU Ear Hook. It ranges from 0.5 mA to 1.0 mA (typical values). The maximum current consumption should not exceed the current demand of OPUS2 by more than 1.5mA.</p> <p>3. Internally in the DUET2 Battery Pack electronic circuit, voltage is regulated to 1.2 V (± 0.1 V).</p>	
Trimmer function verification	To verify the functionality of the 4 trimmer controls to adjust acoustic parameters	Confirm 4 trimmer controls perform as defined.	All acceptance criteria as defined in the attachment of the TP were met. The design requirements are fulfilled.
Connector signals verification	Purpose of test was to verify the electric functionality of the AU Earhook connector, CPU Plug, audio input socket and the programming socket	Measured signal should have the same frequency as the input signal.	All acceptance criteria as defined in the attachment of the TP were met. The design requirements are fulfilled.
Physical Characteristics	To verify the dimensions, weight, power considerations	The weight of the DUET2 Battery Pack is 5.3 g (± 0.5 g) (without batteries). The weight of the AU Ear Hook is 1.3 g (± 0.2 g). The weight of the OPUS2 CPU is defined with max. 2.4g (SP15400). The total system	All acceptance criteria were met. The design requirements are fulfilled.

		(OPUS2 plus AU Ear Hook and DUET2 Battery Pack including batteries) adds up to 14 g (± 1 g). Surfaces that are exposed to view after assembly shall be clean and free of visible scratches and impairments when checked with the unaided eye in normal lighting. (IEC60118-0, IEC60118-0-2 + A1+A2)	
Environmental Requirement	To verify the mechanical and electric performance under environmental stress during daily use	<ul style="list-style-type: none"> •Temperature range for operation: 0°C to 50°C •Temperature range for storage: -20°C to 60°C •Relative humidity range: 10% to 93% (EN60068-2-1, 2-2, 2-30, 2-33, 2-47, 2-56, 2-67) 	All test samples worked within specifications. DUET 2 is robust against environmental influence.
Interference between DUET 2 and OPUS 2	To validate that the Interferences between DUET 2 and OPUS 2 components have no influence on the acoustic output of DUET 2, nor the electric output of the OPUS 2	No significant influence of the acoustic parameters (Freq. Response, Gain, Total Harmonic Distortion (THD) and Equivalent Input Noise) of the DUET 2. No influence on electric output of the OPUS 2.	All acceptance criteria as defined in the attachment of the TP were met.
Electrical safety	To demonstrate the compliance with the relevant standard	Criteria as specified in IEC60601-1:2005 ANSI/AAMI ES60601-1:2005	All applicable tests were performed and the product fulfils the requirements of IEC 60601-1:2005
EMC, ESD, EMI	To demonstrate compliance with the relevant standards	As specified in IEC60601-1-2:2007; EN301 489-3	All applicable tests were performed and

		V1.4.1: ISO 14708-7, Clause 24, 27	the product fulfils the relevant EMC requirements
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Biocompatibility

The DUET 2 uses the exact same body contacting materials as the OPUS 2 (approved in P000025/S029) audio processor. As validated and reviewed in P000025/S029, the DUET2 audio processor is biocompatible.

Packaging and shipping

The packaging of the DUET 2 audio processor is the same as the OPUS 2 (approved in P000025/S029) audio processor. All V&V activities as reviewed in P000025/S029 are valid for the DUET2 audio processor.

iv. SONNET EAS audio processor

The SONNET EAS and SONNET (approved in P000025/S078) audio processors were developed and validated together. Most of the V&V activities are valid for both audio processors, such as electric stimulation, EMC, ESD, EMI, biocompatibility and packaging etc. All V&V activities on the SONNET EAS audio processor have been reviewed accepted in P000025/S078. Table 4 summarizes the nonclinical testing conducted for the assemblies, components, and design requirements that are related to acoustic amplification of the SONNET EAS audio processor.

Table 4. Nonclinical laboratory tests for the SONNET EAS audio processor

Test	Purpose	Acceptance Criteria	Results
Verification of CPU (internal power supply, current consumption, audio input, telecoil input)	To verify that the CPU meets its specifications for functional behavior of internal supply voltage, current consumption, input selection, microphone frequency response and dynamic ranges, telecoil, external audio input	Frequency response and distortion (THD+N) of acoustic output as specified; OSPL 90 according to IEC 60118-0 + A1 as specified; No internal acoustic feedback at maximum gain; No internal magnetic feedback at maximum gain	All acceptance criteria were met. The CPU meets its specifications. The design requirement is fulfilled.
Functional verification of CPU (acoustic output)	To verify that the CPU meets its specifications for functional behavior of acoustic output	Functions of the CPU perform as intended, and operate within prescribed acoustic output levels	All acceptance criteria were met. The CPU meets its specifications. The design

	(device, OSPL90, internal acoustic feedback, internal magnetic feedback)		requirement is fulfilled.
Verification of front-end hearing aid functionality	To verify the hearing aid functionalities of the filterband, frequency range, compressor, compression threshold and ratio, gain, output limit, OSPL90, feedback cancellation etc.	Hearing aid functions as intended, and operate within prescribed characteristics including prescribed latency, filterbank parameters, compression parameters, expansion parameters, sound output levels, feedback cancellation parameters, etc.	All acceptance criteria were met. The design requirement is fulfilled.
Verification of front-end hearing aid firmware	To verify the front-end hearing aid firmware meets its requirement.	Functions of the firmware perform as intended, and operate within prescribed values	All acceptance criteria were met. The design requirement is fulfilled.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant conducted a clinical study to establish reasonable assurance of safety and effectiveness of the MED-EL EAS system in subjects 18 years and older in the US under IDE G040002. Data from this clinical study were the basis for the PMA approval decision. In addition, the applicant has conducted three earlier clinical studies outside of the US on the MED-EL EAS system which are briefly described below.

Outside US studies of MED-EL EAS System

Between 2003 ~ 2006, a study of the MED-EL EAS system (COMBI 40+ M electrode and TEMPO+ plus Oticon Adapto HA) was initiated by the applicant in Europe at five sites as a proof-of-concept evidence to support the EAS indication. Eighteen subjects were implanted and followed up to 12 months post-EAS fitting. Three of the eighteen subjects (16.8%) completely lost their hearing. Three of the eighteen subjects (16.6%) had some preserved hearing but not enough for acoustic amplification. The remaining twelve subjects (66.6%) had sufficient residual low frequency hearing to allow for acoustic amplification. Group mean word recognition scores reportedly improved. The devices used in this feasibility study have undergone significant development to result in the devices included in current supplement submission.

Between 2005 ~ 2010, the applicant initiated a multicenter prospective study in the European Union (Germany and Belgium) with the PULSAR FLEX₂₄ electrode and DUET EAS audio processor, with a follow-up period of 12 months post-EAS fitting. There were three study sites and eighteen subjects were enrolled and implanted with a limited insertion depth of 18 to 22 mm. Residual hearing reportedly was preserved to some extent in all eighteen subjects with no complete hearing loss. The group mean for the low-frequency threshold average across 250-1000 Hz worsened by 21.5 dB at 12 months post-implantation. Group mean word/sentence recognition scores both in quiet and noise and subjective questionnaire scores were reportedly improved from preoperative baseline to 12 months postoperative Electric-only condition and EAS condition.

Between 2010 ~ 2013, a multicenter prospective study was conducted in Japan with the PULSAR FLEX₂₄ electrode and the DUET 2 audio processor, with a follow-up period of 12 months. The Japanese study used the same electrode variant (FLEX₂₄) as the US IDE pivotal study and the upgraded external audio processor DUET 2, which is one of the processors included in current supplement submission. Twenty-four adults were enrolled and implanted with a full insertion depth of 24 mm. Residual hearing reportedly was preserved to allow the use of acoustic amplification in twenty-three out of twenty-four subjects at 12 months post-implantation. The group mean for the low-frequency threshold average across 250-1000 Hz worsened by 19.6 dB at 12 months post-implantation. The magnitude of the improvement in group mean speech perception scores from pre-operative baseline to 12 months post-implantation were reportedly similar to that observed in the European EAS study.

A. Study Design

The pivotal study for the MED-EL EAS system was conducted under IDE G040002 to evaluate the safety and effectiveness of the MED-EL EAS system in individuals 18 years of age and older who demonstrated significant residual low-frequency hearing and profound high-frequency (above 1500 Hz) sensorineural hearing loss.

The study was a prospective, multi-center, non-randomized, non-blinded, repeated-measures clinical study. Both objective and subjective performance data were collected. Each subject served as her or his own control so that postoperative performance was compared to each subject's baseline (preoperative) performance. Seventy-three subjects were implanted with a SONATA FLEX₂₄ or a PULSAR FLEX₂₄ across 14 investigational sites.

Investigational Sites

The following list identifies the 14 investigational sites (all US sites); the number of subjects enrolled at each site is identified in parentheses:

- Boys Town National Research Hospital, Nebraska (2)

- Duke University Medical Center, North Carolina (3)
- Hospital of University of Pennsylvania, Pennsylvania (6)
- Indiana University School of Medicine, Indiana (1)
- Medical College of Wisconsin, Wisconsin (5)
- New York Eye & Ear Infirmary Otolaryngology, New York (4)
- Oregon Health Sciences University, Oregon (3)
- Stanford University, California (3)
- Swedish Neurosciences Center for Hearing & Skull Based Surgery, Washington (1)
- University of Kansas Medical Center, Kansas (6)
- University of Miami, Florida (5)
- University of Michigan, Michigan (2)
- University of North Carolina, North Carolina (35)
- University of Texas SW Medical Center, Texas (3)

1. Clinical Inclusion and Exclusion Criteria

Enrollment in G040002 was limited to patients who met the following inclusion criteria:

- 18 years of age or older at the time of implantation
- Severe to profound sensorineural hearing loss for frequencies > 1500 Hz (i.e., threshold no better than 70dB HL at 2000-8000 Hz). Low-frequency thresholds up to and including 500 Hz should be no poorer than 65 dB HL in the ear to be implanted and the contralateral ear
- CNC word recognition score (mean of two lists) less than 60% inclusively in the ear to be implanted and the contralateral ear
- English spoken as a primary language

Patients were excluded from the study if they met any of the following exclusion criteria:

- Conductive, retrochchlear or central auditory disorders
- Hearing loss in the ear to be implanted that has demonstrated a recent fluctuation at two or more frequencies of 15 dB in either direction in the last 2 years
- Any physical, psychological, or emotional disorder that interferes with surgery or the ability to perform on test and rehabilitation procedures
- Developmental delays or organic brain dysfunction
- Unrealistic expectations on the part of the subject, regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure(s) and prosthetic devices
- Unwillingness or inability of the candidate to comply with all investigational requirements

2. Follow-up Schedule

This study involved up to eight visits before and after implantation, for about a one-year period. Candidacy testing included medical and audiological evaluations to determine study eligibility. A 30-day hearing aid trial was required for those prospective subjects who were not previous users of appropriately fit hearing aids prior to being accepted as a study candidate, which required one or two additional visits. After confirming eligibility, the subject underwent baseline testing. The device was subsequently implanted in one ear in accordance with the subject candidacy criteria. The device was activated following a healing period of 3 to 4 weeks.

The baseline and postoperative measurements are summarized in Table 5. All patients were scheduled to return for follow-up examinations at 3, 6, and 12 months postoperatively. Preoperatively, a baseline evaluation was conducted that included collection of both unaided and hearing-aided threshold measures, and also hearing-aided baseline measures for the primary/secondary effectiveness endpoints. Adverse events and complications were recorded at all visits.

Table 5. Schedule of study visits¹

	Baseline Evaluation	Initial CI Stimulation	Initial EAS Stimulation	3-month Post-operative	6-month Post-operative	12-month Post-operative
Informed Consent	X					
Medical and Hearing History	X					
Verification of Hearing Aid functioning	X			X	X	X
Unaided Hearing Thresholds and Tympanometry	X	X	X	X	X	X
Aided Audiometric Thresholds	X		X	X	X	X
Aided CNC test in quiet	X		X	X	X	X
Aided CUNY sentences-in-noise test	X		X	X	X	X
Adaptive SRT in noise	X		X	X	X	X
Questionnaires (APHAB, HDSS)	X			X	X	X
Psychophysical Ts and Cs and electrical impedance		X	X	X	X	X
Adverse event reporting	X	X	X	X	X	X

¹ Subjects continued to be monitored on a semi-annual basis after the 12-month interval until study closure (may conduct the same measurements as 12-month postoperative evaluation but not required by protocol).

3. Clinical Endpoints

Test Conditions

Three test conditions were proposed: preoperative Acoustic-only (acoustic stimulation to the ear to be implanted), postoperative Electric-only (electric stimulation to the ear to be implanted), and postoperative EAS (simultaneous electric and acoustic stimulation in the implanted ear via the MED-EL EAS system; Note: only one subject who lost residual hearing immediately following surgery early in the study was tested in a bimodal condition (electric stimulation only using the MED-EL EAS system minus the Acoustic Component with contralateral acoustic stimulation)).

Endpoints

Safety Endpoint: The primary safety endpoint was the number and proportion of individuals experiencing an adverse event, defined as any surgical and/or device-related event. The adverse events include anticipated and unanticipated adverse events. The list of anticipated adverse device effects identified by the applicant follows:

1. Sudden changes in residual low-frequency hearing.
2. Total loss of residual hearing.
3. Vertigo, dizziness, or balance problems that did not exist preoperatively or worsened postoperatively.
4. Facial nerve problems.
5. Meningitis.
6. Perilymphatic fistulae.
7. Tinnitus that did not exist preoperatively or worsened postoperatively.
8. Implant Migration/Extrusion.
9. Skin flap problems.
10. Device-related/programming problems.

The applicant did not propose formal statistical hypothesis testing for the safety endpoint but specified following success criteria for the safety endpoint: an observed rate of device related adverse events less than or equal to 8.5%; The two-sided 95% exact confidence bound was presented for the overall device-related adverse event rate, indicating an upper limit of 17.6%.

Primary Effectiveness Endpoint: The primary effectiveness endpoint was CUNY sentence-in-noise scores. The score was compared across two conditions: the Acoustic-only condition (baseline) and the 12-month post-activation EAS condition (ipsilateral Electric + ipsilateral Acoustic). Subjects were tested to determine the overall benefit received from the MED-EL EAS system compared to the preoperative Acoustic-only condition.

An improvement in CUNY sentence score ($CUNY_{\text{post EAS-pre A}}$) was defined as at least a 10 point absolute change in score from pre-operative to the 12-month interval. A t-test was used to evaluate the null hypothesis that the change from baseline is equal to 10.

$$H_0: \mu_{\Delta} = 10$$

$$H_1: \mu_{\Delta} \neq 10$$

A 95% two-sided confidence interval was calculated for the mean change from baseline.

Secondary Effectiveness Endpoints:

- The comparison of CUNY sentence in noise scores between the postoperative EAS condition and the postoperative Electric-only condition ($CUNY_{\text{post EAS} - \text{post E}}$) is used to determine the benefit of the MED-EL EAS system at 12 months. An improvement in CUNY sentence score was defined as a 10 point absolute change in the score. A t-test was used to evaluate the null hypothesis:

$$H_0: \mu_{\Delta} = 10$$

$$H_1: \mu_{\Delta} \neq 10$$

The 98.75% two-sided confidence intervals were calculated for the mean change from baseline.

- The comparison of CNC word scores between the postoperative Electric-only condition and the preoperative Acoustic-only condition ($CNC_{\text{post E-pre A}}$) is used to determine whether subjects would perform the same or better with the Electric-only condition compared to preoperative Acoustic-only condition. Similar performance was defined as the Electric-only condition being no worse than 10 points lower than the preoperative Acoustic-only condition. A t-test was used to evaluate the null hypothesis:

$$H_0: \mu_{\text{CI-AC}} \leq -10$$

$$H_1: \mu_{\text{CI-AC}} > -10$$

The 98.75% two-sided confidence intervals were calculated for the mean change from baseline.

Audiometric Test Methods & Effectiveness Measures

Audiometric Thresholds

Unaided audiometric thresholds were obtained for each ear, with insert earphones, using the standard audiometric technique for pure-tone testing. Aided audiometric thresholds were obtained for each ear in the sound-field using narrow band noise

and the standard audiometric technique with the speakers positioned at 0° azimuth relative to the subject's head. The contralateral ear was masked/plugged during aided testing.

Unaided testing for both ears included air conduction thresholds at 125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz, and bone conduction thresholds at 125, 250, 500, 750, 1000, 1500, 2000, and 4000 Hz. Aided thresholds were measured at the following frequencies: 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz.

The low-frequency hearing threshold was defined as the threshold averaged over the range 250 through 1000 Hz, inclusively, in the implanted ear.

For the purposes of adverse event reporting, any change in the low-frequency hearing threshold that resulted in a profound loss (Pure Tone Average (PTA) across 250-1000 Hz > 90 dB HL) and possibly also total loss (defined as no measurable hearing at the maximum output of the audiometer) in the implanted ear was considered by the applicant as an anticipated adverse event. All cases of profound/total loss of residual low-frequency hearing were included in the adverse event tabulations and analyses.

Effectiveness Measures

Consonant-Nucleus-Consonant (CNC) Word Recognition Test

The CNC Word Recognition Test (Peterson & Lehiste, 1962) is a psychometrically validated test of open set word recognition to determine speech intelligibility in listeners with hearing impairments. This test consists of 10 recorded lists of 50 monosyllabic words. At each test interval, two lists were administered in quiet at 60 dBA in the sound field and scored as percent correct for words and phonemes. Subjects were tested using a configuration where the target speech was presented via a loudspeaker at 0° azimuth.

City University of New York (CUNY) Sentence in Noise Test

The CUNY Sentence-in-Noise Test is a psychometrically validated test to assess CI recipients' ability to understand sentences in the presence of background noise. This test consisted of 50 lists of 12 sentences spoken by an Australian female speaker. At each test interval, four lists of the CUNY sentences were presented at 70 dB SPL with the competing speech weighted noise, to achieve a +10, +5, and 0 dB signal-to-noise, which was determined based on subject's performance in the Electric-only condition. Stimuli were presented from a single loudspeaker located at 0° azimuth.

B. Accountability of PMA Cohort

A total of 79 subjects were consented to be evaluated for participation in the study. Of these 79 subjects,

- 6 were potential candidates, but discontinued participation and did not proceed with implantation. Of these 6:
 - 3 could not secure insurance and withdrew
 - 2 elected to pursue other options (nonsurgical or traditional cochlear implantation). Of these 2:
 - 1 pursued traditional cochlear implantation
 - 1 pursued hearing aid amplification
 - 1 withdrew due to a lengthy insurance issue and subsequent change in hearing outside of candidacy
- The remaining 73 subjects were implanted with the MED-EL EAS system.

Of the 73 subjects who were enrolled and implanted (all implanted unilaterally), all subjects had their device activated and completed the EAS activation interval. At the 12-month interval, 67 subjects (92%) completed the audiometric testing for hearing sensitivity and all effectiveness outcome assessments. One subject was withdrawn at 6-month evaluation due to the electrode array migration out of the cochlea and re-implanted with a standard array. One subject was withdrawn before completing the 6-month evaluation due to health concerns unrelated to the device that resulted in an inability to follow the protocol. One subject withdrew prior to reaching the 12-month interval. Two subjects were lost-to-follow-up. The remaining one subject is still undergoing follow-up. Safety data, however, was collected and monitored throughout the study duration for all 73 implanted subjects.

C. Study Population Demographics and Baseline Parameters

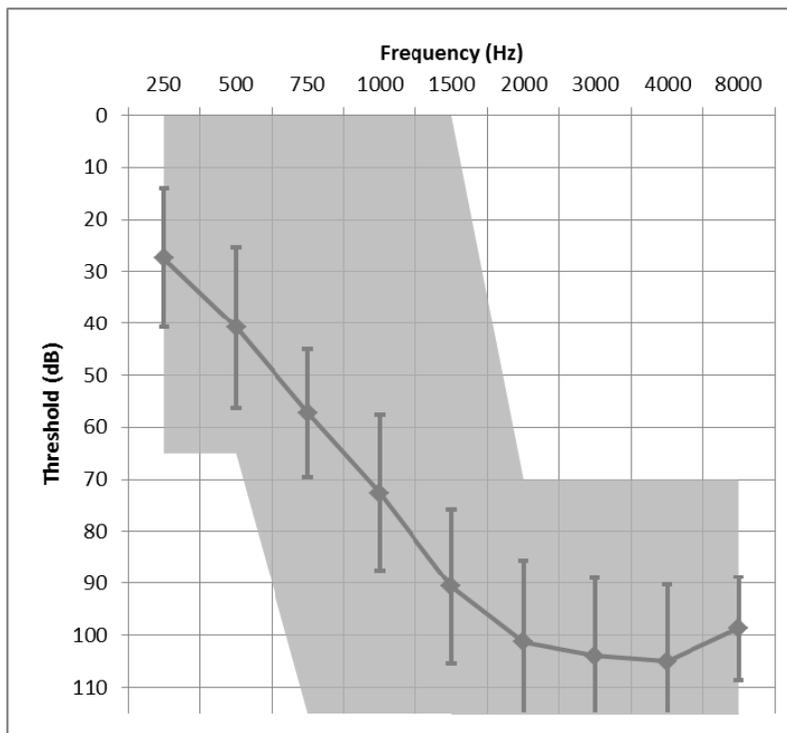
Of the 73 implanted subjects, 42 were female and 31 were male. At the time of implantation, subjects ranged in age from 17 to 76 years (including two subjects implanted under compassionate clearance). The duration of hearing loss ranged from 2 to 60 years. The duration of hearing aid use ranged from 1 – 48 years. Further information on subject demographics is summarized in Table 6 below.

Table 6. Descriptive statistics for subject variables*

Parameter/Category or Statistic	Total (n=73)
Gender	
Male	42.5% (31/73)
Female	57.5% (42/73)
Age (years)	53.7 (73) (17 – 76)
Duration of noticeable hearing loss (years)	
Left	25.7 (73) (2 – 60)
Right	25.7 (73) (2 – 60)
Duration of hearing aid use (years)	
Left	17.4 (73) (1 – 48)
Right	17.4 (72) (1 – 47)
*Numbers are % (Count/Sample Size) or Mean (N) (Min – Max)	

Figure 4 below shows the preoperative unaided air conduction mean thresholds along with ± 1 standard deviation bars in the ear to-be-implanted for all subjects. The shaded region represents the range of audiometric thresholds according to the subject candidacy criteria. Consistent with the study inclusion criteria, hearing thresholds ranged from within normal limits to moderately severe loss up to 500 Hz, sloping downward to severe or profound loss at higher frequencies.

Figure 4. Average pre-operative audiogram and audiometric fitting range (gray region)



D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on all 73 implanted patients. The key safety outcomes for this study are presented below in Table 7 through 9.

Adverse effects that occurred in the PMA clinical study:

Many of the 10 possible anticipated adverse events (defined earlier) were reported by the applicant to have occurred during the study. Adverse events were classified as anticipated/unanticipated, serious/non-serious, or device-related/unrelated. In summary, a total of 35 adverse events were reported (see Table 7 below) to be related to the device or procedure. No adverse events were reported as unanticipated.

Table 7. Number and percentage of adverse events observed for EAS subjects

Events Reported as Device- or Procedure-Related	No. of Events	No. of Subjects	% of Subjects	% Resolved
Type B or Type C tympanogram	8	6	8%	100%
Profound/Total loss of residual hearing ¹	8	8	11%	0%
Conductive hearing loss	5	5	7%	0%
Pain at site	3	3	4%	67%
Electrode lead breakage after excessive micro-movements, caused by patient massaging area ²	1	1	1%	100%
Electrode migration ²	1	1	1%	100%
Occasionally off- balance	1	1	1%	100%
Ulnar nerve palsy after operation	1	1	1%	100%
Telemetry showed high status on electrode channels	1	1	1%	0%

Events Reported as Device- or Procedure-Related	No. of Events	No. of Subjects	% of Subjects	% Resolved
Facial stimulation	1	1	1%	100%
Aural fullness	1	1	1%	100%
Sensation of device shifting when pushing over the implant site	1	1	1%	100%
Temporary shift in hearing threshold	1	1	1%	100%
Beeping/ringing in implanted ear	1	1	1%	0%
Bitter taste on right side of tongue	1	1	1%	100%
Total	35	29*	40%	57%

Notes: ¹Although the profound/total loss of residual hearing was specified in the applicant's protocol to be reported as an adverse event by applicant, smaller amounts of hearing loss are discussed below. ²Electrode lead breakage and electrode migration fall under device-related problems. *Some subjects experienced more than one device-related adverse event.

As listed in Table 7, the most frequently observed adverse events were profound/total loss of residual hearing occurred in 8 of the 73 subjects (11%) and conductive hearing loss occurred in 5 of the 73 subjects (7%), none of which were resolved. Type B or C tympanogram (8%) occurred eight times and was resolved in all cases.

In terms of the unresolved adverse events observed in this study, profound/total loss of residual low-frequency hearing was by far the most frequently observed adverse event, occurring in 8 of 73 (11%) of subjects. No subjects who had profound/total loss of hearing in the implanted ear were explanted or reimplanted with a standard electrode array due to dissatisfaction or poor performance with the MED-EL EAS system. Loss of residual hearing and device explants are discussed further below.

Loss of residual low-frequency hearing

The proportions of subjects stratified by the amount of low-frequency hearing loss at the 3-, 6- and 12-month intervals are summarized in Table 8. The same data,

stratified by postoperative residual low-frequency hearing sensitivity at the 3-, 6- and 12-month intervals, are summarized in Table 9.

Table 8. Proportion of subjects with various amounts of low-frequency hearing loss at 3, 6 and 12 months

Time Point	< 10 dB	10-20 dB	20-30 dB	> 30 dB
3 Month	10/71 (14.08%)	30/71 (42.25%)	18/71 (25.35%)	13/71 (18.31%)
6 Month	11/69 (15.94%)	23/69 (33.33%)	20/69 (28.99%)	15/69 (21.74%)
12 Month	8/67 (11.94%)	25/67 (37.31%)	20/67 (29.85%)	14/67 (20.90%)

Table 9. Proportion of subjects' low-frequency hearing sensitivity at 3, 6, and 12 months

Time Point	Normal	Mild	Moderate	Moderate-Severe	Severe	Profound
3 Month	0/71 (0%)	2/71 (2.82%)	7/71 (9.86%)	30/71 (42.25%)	28/71 (39.44%)	4/71 (5.63%)
6 Month	0/69 (0%)	2/69 (2.90%)	9/69 (13.04%)	26/69 (37.68%)	26/69 (37.68%)	6/69 (8.70%)
12 Month	0/67 (0%)	2/67 (2.99%)	5/67 (7.46%)	28/67 (41.79%)	24/67 (35.82%)	8/67 (11.94%)

As shown in the Table 9, there are eight subjects who had profound hearing loss in the implanted ear at the 12-month follow up visit. Two subjects experienced a total loss of residual hearing immediately after surgery and were unable to use the acoustic component of the audio processor. Six additional subjects experienced a profound loss of hearing within the 12-month follow-up period but were still able to use the acoustic unit based on at least one low-frequency threshold better than 80 dB HL. All eight of these adverse events at the 12-month follow-up visit are reported above in Table 7 as “profound/total loss of residual hearing”.

Device Explants

Two subjects have undergone device explantation. One subject was withdrawn from the study at the 6-month interval, when it was determined that the electrode array migrated out of the cochlea. This subject was subsequently implanted with a standard electrode array. The second subject experienced a device failure after excessive micro-movements caused the lead to break. The micro-movements occurred due to the subject massaging the area over the implant. This subject was

reimplanted with a FLEX₂₄ electrode and maintained residual hearing after the second surgery.

No subjects have been explanted/reimplanted due to loss of residual hearing in the implanted ear, sound quality issues, or poor performance.

2. Effectiveness Results

The analysis of effectiveness was based on the previously defined co-primary and secondary effectiveness endpoints at the 12-month time point.

Primary Effectiveness Endpoint

A statistically significant improvement in mean CUNY sentence in noise score ($CUNY_{\text{post EAS-pre A}}$) occurred from the baseline (preoperative Acoustic-only condition) to the 12-month follow-up interval (postoperative EAS condition). Hence, the primary effectiveness endpoint was met. These data are based on 66 of 67 (99%) subjects who were assessed at the baseline and the 12-month interval. One subject was not tested in the EAS condition due to loss of residual hearing immediately following surgery. When worst-case imputed scores for the missing subject were included in the sample, the primary endpoint was still met: the mean improvement with 95% confidence intervals was 42.4% (33.6%, 51.2%) for the CUNY sentences ($p = 0.000$). These analyses revealed that the result for the primary endpoint is robust to the missing data.

Secondary Effectiveness Endpoints

- For the comparison of CUNY sentence in noise scores between the postoperative EAS condition and the postoperative Electric-only condition ($CUNY_{\text{post EAS - post E}}$), a mean improvement with 95% confidence intervals was 18.4% (-19%, 77%) and was statistically significant ($p = 0.003$). This secondary effectiveness endpoint was met. This data is based on the 66 of 67 (99%) subjects who were able to be tested in both the EAS and Electric-only conditions at the 12-month interval.
- For the comparison of CNC word scores between the postoperative Electric-only condition and preoperative Acoustic-only condition ($CNC_{\text{post E-pre A}}$), a mean improvement with 95% confidence intervals was 17.9% (12.5%, 23.6%) and was statistically significant ($p = 0.000$). This secondary effectiveness endpoint was met. This data is based on the 67 of 67 (100%) subjects who were able to be tested in the preoperative Acoustic-only condition and the postoperative Electric-only condition and condition at the 12-month interval.

3. Subgroup Analyses

Effectiveness Data Stratified by Performance

Table 10 displays the proportion of subjects who performed poorer, similar, and better for the primary endpoint (CUNY_{post EAS- pre A}) and two secondary endpoint metrics (CUNY_{post EAS – post E} and CNC_{post E-pre A}) at the 12-month interval. Over 87% of the subjects exhibited similar or better performance on all three metrics. However, there were small proportions of subjects who performed poorer for CUNY_{post EAS- pre A} (7.8%), CUNY_{post EAS – post E} (13.4%), and CNC_{post E-pre A} (11.9%), respectively, at the 12-month interval.

Table 10. Proportion of subjects who performed poorer, similar, or better in the post-operative EAS or Electric-only condition versus the (ipsilateral) pre-operative Acoustic-only condition at 12 months

	Time Point	Better (SE)	Similar	Worse
CUNY _{post EAS- pre A}	12 Month	56/66 (84.85%)	5/66 (7.58%)	5/66 (7.58%)
CUNY _{post EAS – post E}	12 Month	47/67 (70.15%)	11/67 (16.42%)	9/67 (13.43%)
CNC _{post E-pre A}	12 Month	45/67 (67.16%)	14/67 (20.90%)	8/67 (11.94%)

Exploration of Effects of Baseline Characteristics on Device Effectiveness

Regression analyses were performed on CUNY and CNC scores as a function of the following baseline demographics: sex, age, duration of hearing impairment, pre-operative low-frequency hearing loss, and baseline speech score. Multivariate Analyses were completed for the above baseline characteristics as categorical (e.g., >/< mean) and continuous variables, when applicable. Results for CUNY and CNC improvement are presented below in Tables 11 and 12 (respectively) as a function of baseline demographics. Both sets of analyses show general improvement in all subgroups and yield no statistically significant differences in outcome.

Table 11. CUNY Results as a Function of Baseline Demographics

Variable	Coefficient (SE)	P-Value
Intercept	9.25 (22.50)	0.68
SEX (Female)	-7.39 (6.16)	0.23
AGE	0.07 (0.24)	0.79
HLDURL	-5.24 (11.51)	0.65

Variable	Coefficient (SE)	P-Value
HLDURR	5.39 (11.51)	0.64
Pre-Op Low Frequency Hearing Loss	0.21 (0.25)	0.42
Baseline Speech Scores	-0.12 (0.10)	0.24

Table 12. CNC Results as a Function of Baseline Demographics

Variable	Coefficient (SE)	P-Value
Intercept	72.11 (21.49)	0.00
SEX (Female)	3.41 (5.40)	0.53
AGE	0.04 (0.21)	0.83
HLDURL	0.18 (9.85)	0.99
HLDURR	-0.33 (9.85)	0.97
Pre-Op Low Freq Hearing Loss	-0.05 (0.24)	0.85
Baseline Speech Scores	-1.11 (0.20)	0.00

Exploration of Residual Hearing as a Function of Site

Outcomes related to postoperative residual hearing were investigated across sites to determine the amount of pre-to-post operative threshold shift. Results are presented below in Table 13. No statistically significant site effects were demonstrated.

Table 13. Pre-to-post Operative Thresholds Shift as a Function of Site

Source	DF	Type III SS	Mean Square	F Value	P-Value
SITENO	13	4496.524525	345.886502	1.46	0.1632

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 107 investigators of which none were full-time or part-time employees of the sponsor and 3 investigators 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.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The applicant included test results on the following additional tests in their PMA: the Abbreviated Profile of Hearing Aid Benefit (APHAB) and Hearing Device Satisfaction Scale (HDSS) questionnaires. The comparisons of the APHAB and HDSS questionnaire scores between the postoperative EAS and the preoperative Acoustic-only conditions were conducted to determine patients' subjective perception of the device benefit. Subjects were not instructed to ignore the contralateral ear and, therefore, the comparisons were between the preoperative, bilateral Acoustic condition and the postoperative, everyday listening condition (Electric + bilateral Acoustic). Results from these tests are briefly summarized below.

The Abbreviated Profile of Hearing Aid Benefit (APHAB) – The APHAB (Cox and Alexander, 1995), a self-report questionnaire that is used to qualify the impact of a hearing problem on an individual's daily life, was adopted to assess subjects' perception of hearing disability. The APHAB consists of multiple domains of hearing: hearing in the presence of background noise, hearing in reverberant surroundings, ease of communication, and aversion to sounds. The global score quantifies, across all domains, the frequency of problems before and after the implantation of the MED-EI EAS system. Lower scores correspond to lower disability. A mean reduction of APHAB global score with 95% confidence intervals was 30.2% (-69%, 41%) and was statistically significant ($p < 0.001$). This data is based on the 59 of 67 (88%) subjects who were able to be tested at the baseline and the 12-month interval. The data indicates significant improvement in

subjects' perception of hearing disability from preoperative baseline to 12 months after implantation.

The Hearing Device Satisfaction Scale (HDSS) – The HDSS is a self-assessment questionnaire that assesses subjects' satisfaction with various aspects of the amplification system. Subjects rated their satisfaction level with their hearing aids at the baseline and with their contralateral hearing aid + MED-EL EAS system at the 12-month interval as: “Very Satisfied”, “Satisfied”, “Neutral”, “Dissatisfied”, “Very Dissatisfied”, or “Does Not Apply” in a variety of listening environments. There are 21 sub-categories in total e.g. overall fit/comfort, sound quality of my own voice, effectiveness in background noise, handling/manipulation etc. Increase of satisfaction was defined as improvement in a rating scale for at least one category. The proportion of subjects experiencing no change, decreasing, or increasing satisfaction is displayed below in Table 14. Of all subjects completing the HDSS, 86% indicated an increase in satisfaction at the 12 months follow-up interval. This data is based on the 59 of 67 (88%) subjects who were able to be tested at the baseline and the 12-month interval.

Table 14. Hearing Device Satisfaction Scale (HDSS)

Visit	No Change	Decrease	Increase
12 Months	7/59 (11.86%)	1/59 (1.69%)	51/59 (86.44%)

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ear, Nose, and Throat Devices Panel, 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

One primary and two secondary effectiveness endpoints were defined. For all endpoints, performance at 12 months post implantation was compared to pre-operative baseline. Performance was measured using the MED-EL EAS system (at 12 months) and compared to the preoperative, hearing aided performance in the ear-to-be-implanted (at preoperative baseline). The primary effectiveness endpoint was defined as a mean improvement in CUNY sentence-in-noise scores ($CUNY_{\text{post EAS-pre A}}$). Two secondary effectiveness endpoints were defined as 1) a comparison of CUNY sentence-in-noise scores between the postoperative EAS condition and the postoperative E Alone condition ($CUNY_{\text{post EAS-post E}}$); and 2) a comparison of CNC word scores between the postoperative Electric-only condition and the preoperative Acoustic-only condition ($CNC_{\text{post E-pre A}}$).

Primary Endpoint Results: The mean improvement in CUNY sentences ($CUNY_{post\ EAS-pre\ A}$) was 42.4% with 95% confidence intervals of (33.6%, 51.2%). The improvement was statistically significant ($p = 0.000$), and it was thus concluded that the primary endpoint was met.

Secondary Endpoint Results: The mean improvement in CUNY sentences ($CUNY_{post\ E-pre\ A}$) was 18.4% with 95% confidence intervals of (-19%, 77%). The mean improvement in CNC words ($CNC_{post\ E-pre\ A}$) was 17.9% with 95% confidence intervals of (12.5%, 23.6%). Both secondary endpoints were met.

Overall, the data supports that the MED-EL EAS system provides significant benefit compared to the preoperative Acoustic-only condition, and that electric stimulation alone also provides benefit over the preoperative Acoustic-only condition. Because the majority of subjects (66 out of 67) were tested in the ipsilateral EAS condition, it is expected that subjects would be able to achieve even greater EAS benefit when combining electric hearing and bilateral acoustic hearing together, i.e., the bilateral EAS condition in which patients would typically experience with their CI and HA(s) in daily life.

Other effectiveness measures and analyses

Analysis by study site: The consistency of the postoperative residual hearing was examined across 14 investigational sites by testing for an effect of site in an ANOVA model, based on 67 subjects who completed the 12-month interval evaluation. The results indicated no evidence of site effects on the primary effectiveness endpoints.

Other Effectiveness Measures:

The APHAB Questionnaire: The results from 59 subjects showed a mean 30.2% reduction in the APHAB global score with 95% confidence intervals of (-69%, 41%) indicating significant improvement in subjects' perception of hearing disability from preoperative baseline to 12 months after implantation.

The HDSS Questionnaire: The results from 59 subjects showed that 86% subjects indicated an increase in satisfaction with their MED-EL EAS system at the 12 months follow-up interval compared to that with their preoperative amplification at the preoperative baseline.

B. Safety Conclusions

The risks of the device are based on the data collected in the clinical study conducted to support PMA approval as described above.

The primary safety objective was to report all surgical and/or device-related events, as the number and proportion of individuals experiencing an adverse event.

- Profound/total loss of residual low-frequency hearing and conductive hearing loss were the most frequently observed anticipated unresolved adverse event. Total loss of residual hearing was observed in 8 of 73

subjects (11%). Conductive hearing loss was observed in 6 of 73 subjects (8%).

- Type B or C tympanogram and pain at site were the most frequently observed resolved adverse events and occurring at a rate of 8 and 4%, respectively, in the 73 enrolled and implanted subjects.
- Explantation and reimplantation with a standard/FLEX₂₄ electrode array occurred in 2/73 (3%) of subjects due to electrode lead breakage and electrode migration.

The adverse event rate (40%) exceeded the safety endpoint (8.5%) pre-specified in the IDE study protocol (G040002). However, observed adverse events that were resolved were consistent with those seen with approved cochlear implant systems. Profound/total loss of hearing is the most frequently observed anticipated unresolved adverse event. No subjects who lost the residual hearing in the implanted ear were explanted or reimplanted with a standard electrode array due to dissatisfaction or poor performance with the MED-EL EAS system. Therefore, the adverse event rate observed in the pivotal study is acceptable. It is yet to be determined over the long-term how many additional subjects will experience total loss of residual hearing. The post approval study specified in the approval order is designed to assess the time course of residual hearing loss. Based on the results of this post approval study, the labeling for the MED-EL EAS system will be updated accordingly.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The clinical study results for the MED-EL EAS system demonstrated a statistically and clinically significant benefit (average 42% improvement) from use of the device (EAS condition) at the study endpoint interval (12-month) in speech-in-noise recognition over the preoperative HA performance using the CUNY sentence in noise for speech recognition. 85% of the subjects exhibited better performance on speech recognition at the 12-month interval compared to the preoperative baseline (e.g., CUNY_{post EAS- pre A}). Therefore, the MED-EL EAS system is expected to improve speech recognition in terms of CUNY sentences and CNC words for a majority of the indicated population.

The safety data from this clinical study suggests that the patients tolerated the risks well, especially since most adverse events were device/procedure related to cochlear implantation surgery and were resolved postoperatively. The profound and possibly also total loss of low-frequency hearing that occurred in 8/73 (11%) of subjects at the 12-month follow-up visit is the most frequent, unresolved risk. Among the eight subjects, two subjects experienced total loss and only used the electrical unit of the MED-EL EAS system; six subjects experienced a profound loss of hearing but were still able to use the acoustic unit based on at least one low-frequency threshold better than 80 dB HL. No subjects who had profound/total loss of the residual hearing in the implanted ear were explanted or reimplanted with a standard electrode array due

to dissatisfaction or poor performance with the MED-EL EAS system. Therefore, even for those who experienced permanent residual hearing loss, they still generally obtained greater benefit than the alternative treatments (i.e., hearing aids), suggesting that the risks were tolerable relative to the benefits. The long-term rate of profound/total loss of residual hearing is being studied in a post-approval follow-up study.

Additional factors to be considered in determining probable risks and benefits for the MED-EL EAS system included patient's perspectives on the device benefit.

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 APHAB and HDSS 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 APHAB and HDSS questionnaires (e.g., 30.2% improvement score on APHAB) indicated that patients were able to experience the EAS benefit in their daily lives from the MED-EL EAS 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 support a reasonable assurance of safety and effectiveness of this device when used in accordance with the proposed indications for use. The preclinical testing provided for the device was acceptable. Based on the clinical study results, it is reasonable to expect clinical benefits with use of the MED-EL EAS system in terms of improvement in speech understanding in quiet and noise since the average performance of the study population showed statistically significant improvements in one primary and two secondary endpoint measures. The risks associated with the device, including residual low-frequency hearing loss and conductive hearing loss should therefore be carefully considered by potential candidates and their hearing health-care providers. However, FDA believes that the available data demonstrate that the benefits outweigh these risks in the pivotal study patient population, particularly since the device provided speech-understanding benefit for most subjects, including those individuals who lost residual hearing to the profound levels.

XIV. CDRH DECISION

CDRH issued an approval order on September 15, 2016. The final conditions of approval cited in the approval order are described below.

MED-EL EAS Extended Follow-up Study: This study is an extended follow-up of the subjects who were enrolled in the pivotal study to assess long-term safety and device performance. The study will be conducted as a prospective, non-controlled, non-randomized, multicenter study at the 14 sites. All 68 available subjects who were enrolled in the pivotal study will be invited to participate in the extended follow-up. Study subjects will be followed for a minimum of 5 years post-implantation of the device. 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 secondary safety endpoint includes measures of residual hearing at a minimum of 5 years post-implantation, which will provide an estimation of the proportion of subjects with residual hearing loss at 5 years post-implantation. The effectiveness endpoints will include the within-subject differences for the two speech recognition tests, i.e., word recognition in quiet as evaluated with the Consonant-Nucleus-Consonant (CNC) test, and sentence recognition in noise as evaluated with the CUNY test. The stability of perceived hearing benefits over time will be assessed by employing the APHAB questionnaire. Subjects will be followed on an annual basis until reaching 60 months post-activation; for those who are already outside the 60-month window, one additional visit will be required. Every explanted device will be tested to determine the reason for device failure, and device explantations will be reported as serious adverse events.

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

Cox, R.M. and Alexander, G.C. (1995). The abbreviated profile of hearing aid benefit. *Ear & Hearing*, 16:176-186.

Peterson, F. and Lehiste, I. (1962). Revised CNC lists for auditory tests. *Journal of Speech and Hearing Disorders*, 27(1):62-70.