A Safety Study of the Auditory Brainstem Implant for Pediatric Profoundly Deaf Patients
NCT02102256
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Feasibility/Safety Trial

The investigation will be carried out at two institutions—the University of Southern California (USC) and Children's Hospital of Los Angeles (CHLA). In addition two of the team members (Wilkinson and Schwartz) are from the House Clinic/Huntington Research Institutes. Dr. Eric Wilkinson, Co-Principal Investigator, is an experienced neurotologist skilled in evaluating pediatric patients for CIs, and in conducting a wide variety of neurotological surgical procedures. Dr. Wilkinson has attended two pediatric ABI surgical training courses, directed by Professor Vittorio Colletti in Italy. Dr. Laurie Eisenberg, Co-Principal Investigator, USC, is an experienced clinical scientist and pediatric audiologist, and will oversee the subjects' audiological care and direct the early efficacy study. Surgical implantation will be performed by Dr. Willkinson,in collaboration with: Dr. Marc Schwartz, neurosurgeon, who has extensive adult implantation ABI experience; and Dr. Mark Krieger, neurosurgeon and Chief of Staff at CHLA, who has extensive pediatric craniotomy and posterior fossa pediatric neurosurgical experience. The surgeries will take place at CHLA, with medical examinations at CHLA. The initial stimulation of the device will occur at CHLA, and subsequent audiological care and evaluations at the USC Caruso Center for Childhood Communication. In addition to the primary team, Dennis Maceri, M.D. has agreed to serve as Medical Safety Officer, who has a clinical appointment at the USC Keck School of Medicine (Department of Otolaryngology, Head and Neck Surgery, and Pediatrics). Dr. Maceri has no formal connections to the ABI team. A Data Safety Monitoring Board (DSMB) will be formed after the study commences and will consist of a neurotologist, audiologist, and statistician with clinical trial experience.

Subjects

This Phase I feasibility study will evaluate surgery- and device-related safety in a small number of pediatric (n=10, aged 2 to 6 years) non-NF2 subjects, who are either not currently benefitting from a CI or who have radiological evidence of cochlear nerve deficiency, cochlear aplasia, or post-meningitis complete cochlear ossification. Currently, a CI is the device of choice if there is a cochlea into which a CI can be placed. To be included in this study, there must be evidence the CI has not provided auditory benefit (thresholds below the level of conversational speech and absence of pattern perception). Because the ABI will not be implanted before the child is 2-years-old, a child who receives a CI at age 1 year and who is tracked for 6-12 months, will be evaluated to determine CI benefit. This time frame still enables the child with a CI to take advantage of a sensitive period for auditory and linguistic development with an ABI. Enrolled subjects must have all screening evaluations performed prior to surgery and must meet all inclusion and exclusion criteria. The Principal Investigators will review the results of all screening assessments to determine subject eligibility. In addition, the subject's parents or legal guardians must be thoroughly informed about the study, including the study visit schedule, and required evaluations. The written informed consent must be obtained from the parents or legal guardians prior to enrollment.

Inclusion criteria for subjects with and without a CI:

- Age 2 to 6 years of age (24 months to 72 months)
- Bilateral profound sensorineural hearing loss as documented through behavioral assessments
- A diagnosis of one of the following, based on thin-slice MRI and CT
    - Cochlear aplasia
    - Complete cochlear ossification, post meningitis
    - Cochlear nerve deficiency (aplasia, hypoplasia)
- Strong family support, to include language proficiency of both parents/legal guardian(s) in the child's primary mode of communication and primary educational mode of communication(e.g.,

English) or another form of visual support for communication (e.g., American Sign Language, Signed English, or Cued Speech)
- Reasonable expectations from parents, to be determined informally by clinicians and psychologist, including
    - Understand benefits and limitations of auditory brainstem implant
    - Understand parental role in rehabilitation
    - Understand the child may not be successful in developing spoken language as a primary mode of communication or in developing sufficient oral language skills to allow maximum academic progress in an oral environment
- The child's parents/legal guardians have proficiency in spoken and written English to enable completion of study-related questionnaires
- Informed consent from the child's parents/legal guardian

Inclusion Criterion for subjects with a CI
- Lack of audiological benefit from the implant, at 12 months post-implant(e.g., Neural Response Telemetry, evoked cortical responses, or behavioral responses)

Inclusion Criteria for subjects without a CI
- Lack of audiological benefit after a three month appropriate amplification trial, except for:
    - Post-meningitis subjects with CT evidence of complete ossification
    - CT evidence of cochlear aplasia or cochlear nerve deficiency

Exclusion Criteria
- Cognitive and/or developmental delays which would be expected to interfere with the child's ability to cooperate in testing and/or device programming, in developing speech and oral language, or which would make an implant and subsequent emphasis on aural/oral communication not in the child's best interest
- Anomaly/pathology involving the brainstem and/or cortex
- Retrocochlear pathology resulting from NF2, or other types of cranial nerve/brainstem tumors
- Co-existing medical conditions that require irradiation of the brainstem and/or auditory cortex
- Any medical contraindication, such as
    - Cardiopulmonary or renal disease precluding safe administration of general anesthesia

Protocol Overview

Preoperative baseline measures will include documentation of a diagnosis of cochlear nerve deficiency, cochlear aplasia or complete ossification, with the standard audiological test battery showing lack of 12-month benefit for subjects with a CI. Following surgical implantation of the investigational device and a 4-to-6 week period of healing, the ABI will be activated at CHLA. Programming of the speech processor (mapping) will occur at the USC Caruso Family Center for Childhood Communication and the map will be adjusted and auditory performance assessed at six intervals: device activation, and at 1, 3, 6, 9, and 12 months post-activation. Subjects will be evaluated using an FDA-approved (for NF2 cases) Nucleus speech processor and programmed with an FDA-approved sound processing strategy. A summary of the visit schedule is shown in Table 1.

Each prospective subject's parents/legal guardians will be informed of the nature of the study and the potential risks. Informed consent will be obtained from the parent/legal guardian prior to performing any study-related screening procedures. Review of medical history, MRI and/or CT, pre-surgical evaluations, audiological evaluation, and speech language pathologist assessment. To optimize scheduling convenience for the subject and for the investigational staff, these screening procedures may be performed on more than one day. The screening examinations may take place up to 3 months

(12 weeks) prior to surgery. Screening examinations may be repeated at the discretion of the Principal Investigators.

Neurotology Examination. Prior to surgery, Dr. Wilkinson will conduct a neurotologic examination at CHLA. One week (±1 day) after the subject is released from the hospital, he will conduct a follow-up examination. He will assess the status of the incision, facial nerve function, and the implanted ear. Dr. Wilkinson will repeat the neurotology examination at Visits 7 and 10, in conjunction with the audiology/device programming visits.

Table 1. Phase I evaluation and visit schedule

Visit #	1	2	3	4	5	6	7	8	9	10	11-12
		Day 0	Day 1-4	Wk 1	Wk 4-6	M 1	M 3	M 6	M 9	M 12	Yr 2-3
Activity	Screen	Implant	In-hospital		Activate device	Device Fitting/Evaluation					Early Efficacy
Informed consent	X										
Medical History	X										
Audiological tests	X										
Psychological tests	X										
Vital signs	X	X	X		X						
Physical examination	X										
Chest x-ray, EKG	X										
Vaccinations	X										
CT and MRI	X										
Laboratory tests	X										
Neurotology exam	X			X			X			X	
EABR		X			X						
Soundfield Thresholds						X	X	X	X	X	X
Monitor vital signs					X	X	X	X	X	X	X
Device Fitting (“Mapping”)					X	X	X	X	X	X	X
IT-MAIS/MAIS	X					X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X
Communication Battery										X	X

Medical History and Examination: ABI candidates will undergo a comprehensive examination by the pediatric anesthesiologist at CHLA to evaluate for coincident medical problems involving the cardiopulmonary, neurological, ophthalmological, renal, and hematologic systems. Coincident medical

problems will be stabilized prior to consideration for surgery. The pediatric anesthesiologist will send a written report to Drs. Wilkinson and Krieger with a recommendation regarding the subject's fitness for a craniotomy and additional anesthesiology during the initial device activation.

Vaccinations. Documentation of childhood vaccinations is required for advancing to surgery. If the pediatrician cannot find documentation of the normal childhood vaccinations, he/she will order those vaccinations for the subject. Surgery will not take place until at least 14 days have elapsed from the vaccination to development of antibodies (http://www.cdc.gov/mmwr/preview/mmwrhtml/m2e731a1.htm**).** Specifically, the Center for Disease Control (CDC) recommends the following vaccinations for children aged 24 to 71 months of age (website accessed April 6, 2012, http://www.cdc.gov/vaccines/vpd-vac/mening/cochlear/dis-cochlear-gen.htm)

2 doses of 13-valent pneumococcal conjugate (PCV-13)
23-valent pneumococcal polysaccharide (PPSV)
Haemophilus influenza type b conjugate (Hib)

Diagnostic Imaging. All subjects selected for ABI will have already been studied by CT and MRI in order for a diagnosis of cochlear nerve deficiency, complete cochlear ossification, or absence of a cochlea, or for a CI. The CT provides detailed information about the petrous bone and cochlea. The MRI provides information regarding the status of the cochlear nerve within the cerebellopontine angle**.** To make the determination of cochlear nerve deficiency, the CT is examined for presence of the cochlear aperture at the base of the cochlea. If there is no opening to the cochlea, there is no cochlear nerve. If an opening is detected, the opening will be measured. If the opening is less than 1.4mm in diameter (normal is 1.4 – 3.0 mm, Huang et al., 2012; Kang et al., 2010; Miyasaka et al., 2010), cochlear nerve deficiency exists. Finally, the IAC will be measured and if less than 4 mm in diameter, cochlear nerve deficiency exists (Huang et al., 2012; Song et al., 2011). If the CT suggests a small cochlear nerve, the MRI sagittal oblique slices will be examined for evidence of the 4 cranial nerves. If the auditory nerve is not detected, cochlear nerve deficiency exists (Tamrazi et al., 2011). Detection of cochlear aplasia and complete cochlear ossification are more straightforward. For cochlear aplasia, a simple absence of the end organ on CT or MRI confirms the diagnosis. For complete cochlear ossification, a lack of T2 signal in the cochlea on MRI confirms the diagnosis.

Pre-operative Audiology, Speech Pathology, Psychological, and Educational Assessment.

Sound awareness behavioral testing

Infant-Toddler Meaningful Auditory Integration of Sound (IT-MAIS)

A Speech-Language pathologist (SLP) will perform assessments of communication skills in the child's main communication mode (oral, sign, other), including informal and parent-report assessments of communicative intent in very young children and an oral motor examination. For children for whom there are psychological concerns, a clinical psychologist familiar with developmental norms for children will perform tests of non-verbal IQ, appropriate to the child's age and development to determine the child's ability to accommodate to an ABI. An Educational Liaison, familiar with the educational services and system in the local area, will evaluate the child's intervention/educational programming.

ABI Surgery

In the young pediatric subject, the mastoid is not well developed, and the retrosigmoid approach must be utilized. This approach has been demonstrated to be safe with a low complication rate in both adults and children. Professor. Colletti will be attending the first three surgeries to provide on-site expertise and training. We have budgeted 2 trips to ensure this requirement is met. Surgery is carried out using general endotracheal intubation with standard pediatric neuroanesthetic technique to promote brain relaxation. Adequate intravenous access is obtained with placement of peripheral or

central venous lines. The subject is positioned supine using a Mayfield horseshoe headrest. The head is turned approximately 45 degrees toward the contralateral side. In adults, a curvilinear incision approximately 6 cm in length is made 2 cm behind the ear. The deep fascia is incised, and suboccipital muscles are partly detached from the posterior face of the mastoid and the occipital bone in the subperiosteal plane. A retrosigmoid craniotomy approximately 2.5 cm in diameter is then performed. Its anterior and superior limits are the posterior edge of the sigmoid sinus and inferior edge of the transverse sinus, respectively. After completion of the craniotomy, a pocket is created in the subgaleal plane immediately superior and posterior to the craniotomy site. Adequate pocket size is confirmed using a device dummy that conforms to the size and shape of the ABI receiver. The periosteum is then opened, and a limited trough is drilled using diamond-tip burrs in the shape of the receiver body and very proximal portion of cable. The dura is incised with flaps based upon the sinuses. A self-retaining retractor is set up, but its use is minimized. Cottonoids are used to protect the cerebellar hemisphere. Under high-power magnification, the cerebellar hemisphere is gently elevated, and cerebrospinal fluid is drained from the basal cisterns. The lower cranial nerves, facial nerve and any remnant of vestibulocochlear nerve, and the trigeminal nerve are identified, and arachnoid overlying these structures is widely opened using microdissectors. Any superior or inferior petrosal veins inhibiting mobilization of the cerebellar hemisphere are coagulated and divided. The flocculus is dissected free of any adherence to underlying nerves of the cerebellopontine angle.

Placement of the ABI Electrode Array. The Nucleus 24 ABI features a multichannel electrode lead that terminates in twenty-one 0.7 mm platinum disk-electrodes. The 21 platinum contacts are arranged on the surface of a silicone rubber pad in three rows of seven and are surgically placed on the surface of the brainstem; specifically, on the surface of the cochlear nucleus. An external, battery operated speech processor is worn behind the ear.

One difficulty unique to ABI implantation is the identification of anatomical landmarks, particularly in a developmentally abnormal or anatomically distorted region. In normal anatomy, the vestibulocochlear nerve is located in direct contiguity with the cochlear nucleus. Even in highly distorted or abnormal anatomy (e.g., in the absence of a vestibulocochlear nerve) the choroid plexus and ninth cranial nerve reliably provide guides for locating the foramen of Luschka. In some cases, however, the opening to the foramen is indistinct or obstructed by a thin membrane. Exploration of this region is facilitated by brain relaxation, achieved via cerebrospinal fluid outflow after opening of the cerebellopontine cistern and neuroanesthetic techniques including mannitol administration and hyperventilation. The posterior-ventral and dorsal cochlear nucleus, the most accessible portions of the cochlear nucleus complex for electrical stimulation, are located along the surface of the lateral recess of the fourth ventricle and can be visualized. Various landmarks are used to locate the foramen of Luschka, which affords access to the fourth ventricle. Typically, the choroid plexus, which covers the foramen of Luschka, lies within a triangle formed by the VIII cranial nerve, the IX cranial nerve, and the lip of the foramen of Luschka. The most important landmark to identify in the cochlear nucleus area is the VIII cranial nerve because the cochlear nucleus complex may be prominent in the prolongation of this nerve. In children with cochlear nerve deficiency, this landmark was lacking and the projection of the IX cranial nerve is followed and directly leads to the foramen. The entry into the fourth ventricle can be obscured by the cerebellar flocculus and covered by the choroid plexus, which can fill the lateral recess of the fourth ventricle and protrude from the foramen of Luschka. To approach the fourth ventricle, the arachnoid over the foramen is cut, the venous and arterial net are detached and elevated, and the flocculus and the choroid plexus are retracted. To this end, rostromedial retraction of the cerebellum is generally necessary. The choroid plexus, projecting from the lateral recess and overlying the cochlear nucleus complex, is followed and the entrance to the lateral recess is found. In our experience, microsurgical dissection to reach the cochlear nucleus area shows an anterior inferior cerebellar artery loop in 25%, the taenia of the choroid plexus in 94%. The foramen of Luscka is opened and easy to find in 96% of children but needs careful dissection in 4%. After clear identification of the cochlear nucleus area, the ABI device is prepared for insertion. The receiver body is held in place using its magnet, which is

attached to a small surgical instrument clamped to the operative drapes immediately superior to the incision. The ground electrode is then placed deep to the temporalis muscle immediately superior to the external ear canal. Under high-power magnification, the electrode array can be completely inserted into the lateral recess with the aid of a small forceps.

Intraoperative Monitoring. The purpose of intraoperative monitoring is to aid in positioning the electrode array so maximum stimulation can be achieved on as many electrodes as possible.This is obtained through electrically evoked auditory brainstem responses (EABRs). Recording electrodes for EABRs are positioned at the vertex (Cz, positive electrode) and over C7 (negative electrode) on the neck, with a ground electrode at the front. After ABI insertion, the speech processor is placed within a sterile sheath and the coil is positioned over the receiving antenna of the implant and EABRs recorded. The cochlear nuclei are stimulated using biphasic electrical stimuli of 150 microseconds per phase at a stimulus rate of 25 Hz. If no response is observed on any electrode at 190 clinical units the stimulus intensity can be increased to 220 clinical units. Selected bipolar pairs of electrodes should be stimulated in different portions of the array to confirm the correct position of the ABI. If no evoked EABR wave is detected in the first 4.5 msec of recordings, the position of the array in the lateral recess should be modified. The overall positioning of the electrode array can be assessed by recording from electrode pairs located on opposite portions of the electrode array. Once the overall electrode array position has been established then electrodes are stimulated in more selective regions (distal, median, and proximal) of the array to map the area more selectively and to confirm a good contact between the electrodes and the cochlear nucleus. Neural responses can be distinguished from stimulus artifacts by reversing the polarity of the stimulus current. Inversion of the stimulus artifact without inversion of the neural response can thus be observed. The ABI device is stimulated to determine the presence of electrical waves. Once reliable EABRs are obtained, the mesh surrounding the electrode carrier is bent back toward the brainstem to stabilize the implant device. In addition, small tufts of teased Teflon pledgets are inserted into the foramen to improve stabilization. Cranial nerves VII, IX, X, and XI are monitored with a continuous electromyography recording system (NIM-Response 2.0, Medtronic, Jacksonville, FL) and, if needed, with monopolar electrical stimulation for identification of the nerves.

Receiver Placement and Closure. After EABR testing is concluded and electrode array placement is confirmed, the receiver is carefully placed in the subgaleal pocket with the receiver secured in the previously drilled trough. Further irrigation is carried out to ensure hemostasis, and the dura is sutured around the cable. Given presence of a cable transiting through the dural opening into the subarachnoid space, water-tight dural closure is not possible. The dural closure is therefore reinforced using an appropriately-shaped on-lay dural substitute, such as Duragen (Integra, Plainsboro, NJ). Cautious closure of mastoid air cells with bone wax or fat should be done initially at craniotomy and again at closure. Early recognition and correction of raised intracranial pressure are also important because it can predispose a subject to CSF leakage. If an adequate bone flap was preserved, it is secured in place in standard fashion, and a multi-layer scalp closure is carried out. The wound is dressed with a standard head wrap.

Post-Implantation Surgical Care. Subjects will be admitted to the Pediatric Intensive Care Unit for 24 hours following surgery. Subjects will be administered standard intensive care monitoring including continuous pulse oximetry, noninvasive blood pressure monitoring, pulse rate monitoring, and continuous electrocardiographic tracing. The subject is extubated in the operating room, and recovery from anesthesia is carried out in the intensive care unit. Parenteral and enteral analgesia is utilized as needed, but sedation is otherwise avoided. The subject is mobilized, and diet is advanced on the first postoperative day. Intravenous fluids are weaned as needed intake increases. A gauze head wrap will be maintained for the first 2 postoperative days. After 24 hours in the intensive care unit, the subject will be transferred to the pediatric medical-surgical floor for up to 3 additional days. The subject's wound is examined on each post-operative day but is kept covered to avoid manipulation by the subject. In the absence of any medical or surgical concerns, and if the subject is taking adequate nutrition and liquids by mouth, he/she will be discharged. Post-operative imaging (CT) is carried out only when

warranted clinically. On postoperative day 3, the gauze head wrap will be removed. If the surgical wound is dry and shows no evidence of cerebrospinal fluid leak, the subject will be observed. If there is any evidence of cerebrospinal fluid leak, the subject will undergo a revision procedure to close the leak.

Post Surgical ABI Activation and Fitting Procedures
An EABR under sedation will be conducted at CHLA and behavioral device fitting (programming of the speech processor) will be conducted at USC. The EABR testing will be carried out 4 – 6 weeks after surgical implantation, after the incision has healed. The child will be sedated and the electrodes stimulated in a "wide" and then "narrow" test pattern. The wide stimulation is as above, and the narrow test pattern will stimulate close-by electrodes (5 bipolar positions: 14 – 20, 8 – 2, 15- 21, 9 – 3, 16 – 7).

At least one day and no greater than 7 days after the post-operative EABR, the subject will be seen at the USC Caruso Center for Childhood Communication for initial device mapping. The fitting audiologist will have the results of the EABR, both intraoperatively and under sedation, to assist in programming. Age-appropriate behavioral mapping techniques used with pediatric CI recipients will be used to determine optimal current level settings and speech processor program parameters. Electrodes are stimulated individually and a behavioral threshold response is sought either through use of visual reinforcement or conditioned play techniques. Mapping starts with electrodes that produce the most robust auditory response during the EABR recording. Stimulation levels are initially set to 40 clinical units below the threshold level measured under anesthesia and slowly increased. Pediatric audiologists will also watch carefully for signs of non-auditory stimulation; tingling sensations along the ipsilateral body, dizziness from flocculus activation, or facial motor activation from the VII nerve. If such non-auditory responses are observed, that electrode will be turned off and not used in the speech processor map. Once an auditory response is observed, the stimulation level will be gradually increased, watching for signs of distress or discomfort in the child. Initial settings will be conservative to avoid producing any adverse response, so that the child does not associate auditory sensations with any type of discomfort.

The ACE encoder strategy is the strategy most commonly used in CI recipients and pediatric NF2 ABI recipients. Initially, the upper level of stimulation (comfort or C-levels) is set behaviorally and the lower level of stimulation (T-levels) is set 10-20 units below Cs. Care is taken to see that there are no adverse reactions to stimulation at C level on any electrode. Once a core set of electrodes is determined or "mapped," the microphone is activated and the child is able to hear environmental sounds. Levels are then raised slowly, with the child under careful observation, to observe his/her responses. The goal for behavioral initial stimulation is for the child to wear the equipment comfortably, have access to moderate to loud speech and environmental sounds, without exceeding comfort levels. The parents/legal guardians will also be instructed on the proper care of the external speech processor, including how to turn the device on/off, volume control, and sensitivity settings.

At subsequent appointments, electrodes may be added to the map and the mapping levels are raised and refined according to the child's responses, with the goal of providing access to sounds across the speech frequency spectrum. At subsequent visits attempts will also be made to add electrodes to the map that might have produced an uncertain response at initial stimulation and so were not initially included in the map.

Post-activation Audiological Assessments
At each of the post-activation visits, the ABI will be evaluated by the audiologist for appropriate fitting of the speech processor. If necessary, the audiologist will adjust the map as necessary. We plan to assess these subjects beyond the 1-year safety study to explore early efficacy. For this Phase I trial, subjects will be tracked annually for 2 years following completion of the 12-month safety study. The subjects who undergo ABI surgery will complete the safety study within the 5-yeargrant timeline. This

extended test battery includes behavioral measures in the developmental domains of audiology, speech perception/recognition, speech-language, and adaptive behavior.

Sound Field Auditory Thresholds Standard audiometric techniques will be performed for measuring sensitivity to sound with the ABI activated. Visual reinforcement audiometry will be performed to measure sound field thresholds, until the child is 30 to 36 months of age. Conditioned play audiometry will be performed when the child is approximately 30 to 36 months of age and older. Stimuli will be delivered via loudspeaker and consist of live-voice speech and warbled tones or narrow-band noise for 250, 500, 1000, 2000, 4000, and 6000 Hz.

Speech Perception (Hierarchical approach, i.e., child progresses to more difficult open-set tests if successful on the easier closed-set tests)

Infant-Toddler Meaningful Auditory Integration of Sound (IT-MAIS)
Ling 6-Sound Test
Test of Auditory Comprehension
Pediatric Speech Intelligibility Test
Lexical Neighborhood Test

Speech and Language:
Pre-School Language Scale, Fifth Edition (PLS-5)
Identifying Early Phonological Needs in Children with Hearing Impairments (IEPN)
Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4)

Adaptive Behavior:
Vineland Adaptive Behavior Scales – 2nd Edition

Endpoints and Statistics

There are no endpoints to this study because this is a feasibility study with a maximum of 10 subjects. Statistics are descriptive.