MED EL

Protocol: Electric Acoustic Stimulation Extended Follow-up Post Approval Study-P000025/PAS001

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Electric-Acoustic Stimulation Extended Follow-up

Post-Approval Study

PAS: P000025/S092

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1. Abbreviations

AE	Adverse Event
APHAB	Abbreviated Profile of Hearing Aid Benefit
CFR	Code of Federal Regulations
CNC	Consonant-Nucleus-Consonant
CRF	Case Report Form
EAS	Electric-Acoustic Stimulation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HL	Hearing Level
IDE	Investigational Device Exemption
IRB	Investigational Review Board
PI	Principal Investigator
PTA	Pure-tone Average
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNR	Signal-to-Noise Ratio
SOP	Standard Operating Procedure
SPL	Sound Pressure Level
UP	Unanticipated Problem

2. Statement of Compliance

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 58, 21 CFR Part 812)
- ICH E6

All investigators involved in the conduct of this study will be informed about their obligations in meeting the above commitments.

3. Background

The MED-EL Electric-Acoustic Stimulation (EAS) Cochlear Implant System was studied extensively under a clinical trial (IDE G040002), which concluded in 2016. Data on 73 subjects enrolled in the clinical trial was submitted for PMA approval, which was issued by FDA on September 15, 2016. As part of the PMA approval, MED-EL agreed to conduct a post-approval study involving

extended follow-up (five years) of the 73 existing clinical trial subjects to monitor safety and effectiveness.

a. Device Description

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. EAS is intended to provide electric 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 combination of acoustic (hearing aid) and electrical stimulation to the same ear is made possible through the external audio processor (either SONNET EAS, DUET 2 or DUET) working in conjunction with the internal cochlear implant with a +FLEX24 electrode variant, which together make up the MED-EL EAS System.

b. Indications for Use

All subjects enrolled in this study will have met the candidacy criteria for the clinical trial (G040002); therefore, the following indications for use of the MED-EL EAS System is for informational purposes only.

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.

EAS is contraindicated for individuals who have the following conditions:

- Deafness due to lesions of the acoustic nerve or central auditory pathway
- Active external or middle ear infections, with or without tympanic membrane perforation
- Absence of cochlear development
- Intolerance of the material used in the implant (medical grade silicone, platinum, platinum iridium and titanium)
- Inability to use amplification and or have cochlear malformations with a history of fluctuating hearing loss (or presenting with an etiology associated with fluctuating hearing loss).

c. Risk-Benefit Statement

As these subjects previously participated in the EAS clinical trial, the risks associated with continuing in the extended follow-up study are low. As demonstrated in the clinical trial, 97% of subjects benefitted from use of EAS, when comparing subjective questionnaires and/or speech tests at 12 months post-operative to pre-operative results. A known risk of implantation for EAS subjects is the loss of residual hearing. Subjects enrolling in the extended follow-up study may experience loss of residual hearing five years or more post-implantation. Any loss of hearing occurring multiple years after surgery will be reported as an adverse event in the interim reports. However, subjects will not be incurring any additional risk by participating in the extended follow-up study. The risks inherent to implantation (i.e., loss of residual hearing) have already been realized and do not apply to the extended follow-up study.

4. Purpose of the Study

The purpose of this post-approval study is to evaluate the long-term safety and effectiveness of the MED-EL EAS System. Up to 68 subjects from the US clinical trial will be followed to 60 months post-implantation.

5. Study Design & Objectives

a. Study Design

This study will be conducted as a prospective, non-controlled, non-randomized, multicenter study. Subjects will be followed on an annual basis until reaching the 60 month post-implantation interval. For subjects who are already outside the 60-month window, one additional visit will be required.

b. Study Population

Up to 68 subjects from the original EAS clinical trial (G040002) will be invited to participate. As some subjects from the original clinical trial will be lost to follow-up, the actual number of subjects included in the post-approval study will be less than 68. The defined minimum sample size is 80% (i.e. ≥55) of the US clinical trial subjects.

Subjects will have met the following inclusion criteria as part of the original clinical trial:

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

Patients were excluded from the original clinical trial if any of the following criteria were met:

- Conductive, retrocochlear, or central auditory disorder
- 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
- Unwillingness or inability of the candidate to comply with all investigational requirements

c. Study Objectives

Long-term effectiveness of EAS will be assessed by speech perception testing completed through five years post-implantation. Individual performance will be measured by CNC words and CUNY sentences in noise at the five-year post-operative visit compared to pre-operatively and the 12-month post-activation interval. Subjects who are already outside the five-year post-implantation window will be tested one additional time.

Long-term safety will be assessed by monitoring the type and frequency of reported adverse events. Adverse events will be reported by the number and proportion of subjects experiencing device-related adverse events. Hearing sensitivity will also be measured by calculating the low-frequency pure-tone average and shift in low-frequency residual hearing.

d. Sample Size Calculation

The sample size requirements are based on the desire for adequate power for the primary effectiveness endpoint. The hypothesis test is a paired one-sample non-inferiority test of the mean CNC word score. The test will be performed at the one-sided 0.05 alpha level based on a 10% non-inferiority margin. The planned minimum sample size of 55 subjects would yield 90% power for this endpoint, based on an assumed difference of zero and a standard deviation of 25. A higher degree of power would be maintained for a smaller standard deviation.

6. Study Endpoints

a. Primary Effectiveness Endpoint

The primary effectiveness endpoint will be CUNY sentence test score in noise at five years (60 months) post-implantation compared to the 12-month follow-up interval. Subjects will be tested as the same signal-to-noise ratio as they were at the 12-month interval. One condition will be tested – either EAS or CI Alone, depending on the subject's residual hearing. Scores will be compared to the same condition at the 12-

month follow-up interval. Scores at the five year follow-up interval will be stable or better than the 12-month follow-up interval. Stability is defined as ±10 percentage points, while a better score would be greater than 10 percentage points improved from the 12-month score.

The statistical hypothesis test is as follows:

Ho: $\mu_\Delta \leq -10\%$
Ha: $\mu_\Delta > -10\%$

Where $\mu_\Delta$represents the mean difference in CUNY word score in noise at five years post-implantation compared to the 12 month follow-up interval. Rejection of the null hypothesis will indicate non-inferior performance at five years relative to 12 months for CUNY word score in noise.

The non-inferiority margin of 10% helps maintain power for the planned sample size and would produce clinically acceptable results in that the five year results would need to be sufficiently similar to the 12 month results to achieve success for this hypothesis test.

Conditional on successful non-inferiority of the secondaryprimary endpoint, a superiority test for the endpoint will be performed. Since this is a closed testing procedure, there is no type I error inflation.

b. Secondary Effectiveness Endpoint

The secondary effectiveness endpoint will be CNC word score in quiet at five years (60 months) post-implantation compared to the 12-month follow-up interval. One condition will be tested – either EAS or CI Alone, depending on the subject's residual hearing. Scores will be compared to the same condition at the 12-month follow-up interval. Scores at the 5 year follow-up interval will be stable or better than the 12-month follow-up interval. Stability is defined as ±10 percentage points, while a better score would be greater than 10 percentage points improved from the 12-month score.

The statistical hypothesis test is as follows:

Ho: $\mu_\Delta \leq -10\%$
Ha: $\mu_\Delta > -10\%$

Where $\mu_\Delta$represents the mean difference in CNC word score in quiet at five years post-implantation compared to the 12 month follow-up interval. Rejection of the null hypothesis will indicate non-inferior performance at five years relative to 12 months for CNC word score in quiet.

The non-inferiority margin of 10% helps maintain power for the planned sample size and would produce clinically acceptable results in that the five year results would need to be sufficiently similar to the 12 month results to achieve success for this hypothesis test.

Conditional on successful non-inferiority of the primarysecondary endpoint, a superiority test for the endpoint will be performed. Since this is a closed testing procedure, there is no type I error inflation.

c. Secondary Effectiveness Endpoint

An additional secondary endpoint will be global score on the APHAB questionnaire, completed based responses in the everyday listening condition at five years (60 months) post-operatively. Scores will be compared to the 12-month follow-up interval. Stability will be noted as ±10 percentage points.

The statistical hypothesis test is as follows:

Ho: $\mu_\Delta \geq 10\%$
Ha: $\mu_\Delta < 10\%$

Where $\mu_\Delta$represents the mean difference in global APHAB score at five years post-implantation compared to the 12 month follow-up interval. Rejection of the null hypothesis will indicate non-inferior performance at five years relative to 12 months for global APHAB score.

The non-inferiority margin of 10% helps maintain power for the planned sample size and would produce clinically acceptable results in that the five year results would need to be sufficiently similar to the 12 month results to achieve success for this hypothesis test.

d. Primary Safety Endpoint

Adverse events will be collected and reported throughout the duration of the post-approval study. The primary safety endpoint will be the number and proportion of subjects experiencing device-related adverse events.

Expected adverse events include those listed in the original clinical trial protocol, in particular:

- Profound or total loss of residual hearing
- Infection or inflammation
- Vertigo, dizziness, or balance problems
- Tinnitus
- Implant migration/extrusion
- Skin flap problems
- Device-related or programming problems
- Uncomfortable sounds during stimulation
- Temporary pain or numbness
- Device failure leading to explantation

Should an explantation occur, the explanted device will be analyzed and adverse events will be reported to FDA as serious.

There is no planned formal statistical hypothesis test for the primary safety endpoint. Numbers of adverse events and percentages of subjects with adverse events will be reported.

e. Secondary Safety Endpoint

Residual hearing at five years (60 months) post-operatively will be analyzed and reported. Results will be summarized and presented as the amount of low-frequency pure-tone average (125, 250, 500, 750 and 1000 Hz) shift, the degree of residual hearing, and as a function of the HEARRING scale.[1] Hearing sensitivity will be determined through pure-tone audiologic threshold testing. Testing will include air conduction and bone conduction testing at frequencies from 125 – 8000 Hz.

7. Data Analysis

a. Effectiveness Analysis

The difference in CUNY score from the 12-month follow-up interval to the five-year follow-up interval, the difference in CNC score from the 12-month follow-up interval to the five-year follow-up interval, and the difference in APHAB score from the 12-month follow-up interval to the five-year follow-up interval will each be analyzed by a one sample paired t-test for a mean based on a non-inferiority framework.

Additional analyses may be performed to provide further descriptive information on endpoints (e.g. endpoints at 2 years, 3 years, etc. and subscales of AHAPB, stratified analyses for APHAB, etc.). These will include as appropriate means and standard deviations, and counts and percentages.

b. Safety Analysis

Adverse events will be reported as the number and proportion of subjects experiencing device-related adverse events. Device-related adverse events will be those where cause of the event cannot be ruled out as being related to the cochlear implant system. The type and frequency of adverse events will also be reported.

8. Study Procedures & Schedule

Subjects will be followed on an annual basis for five years (60 months) post-implantation. Subjects who have not reached five-years (60-months) post-implantation will return once per year for testing (i.e., 3-years post-operative and 4-years post-operative). Many subjects from the

[1] Skarszynski, H; Heyning, P; Agrawal, S; Arauz, S. Towards a consensus on a hearing preservation classification system. Acta Oto-Laryngologica, 133(564), 2013, p. 3-13.

original clinical trial have already been implanted for more than five years. Subjects with greater than five years of implantation will return to the investigative site for one additional follow-up visit, which will be reported as their study endpoint. The 12-month follow-up interval from the original IDE clinical trial will be used for the comparison for all data collected during the post-approval study.

a. Enrollment

Subjects will be enrolled in the post-approval study based on participation in the original clinical trial. An informed consent form will be signed by each participant prior to enrolling him or her into the post-approval study.

b. Study Procedures

At each annual follow-up (or at the subject's final follow-up for those outside of five years of implantation) unaided and aided testing will be completed. The same testing will be completed regardless of the interval for which the subject is being seen. Prior to completing aided speech testing, the external device should be checked. Unaided threshold testing will be used to determine whether the subject will be tested in the EAS or CI Alone condition. At each interval the following data will be collected:

- Unaided audiologic threshold testing , insert earphones
  - Pure-tone air conduction thresholds, 125 – 8000 Hz
  - Pure-tone bone conduction thresholds, 500 – 4000 Hz
- Aided (EAS or CI Alone) speech testing in quiet, soundfield
  - CNC Words in quiet at 70 dB SPL
  - One list of 50 words will be presented
  - Lists will be randomized
- Aided (EAS or CI Alone) speech testing in noise, soundfield
  - CUNY Sentences in noise at 70 dB SPL
  - SNR will reflect the subject's previously tested SNR at 12 months
  - Speech and noise will be presented at 0° azimuth
  - Four lists of 12 sentences each will be presented
  - Lists will be randomized
- Subjective Questionnaire
  - APHAB

Aided testing in the soundfield should be completed with the non-implanted ear plugged or masked, as applicable.

c. Summary of Study Procedures

		Time of Enrollment	Annual Follow-up	Final Follow-up
	Informed Consent	X		
	Unaided thresholds		X	X
Aided Speech Testing (70 dB SPL)	CNC Words One list of 50 words		X	X
	CUNY Sentences Four lists of 12 sentences SNR 0/+5/+10 dB		X	X
	APHAB		X	X

d. Adverse Events

All adverse events require the completion of the Adverse Event Case Report Form. Adverse events will be classified as anticipated or unanticipated. For the purposes of this study, all adverse events other than the risks delineated in the original clinical trial protocol (see below) will be considered unanticipated.

- Dizziness
- Increased vertigo
- Delay of scar healing
- Taste impairment
- Temporary pain or numbness
- Increased tinnitus
- Facial nerve stimulation
- Uncomfortable sounds during stimulation
- Meningitis
- Loss of residual hearing
- Device failure or explantation

Adverse events will also be categorized as serious/non-serious and according to relatedness to the study device or procedures. Any unanticipated, serious, device-related adverse event should be reported to MED-EL and the investigator's IRB no later than 10 days after the investigator becomes aware of the event. MED-EL will evaluate

and report all unanticipated, serious, device-related adverse events to FDA within 10 working days after receiving notification of the event.

Anticipated adverse events will be reported to MED-EL in a timely manner. Adverse events will be reported to FDA and the reviewing IRBs in interim reports. Device failures or explantations will be reported as anticipated, serious, device-related adverse events.

e. Study Completion

Each subject's participation in the post-approval study will be considered complete when they have reach five years post-implantation or when they have completed one additional study visit (for those implanted for more than five years at the time of enrollment).

Subjects may withdraw from the post-approval study at any time. The reason for withdrawal will be reported to FDA. In case of a subject that becomes lost to follow-up, the investigator will document the attempts to follow-up with the subject prior to reporting the subject as withdrawn.

9. Data Collection

a. Institutional Review Board

The protocol, informed consent form, and any participant materials will be submitted to the IRB for review and approval. IRB approval of both the protocol and informed consent must be obtained prior to beginning enrollment. Any amendment to the study protocol must also receive IRB approval before those changes are implemented in the study. Changes to the consent form will also be submitted to the IRB; at that time a determination as to whether or not previously consented subjects need to be re-consented will be made.

b. Informed Consent

Subjects will be required to sign an informed consent prior to initiating any study-related activity. Potential participants must be informed as to the purpose of the study and the potential risks and benefits known, or that can be reasonably predicted or expected. These risks are described in the written consent form.

Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and will answer any questions that may arise. All participants will receive a verbal explanation of the purpose, study procedures, and potential risks of the study and their rights as research participants.

The participant will sign the informed consent prior to being enrolled in the study. The investigator administering the informed consent will sign and date the form to indicate

the document was sufficiently explained to the subject and their signature was witnessed. Consent may be withdrawn at any time during participation in the study. A copy of the signed informed consent will be provided to the subject, while the original will be retained by the investigator in the study file.

c. Data Collection Forms

The investigator will be responsible for maintaining complete and accurate documentation of study procedures and medical records, including informed consent forms, for the duration of the study. Correspondence with the IRB, clinical monitor, and MED-EL in general should also be maintained. Data on subjects will be collected in an anonymous manner, and any records sent to MED-EL should be de-identified.

The investigator is responsible for ensuring completeness, legibility, and accuracy of the data reported. Source documentation should be completed in a neat, legible manner to ensure accurate interpretation of the data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, write over, or use correction fluid or tape on the original document.

d. Monitoring

Appropriately trained clinical monitors will have access to all study documents for monitoring, as required. Case report forms provided to MED-EL will be monitored for completeness and accuracy. Adverse events will be reviewed by the clinical monitor to continuously assess the primary safety endpoint.

e. Quality Assurance and Control

MED-EL will implement all necessary procedures to ensure the integrity of case report forms. Standard Operating Procedures (SOPs) will be utilized to ensure accuracy of the data. When case report forms are received, the forms will be reviewed for completeness and to identify any inconsistencies or errors.

Investigators will be trained to make corrections only by approved methods (i.e., a single line through the incorrect entry, correction, initialed, and dated). Any discrepancies found in the case report forms by the clinical monitor should be brought to the attention of the investigator.

For the data management process, data will be entered into a database using accepted data entry techniques. A sample of the database will be compared to the case report forms during internal audits to ensure accuracy of the database. More comprehensive evaluation of the database will be performed as required.

10. Reporting Requirements

MED-EL will complete and submit semi-annual interim reports beginning six months from approval of the protocol for the first two years of the study. At that time point, reports will be

submitted annually until the final report is completed and submitted. Interim reports will contain information including study enrollment by site, data collected, and adverse events.

11. Study Milestones

The study will be initiated immediately after receiving FDA approval. Fourteen sites (previously involved in the clinical trial) will be contacted at that time to begin the IRB submission process. Subjects will be enrolled over the first year of the study, with heaviest enrollment coming immediately following IRB approval at each site.

It is anticipated that 57 of the potential subjects will require only one visit to reach the study endpoint. Additionally, 10 of the potential subjects will require two visits to reach the study endpoint, while one potential subject will require three visits to reach the endpoint. Based on this, we expect that the study will be completed within three years of enrollment of the first subject.

12. References

Skarszynski, H; Heyning, P; Agrawal, S; Arauz, S. Towards a consensus on a hearing preservation classification system. Acta Oto-Laryngologica, 133(564), 2013, p. 3-13.