Cochlear®
Hear now. And always

Cochlear™ Nucleus® Implants Results of Clinical Studies

United States of America

For Professionals and Recipients

Contents

Glossary

Terms used in this document

Best-aided listening condition – Best-aided is the best listening condition for a particular person in relation to their hearing loss. For example, if they have bilateral hearing loss, the best-aided condition might be having implants or hearing aids in both ears.

Bilateral – Relating to both ears.

Bimodal – Use of a hearing aid with a cochlear implant.

Cochlea – Part of the inner ear that converts mechanical vibrations into electrical impulses.

Cochlear™ Nucleus® 24 cochlear implant system – The Cochlear Nucleus cochlear implant and sound processor including coil/cable, battery module and remote controls.

Moderate hearing loss – Hearing loss in the range of approximately 40–55 dB HL.

Moderately severe hearing loss – hearing loss in the range of 56-70 dB HL.

p-value – probability value

Paediatric – Relating to individuals from birth through age 21.

Perilinguistic – During language acquisition.

Postlinguistic – After language acquisition.

Prelinguistic – Before language acquisition.

Profound hearing loss – Hearing loss of approximately 90 dB HL or greater.

Sensorineural – Relating to the inner ear.

Severe hearing loss – Hearing loss in the range of approximately 71–90 dB HL.

Single-sided deafness – Profound hearing loss in one ear and normal or near normal hearing loss in the other ear.

Unilateral – Relating to one ear.

Acronyms used in this document

AE – adverse event

BKB-SIN – Bamford Kowall Bench sentences in noise test

CI - cochlear implant

CNC – consonant nucleus consonant

HINT – hearing in noise test

IQR – interquartile range

MRI – magnetic resonance imaging

NH – normal hearing

RMS – root mean square

S0N$_{NH}$ – speech from front, noise from right (NH side)

SSQ – speech, spatial, and qualities

SD – standard deviation

UHL – unilateral hearing loss

About this document

Clinical studies were performed to test whether the Cochlear Nucleus cochlear implant system was safe and effective for use. Participants who were part of the studies had either bilateral sensorineural hearing loss or single-sided deafness (SSD).

The following information summarises adverse events (AEs) for adults and children implanted with the Cochlear Nucleus 24 cochlear implant system. The studies referenced below included individuals with bilateral sensorineural hearing loss and single sided deafness (SSD); however, safety information may apply to any person who receives a cochlear implant.

Summary of safety data - adults

Adult safety data are based on a total of 133 patients implanted with the Cochlear Nucleus 24 cochlear implant during the adult clinical investigation at 27 US sites.

- 20 patients experienced either a medical or surgical complication, or a device-related complication.
- 11 of the 20 complications were medical or surgical in nature and the remaining nine were device-related.
- 18 of the 20 AEs resolved without surgical or extensive medical intervention.

Medical or surgical complications[1]

- One patient experienced device migration which required revision surgery to reposition the device.
- One patient experienced a wound haematoma which required minor surgery to resolve.
- One patient experienced a slightly compressed electrode array and the surgeon elected to remove the device and replace it with a second one during the initial surgery.
- Four patients experienced facial nerve stimulation. All cases of facial nerve stimulation were resolved through reprogramming.
- Two patients experienced tinnitus related to cochlear implant use.
- One case resolved without intervention and the second case was resolved through reprogramming.
- One patient experienced short-term postoperative dizziness which resolved without medical treatment.
- One patient experienced fluctuating psychophysical levels related to a relatively thick (10+ mm) skin flap. This case was resolved through replacement of external equipment.

Device-related complications

- No device failures or other serious device malfunctions occurred during this study.
- Four patients experienced electrode insulation faults (short circuits) that were resolved through reprogramming.
- Two patients were inadvertently overstimulated during device programming.
- One patient reported a nonauditory sensation during device programming.
- Two patients experienced a mild skin reaction to the sound processor cable. These were resolved completely with topical medical treatment.

[1] Medical or surgical complications would be classified today as a procedure related adverse event.

Summary of safety data - children 12 months and older

Paediatric safety data are based on a total of 234 children implanted with the Cochlear Nucleus cochlear implants for two clinical investigations.

For the first clinical investigation, 150 children were implanted with Cochlear Nucleus 24 cochlear implants:

- 24 patients experienced 27 medical or surgical complications, or device related complications.
  - 9 of the 27 complications were medical or surgical in nature.
  - The remaining 18 were device-related complications.
  - 24 of the complications resolved without surgical or extensive medical intervention.

Medical or surgical complications[1]

- One postmeningitically deafened child with bilaterally ossified cochleae failed to experience auditory stimulation through the fully functional cochlear implant.
- One patient developed streptococcal meningitis less than 24 hours following cochlear implant surgery. The infection was successfully managed with medical treatment.
- One patient experienced a wound infection that was resolved through surgical explantation of the device.
- One patient experienced extracochlear electrode placement related to a congenital malformation of the inner ear. This complication was resolved through surgical explantation of the device.
- Two patients experienced slight compression of the electrode array which resulted in two short-circuited electrodes in one case and no electrode anomalies in the other. The case with electrode short circuits was resolved through reprogramming.
- One patient experienced facial nerve stimulation related to a severe congenital malformation of the inner ear. This complication was resolved through reprogramming, however, the patient continues to experience occasional slight facial nerve stimulation.
- Two patients experienced mild short-term postoperative dizziness. Both cases resolved without medical intervention.

Device-related complications

No device failures or other serious device malfunctions were observed.

- 13 patients experienced electrode faults (short-circuit or open-circuit electrodes) on one or more electrodes. All of these cases were resolved through reprogramming.
- One patient experienced non-auditory sensations during psychophysical testing. This case was resolved through reprogramming.
- One patient experienced an unanticipated overstimulation. This complication was resolved through replacement of external equipment.
- Three patients experienced mild skin reactions to the sound processor cable:
  - One case was resolved through covering the cable.
  - One case was resolved through an alternative polyurethane coating of the cable.
  - One case resolved spontaneously without intervention.

[1] Medical or surgical complications would be classified today as a procedure related adverse event.

Summary of safety data - children 9 months to 12 months old

Premarket study

Cochlear performed a premarket, prospectively-designed, retrospective analysis from its own registry data to establish a reasonable assurance of safety of implantation with the Cochlear Nucleus 24 cochlear implant system for paediatric patients between the ages of 9 months and 12 months.

The retrospective review of 83 children that were between 9 months and 12 months of age and implanted with Cochlear Nucleus cochlear implants was completed for this analysis.

Device-related complications, such as electrode faults, were not captured in this study.

Twenty-four patients experienced 28 medical or surgical complications and 26 of the complications were resolved without major surgical or medical intervention:

- Six patients experienced minor postoperative complications, four of which were resolved without medical intervention.
- Two patients experienced cerebral spinal fluid leakage perioperatively. These were repaired during the cochlear implant surgery.
- One patient required a revision surgery with reimplantation.
- Two patients experienced postoperative infections including mastoiditis, postauricular abscess, and surgical site infection. All the infections were medically managed.
- Two patients developed seromas and one of these patients was reimplanted.
- Two patients experienced temporary facial weakness which resolved with steroid administration. There were no reports of postoperative meningitis.

Overall, the above AEs are typical surgical, procedure or device events observed in children implanted at a relatively young age.

Additionally, in February 2020, Cochlear performed a systematic literature search in PubMed and EMBASE databases to assess safety of implantation with a Cochlear Nucleus cochlear implant in children between the ages of 9 months and 12 months.

A multi-step literature search process resulted in a final set of studies (49 peer-reviewed articles) representing additional relevant research on cochlear implantation for patients less than 12 months old. Safety studies that included children implanted at less than 12 months old covered a broad range of topics from surgical complications including:

- anaesthesia
- blood loss
- postoperative pain and dizziness
- wound healing problems
- infections.

The research literature reviewed on surgical and postoperative outcomes reported specific to the population under the age of 12 months at implantation did not identify an elevated incidence of complications.

Post-approval study

Summary of the post-approval study methods

Cochlear performed a post-approval, prospectively-designed, retrospective analysis among 83 patients who were enrolled in the premarket study and 50 additional patients – data collected out to two years postoperatively – to assess long-term safety of cochlear implantation in children between 9 months and 12 months of age.

The purpose of this study was to supplement the premarket study with:

- additional patient profiles of children implanted more recently
- longer-term outcomes data.

Data was collected from medical records and chart notes.

Summary of the post-approval study results

Adverse events (AEs) included any device, procedure, and otologic-related unexpected medical occurrences occurring from time of surgery through two years postoperatively.

The AEs were classified as major or minor AEs using well-established criteria (Cohen & Hoffman, 1991).

- Major AEs were defined as those requiring hospitalisation and/or additional surgical intervention.
- Minor AEs were defined as those using the expected route of treatment and/or medication.

Seventeen new AEs were reported in this post-approval dataset of 133 total patients.

- 6 AEs were reported for the extended study group of 83 patients for either:
  - AEs spanning between 6 months to 24 months postoperatively
  - or AEs that had not been previously reported in the original dataset.
- 11 AEs were reported for the 50 new patients.

Of the 17 new AEs, five were considered major AEs and 12 were considered minor AEs:

- Four patients experienced postoperative complications.
- Eight patients experienced ear-related infections, four of which were considered major AEs:
  - one patient developed seroma and was reimplanted.
  - one patient with bilateral acute otitis media was re-hospitalised for myringotomy and tubes.
  - one patient was noted to have recurrent ear infections.
  - one patient reported chronic middle ear dysfunction.
- One patient was readmitted to the hospital postoperatively with a fever and received fluids and antibiotics, categorised as a major AEs.
- One patient experienced cerebral spinal fluid leakage during surgery.
- Three patients experienced minor AEs that did not fall into the categories above.

There were no unanticipated AEs reported in this new dataset of 133 patients. All 17 AEs were reported as resolved.

Primary safety endpoint

The combined dataset of 133 patients demonstrates the overall safety of cochlear implantation in children between 9 months and 12 months of age. The rate of AEs gathered in the post-approval study is qualitatively similar to the AEs reported in the original premarket study from 6 months to 24 months. There were differences seen between the groups 0 months to 6 months, with a higher rate of AEs for the premarket study group. Refer to *Table 1*.

Group	0-6 months postoperative	6-24 months postoperative	0-24 months postoperative
83 premarket study patients (N=143 ears)	42 AEs (29.4%)	5 AEs (3.5%)	47 AEs (32.9%)
50 new patients (N=82 ears)	9 AEs (11.0%)	2 AEs (2.4%)	11 AEs (13.4%)
133 combined patients (N=223 ears)	51 AEs (22.7%)	7 AEs (3.1%)	58 AEs (25.8%)

Table 1: *Primary safety endpoint*

Group: premarket study patients

A total of 42 AEs for patients initially enrolled during the premarket study were collected and resolved between 0 months and 6 months postoperatively, yielding a complication rate of 29.4%.

An additional 5 AEs were collected and reported as resolved during the expanded 6 month to 24 month postoperative time window for this patient group.

Of the 5 AEs reported during this time window:

- two were new AEs
- three were previous AEs that began during the 0 month to 6 month postoperative window, but were not resolved until 6 months to 24 months postoperatively.

These 5 AEs yield a complication rate of 3.5%.

There was a total complication rate of 32.9% for the 47 AEs collected 0 months to 24 months for this group.

Group: new patients

A total of 9 AEs were reported for the new patients during the 0 months to 6 months postoperative time period, yielding a complication rate of 11%.

- Two AEs began during the 0 months to 6 months reporting window but were not resolved until the 6 month to 24 month period, yielding a complication rate of 2.4%.
- No AEs beginning beyond the 6 month time period were reported for this new patient group.

There was a total complication rate of 13.4% for AEs collected 0 months to 24 months for this group.

Complication rates for the premarket study were collectively higher than the new patients, especially in the 0 months to 6 months range. However, there is evidence of surgical protocol improvement for the postmarket study, leading to improved surgical outcomes and decreased reported complication rates.

Group: combined patients

Of the 58 AEs reported across the combined group of 133 patients, with data collected 0 months to 24 months postoperatively:

- 13 AEs met criteria as a major AE equating to an incidence rate of 5.8%.
- 45 AEs met criteria as a minor AE, equating to an incidence rate of 20.0%.

Findings of this post-approval study align with published cochlear implant literature specific to the paediatric population for major AEs related to cochlear implants, which ranges between 1.5% and 6.6% of all cases across variable postoperative time periods.

Minor AEs in this combined dataset were reported at a higher incidence rate than published literature due to variation in categorisation criteria and reporting timelines.

In summary, data collected as part of the premarket study and this subsequent post-approval study provide a dataset of over 100 patients who received a Cochlear Nucleus cochlear implant between 9 months and 12 months of age. Data was collected postoperatively out to two years or date of final protocol approval (May 15, 2020).

The data provided continues to support the safety of cochlear implantation with the Cochlear Nucleus device in infants as young as 9 months of age. Findings of this post-approval study demonstrate agreement with previously published literature (Cohen & Hoffman, 1991; Farinetti et al., 2014; Ikeya et al., 2013; Loundon et al., 2010; Petersen et al., 2018) for the primary safety endpoint.

Summary of effectiveness data - adults

The following information summarises effectiveness data for adults implanted with the Cochlear Nucleus 24 cochlear implant system.

Unilateral hearing loss (UHL) / single-sided deafness (SSD)

Cochlear analysed retrospective data to demonstrate the effectiveness of cochlear implantation in adults with SSD. For the data analysed:

- the ear to be implanted had a profound sensorineural hearing loss (PTA of 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) ≥ 70 dB HL, and an aided CNC word score of ≤ 10%
- the contralateral ear had normal or near normal hearing (PTA 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz) ≤ 30 dB HL.

This study was a prospective analysis of previously collected data from a Cochlear sponsored multicentre prospective feasibility study and real world data.

- The feasibility study had 10 participants (N=10).
- The real world data was collected from two cochlear implant centres who had data available for 32 participants (N=32).
- Data was analysed for a total of 42 participants.

Effectiveness testing included speech recognition testing using:

- Hearing in Noise Test (HINT)
- Bamford Kowal Bench Sentences in Noise Test (BKB-SIN)
- Localisation testing.

Patient reported outcomes were evaluated using:

- Speech, Spatial, and Qualities (SSQ) Questionnaire
- Iowa Tinnitus Handicap Questionnaire.

Audiometric thresholds were also obtained for each ear.

Description of tests

Hearing in Noise Test (HINT)

The Hearing in Noise Test or HINT (Nilsson et al., 1994) is a test made up of 25 10-sentence lists used to test how well an individual understands in noise. The sentences are presented in noise which is filtered to match the long-term average spectrum of the sentences. The HINT is an adaptive test whereby the signal-to-noise ratio (SNR) is increased or decreased by a fixed amount based on the listener's ability to repeat the sentences correctly or not.

Bamford Kowall Bench Sentences in Noise Test (BKB-SIN)

The BKB-SIN Test (Etymotic Research, 2005) includes 18 lists of sentences. The sentences are spoken by a single male talker, are 5-6 words in length and are at a 1st grade reading level. The sentences are presented in noise using 4-talker babble. The test starts out easy where the sentences are presented much louder than the noise and depending on a listener's ability to correctly repeat the words in the sentence, the sentences are either made softer or louder until a level is reached where 50% of the words in a sentence are repeated correctly.

Localisation testing

Localisation is the ability to tell where a sound is coming from. Localisation testing was assessed by delivering a noise from one of 12 locations. The locations are numbered one through 12 on a response sheet, from right to left. The sound comes from a speaker positioned to represent an arc from 97.5° (on the right) to 262.5° (on the left) of the participant. There is a 15° separation between each speaker. The participant selects one number to indicate the perceived location of the sound.

Evaluation methods

Speech, Spatial, and Qualities (SSQ) Questionnaire

The SSQ is a validated self-assessment metric commonly used in hearing aid and cochlear implant research. It is designed to measure self-reported auditory disability across a wide variety of domains, reflecting the reality of hearing in the everyday world. There are 49 questions (SSQ-49) scored by the participant using a scale of 0 through 10, where 0 corresponded to minimal ability and 10 corresponded to complete ability. There are three specific hearing domains assessed:

1. Speech hearing scale – This includes hearing speech in quiet and in noise, in one-on-one conversation and in groups or meetings.
2. Spatial hearing scale – This includes hearing where sounds are coming from, distance, movement, and ability to segregate sounds.
3. Qualities of sound scale – This includes ease of listening, naturalness, clarity, identification of different speakers, musical pieces and instruments, as well as everyday sounds.

Iowa Tinnitus Handicap Questionnaire

The Iowa Tinnitus Handicap Questionnaire was used to assess tinnitus. Tinnitus was assessed before and after the cochlear implant was turned on. There are 27 questions that fall into three factors.

1. Factor 1 examines social, physical and emotional wellbeing.
2. Factor 2 examines hearing abilities.
3. Factor 3 examines an individual's view of tinnitus.

Effectiveness testing: speech recognition results

The primary and secondary effectiveness objectives and endpoints of the study are shown in *Table 2*.

Primary effectiveness objective	Primary effectiveness endpoints
To evaluate if the restoration of hearing sensation in both ears results in improved spatial hearing for speech in noise, when the target and competing signals are spatially separated.	1. The improvement in sentences in noise scores obtained postactivation in the bimodal listening condition, cochlear implant + normal hearing (CI + NH), compared to scores obtained preoperatively in the best listening condition, normal hearing (NH) alone, or hearing aid + normal hearing (HA + NH) when the speech is presented from the front and noise to the normal hearing ear ($S0N_{NH}$). 2. The improvement in group and individual bimodal (CI + NH) sentence in noise scores compared to scores obtained postoperatively with the NH ear alone, cochlear implant off (CI off) when speech is presented from the front and noise is presented to the NH configuration ($S0N_{NH}$).
Secondary effectiveness objectives	**Secondary effectiveness endpoint**
To evaluate if the restoration of hearing sensation in both ears results in improved spatial hearing for locating sound sources in the horizontal plane.	Group and individual bimodal (CI + NH) localisation scores Root Mean Square (RMS) error will be compared with NH ear alone (CI off) scores at the most recent postactivation evaluation.

Table 2: *Summary of study effectiveness objectives and endpoints*

Primary effectiveness endpoint

Co-primary effectiveness endpoint 1: Bimodal (CI + NH) performance relative to preoperative performance

Twenty three (23/42) participants had preoperative and postactivation data and were included in the analysis.

As shown in *Table 3*, when speech was presented from the front speaker and noise to the NH ear ($S0N_{NH}$), there was a postactivation improvement in the bimodal listening condition (CI + NH) compared to the best preoperative listening condition. On average, participants experienced an improvement of 2.8 dB, (95% confidence interval, -4.1 to -1.4). A negative value connotes benefit with a cochlear implant for this test.

	Preoperative (HA + NH alone)		Postactivation (CI + NH)	
	N	Mean ± SD[1] Median (IQR)[2]	N	Mean ± SD Median (IQR)
Sentence recognition in noise HINT/BKB SIN $S0N_{NH}$	23	0.9 ± 3.3 0.6 (-1.0, 2.7)	23	-1.9 ± 2.6 -1.6 (-3.1, -1.0)

	Difference			
	N	Mean ± SD Median (IQR)	95% confidence interval	1-sided p-value (mean difference < -1.5)
Sentence recognition in noise HINT/BKB SIN $S0N_{NH}$	23	-2.8 ± 3.1 -2.5 (-4.3, -1.2)	(-4.1, -1.4)	0.032

Table 3: *Co-primary effectiveness endpoint 1: Bimodal (CI + NH) performance relative to preoperative performance*

1 SD = standard deviation
2 IQR = interquartile range

Co-primary effectiveness endpoint 2: Bimodal (CI + NH) performance relative to NH ear alone (CI off) performance postoperatively

Table 4 summarises the results for 38 participants, who had data available postactivation comparing performance in the bimodal listening condition (CI + NH) compared to performance in NH ear alone condition (CI off).

The postactivation interval ranged from 3 months to 86 months with a mean of 20 months. Improvement was found in the bimodal condition (CI + NH) compared to NH alone (CI off) for speech understanding in noise ($S0N_{NH}$).

Participants on average experience a 1.5 dB improvement (95% confidence interval, -2.1 to -0.9) in the bimodal condition compared to listening with the NH ear alone. A negative value connotes benefit with a cochlear implant for this test.

	Postactivation (CI off) NH alone		Postactivation (CI on + NH)	
	N	Mean ± SD Median (IQR)	N	Mean ± SD Median (IQR)
Sentence recognition in noise HINT/BKB SIN $S0N_{NH}$	38	-0.7 ± 2.3 -1.2 (-1.6, 1.0)	38	-2.2 ± 2.5 -1.9 (-4.1, -1.0)
	Difference			
	N	Mean ± SD Median (IQR)	95% confidence interval	1-sided p-value
Sentence recognition in noise HINT/BKB SIN $S0N_{NH}$	38	-1.5 ± 1.8 -1.6 (-2.8, 0.0)	(-2.1, -0.9)	< 0.001

Table 4: *Co-primary effectiveness endpoint 2: Bimodal (CI + NH) performance relative to NH ear alone (CI off) performance postoperatively*

These analyses support that both co-primary endpoints were met for this study, namely:

- For speech understanding in noise, when the speech is presented from the front speaker and noise is presented to the NH ear, there was a significant improvement of 2.8 dB, (95% confidence interval, -4.1 to -1.4) postactivation at the most recent evaluation in the bimodal (CI + NH) listening condition compared to preoperative hearing performance.
- For speech understanding in noise, when the speech is presented from the front speaker and noise is presented to the NH ear, there was a significant difference at the most recent evaluation interval in the bimodal (CI + NH) listening condition compared to NH alone (CI off). Mean improvement was 1.5 dB (95% confidence interval, -2.1 to -0.9).

In examining individual subject performance, it was found in the preoperative best bilateral listening (HA + NH / NH alone) to postactivation (CI + HA) comparison that:

- 18/23 (78%) participants demonstrated a clinically meaningful preoperative to postactivation improvement of 1.0 dB (10% improvement), with a range of -1.2 dB to -9.5 dB, (note that a negative score connotes improvement)
- 3/23 (13%) participants scored equal to their preoperative performance, with a range in difference scores from 0.0 dB to +0.8 dB
- 2/23 (9%) participants had a difference score ≥ +1.0 dB, consistent with a decline in performance.

When comparing performance postactivation in the bimodal condition (CI + NH) (CI on) compared to NH ear alone (CI off), it was found that:

- 25/38 (66%) participants demonstrated a clinically meaningful improvement with CI on of 1.0 dB (10% improvement) with a range of -1.0 dB to -6.2 dB, (note that a negative score connotes improvement)
- 11/38 (30%) participants scored equal to their NH alone score, with a range of difference scores from -0.7 dB to +0.8 dB
- 2/38 (5%) participants had a difference score > +1.0 dB, consistent with a decline in performance.

In the clinical study, it was found that 8/38 (21%) experienced a decrease in speech understanding in noise when speech was presented from the front speaker and noise was directed to the cochlear implant side, suggesting potential interference of the overlapping electric and acoustic signal in bilateral hearing.

Additionally, a few published studies (Speck et al., 2020, Deep et al., 2021, and Zeitler et al.,2019) reported that there was a low incidence of cochlear implant nonuse presumably because of lack of perceived benefit of the cochlear implant. Given these results, it is reasonable to conclude that a small number of recipients experience perceptual interference of overlapping acoustic and electric bilateral hearing.

Cochlear performed subgroup analyses to examine the consistency of co-primary effectiveness endpoints. The subgroups examined were:

- gender
- median age at implant
- median duration of hearing loss at baseline
- etiology of hearing loss
- evaluation interval
- median baseline/preoperative speech in noise score
- median baseline CI off speech in noise score
- preoperative pure tone average (PTA).

Results indicated that the only baseline characteristics that affected primary endpoint 1 were:

- Duration of hearing loss

  The mean score for participants below or equal to the median duration of hearing loss of two years was significantly poorer than that for duration of hearing loss above two years.
- Etiology of hearing loss

  It was found that those participants with an etiology of sudden sensorineural hearing loss performed significantly better than those with Meniere's disease or the other group.
- Preoperative speech in noise score

  This result should be interpreted with caution as the majority of etiologies were classified as other. It was found that those participants who had poorer preoperative speech in noise scores demonstrated significantly greater improvement.

For coprimary effectiveness endpoint 2, the only baseline characteristic that affected the endpoint was baseline speech in noise for the spatial configuration $S0N_{NH}$ obtained in the CI off condition (NH alone).

Participants with poorer speech understanding in noise (> 1.2 dB) in the CI off condition demonstrated significantly more improvement in the bimodal listening condition (CI + NH).

There were no differences in the consistency of primary endpoints across investigational sites.

Secondary effectiveness endpoint

Twenty-four participants had localisation data available for analysis. *Table 5* on page 21 summarises the results on the localisation test showing the RMS error. The RMS error was significantly improved by 18.8 degrees in the bimodal condition (CI + NH) compared to the CI off condition (NH alone).

For coprimary effectiveness endpoint 2, the only baseline characteristic that affected the endpoint was baseline speech in noise for the spatial configuration $S0N_{NH}$ obtained in the CI off condition (NH alone).

Participants with poorer speech understanding in noise (> 1.2 dB) in the CI off condition demonstrated significantly more improvement in the bimodal listening condition (CI + NH).

There were no differences in the consistency of primary endpoints across investigational sites.

Secondary effectiveness endpoint

Twenty-four participants had localisation data available for analysis. Table 5 summarises the results on the localisation test showing the RMS error. The RMS error was significantly improved by 18.8 degrees in the bimodal condition (CI + NH) compared to the CI off condition (NH alone).

	CI off		CI on	
	N	Mean ± SD Median (IQR)	N	Mean ± SD Median (IQR)
Localisation (RMS error)	24	54.3 ± 16.8 52.2 (41.8, 63.0)	24	35.5 ± 16.7 33.0 (26.4, 44.5)

	Difference			
	N	Mean ± SD Median (IQR)	95% confidence interval	1-sided p-value
Localisation (RMS error)	24	-18.8 ± 16.1 -18.9 (-26.7, -11.8)	(-25.6, -12.0)	< 0.001

Table 5: *Localisation outcomes*

Patient reported outcomes

There were 14 participants who completed the SSQ preoperatively and 10 participants who completed it at 6 months postactivation. As shown in *Table 6* on page 22, there was a significant mean improvement on each subscale, with the biggest difference found on the Spatial Hearing subscale. Preoperative to postactivation mean differences were significant based on paired t-tests.

	Preoperative		6 months postactivation	
	N	Mean ± SD Median (IQR)	N	Mean ± SD Median (IQR)
Speech and hearing	14	4.26 ± 1.15 4.09 (3.40, 5.07)	10	6.18 ± 1.37 6.45 (5.50, 7.10)
Spatial hearing	14	3.19 ± 1.67 3.60 (1.70, 4.70)	10	5.66 ± 2.04 5.65 (5.20, 7.50)
Sound qualities	14	6.24 ± 1.44 6.00 (5.10, 7.39)	10	6.89 ± 1.51 6.50 (5.70, 7.20)
Total	14	4.56 ± 1.09 4.65 (3.90, 5.20)	10	6.25 ± 1.44 6.15 (5.40, 7.30)

	Difference			
	N	Mean ± SD Median (IQR)	95% confidence interval	1-sided p-value (Mean difference > 0)
Speech and hearing	10	2.09 ± 1.59 2.15 (1.00, 2.60)	(0.95, 3.23)	0.001
Spatial hearing	10	2.38 ± 1.34 2.70 (0.70, 3.30)	(1.42, 3.34)	< 0.001
Sound qualities	10	1.04 ± 1.24 1.05 (0.50, 1.70)	(0.15, 1.93)	0.013
Total	10	1.84 ± 1.17 1.80 (1.20, 2.50)	(1.00, 2.68)	< 0.001

Table 6: *Preoperative to 6 month postactivation statistical outcomes for the SSQ-49*

Iowa Tinnitus Handicap Questionnaire

Preoperative and postactivation data were available for 10 participants. At 6 months postoperative, 6 of the 9 (67%) participants with preoperative to postactivation scores reported an improvement in their tinnitus. At 12 months, 7/10 (70%) participants reported an improvement in their tinnitus.

Summary of effectiveness data - children 9 months to 12 months old

The following information summarises effectiveness data for children implanted with the Cochlear Nucleus 24 cochlear implant system.

Premarket study

In February 2020, Cochlear performed a systematic literature search in PubMed and EMBASE databases to assess effectiveness of implantation with a Cochlear Nucleus cochlear implant in children between 9 months and 12 months of age.

A multi-step literature search process resulted in a final set of studies (49 peer-reviewed articles) representing additional relevant research on cochlear implantation for patients less than 12 months old.

Effectiveness outcomes from the literature data support that implantation before 12 months of age supports paediatric cochlear implant recipients' improved speech and language development.

Post-approval study

Summary of the post-approval study methods

Cochlear performed a post-approval, prospectively-designed, retrospective analysis among 83 patients who were enrolled in the premarket study and 50 additional patients – data collected out to two years postoperatively – to gather effectiveness information on cochlear implantation in a population between 9 months and 12 months of age.

Summary of the post-approval study results

Primary effectiveness endpoint

The primary effectiveness endpoint of this post-approval study was to evaluate the performance of the cochlear implant on commonly validated and used parental questionnaires (Uhler & Gifford, 2014).

Available IT-MAIS and LittlEARS questionnaires data were collected preoperatively and postoperatively out to two years, or date of final protocol approval, for both sets of patients.

Infant Toddler Meaningful Auditory Integration Scale (IT-MAIS)

The IT-MAIS is a parental questionnaire designed to assess the auditory skill development in infants and toddlers. The questionnaire is administered by a clinician to parents/caregivers in an interview style. It consists of 10 probes designed to assess various auditory behaviours. Each probe has a possible score ranging from 0 (never) to 4 (always). Examples of additional follow up questions that can be asked by the clinician are provided for each probe in order to help determine an appropriate ranking for each probe. The questionnaire is scored out of a total of 40 possible points. The questionnaire can be administered before and after cochlear implantation.

LittlEARS

The LittlEARS is parental questionnaire designed to assess auditory skill development in infants and toddlers. It consists of 35 yes/no questions that ask parents/caregivers to identify whether their child exhibits a certain auditory response or behaviour. Examples are provided for each question. 1 point is provided for each auditory response that is answered as a "yes". The questionnaire is scored out of a total 35 possible points. The questionnaire can be administered before and after cochlear implantation.

Analysis was completed for two population groups:

1. Intent to Treat – consists of all participants who had an available baseline assessment.
2. Per Protocol – consists of only those participants with available assessments at both the preoperative and postoperative time points.

As shown in *Table 7* and *Table 8* on page 25, children in this post-approval study who underwent cochlear implantation between the ages of 9 months and 12 months demonstrated a significant improvement in auditory skill development compared to their preoperative baseline.

The tables provide LittlEARS and IT-MAIS scores reported as a percent correct. Children included in this post-approval study demonstrated significantly improved auditory skill development compared with their baseline performance, with children exhibiting an average improvement of 61.4% at ~9-month post-implantation compared with their preoperative scores.

Questionnaire	Preoperative		Postoperative	
	N	Mean ± SD[1] Median (min, max)	N	Mean ± SD Median (min, max)
LittlEARS	28	15.8 ± 19.1 5.7 (0, 54)	62	81.6 ± 20.3 88.6 (17, 100)
IT-MAIS	33	16.8 ± 16.3 12.5 (0, 78)	35	76.9 ± 21.7 85.0 (3, 100)

Questionnaire	Difference			
	N	Change Mean ± SD Median (min, max)	Change Mean (95% confidence interval)[2]	p-value[3]
LittlEARS	20	61.4 ± 27.4 67.1 (3, 100)	60.7 (38.4, 82.9)	< .0001
IT-MAIS	25	58.5 ± 23.9 62.5 (-3, 100)	55.4 (9.1, 101.8)	0.0308

Table 7: *Primary effectiveness endpoint - Intent to Treat*

Questionnaire	Preoperative		Postoperative	
	N	Mean ± SD Median (min, max)	N	Mean ± SD Median (min, max)
LittlEARS	20	15.7 ± 20.7 5.7 (0, 54)	20	77.1 ± 20.9 82.9 (31, 100)
IT-MAIS	25	15.7 ± 16.7 10.0 (0, 78)	25	74.2 ± 24.0 77.5 (3, 100)

Questionnaire	Difference			
	N	Change Mean ± SD Median (min, max)	Change Mean (95% confidence interval)	p-value
LittlEARS	20	61.4 ± 27.4 67.1 (3, 100)	61.4 (48.6, 74.3)	< .0001
IT-MAIS	25	58.5 ± 23.9 62.5 (-3, 100)	58.5 (48.6, 68.4)	< .0001

Table 8: *Primary effectiveness endpoint - Per Protocol*

1 SD = standard deviation.
2 The mean and confidence interval for change, and p-value, are based on multiple imputation.
3 The p-values are based on two-sided paired t-test.

When comparing outcomes of this post-approval study to published literature, please note the literature refers to hearing age – when the cochlear implant was activated – whereas Cochlear's dataset for IT-MAIS and LittlEARS questionnaires refers to time from cochlear implant surgery.

To appropriately compare Cochlear's dataset to published literature, postoperative performance by hearing age has been provided at various intervals, up to 24 months, as shown in *Table 9* on page 27 and *Table 10* on page 29.

Study	Preoperative score Mean (% correct)	Postoperative score Mean (% correct)	Change pre- to postoperative score Mean (% correct)
PAS Intent to Treat 9.0 mo-11.99 mo	5.5 (15.8%)	9.9 mo postop: 28.5 (81.6%)	9.9 mo: 21.5 (61.4%)
PAS Per Protocol 9.0 mo-11.99 mo	5.5 (15.7%)	9.0 mo postop: 27 (77.1%)	9.0 mo: 21.5 (61.4%)
May-Mederake et al. (2010) under 12 mo at implant	7 (20%)	6 mo hearing age: 17 (48.6%)	6 mo: 10 (28.6%)
		9 mo hearing age: 23 (65.7%)	8 mo: 14 (45.7%)
		12 mo hearing age: 28 (80%)	12 mo: 21 (60%)
		18 mo hearing age: 35 (100%)	18 mo: 28 (80%)
		24 mo hearing age: 35 (100%)	24 mo: 28 (80%)
May-Mederake et al. (2010) over 12 mo at implant	15 (42.8%)	6 mo hearing age: 21 (60%)	6 mo: 6 (17.2%)
		9 mo hearing age: 24 (68.6%)	8 mo: 9 (25.8%)
		12 mo hearing age: 27 (77.1%)	12 mo: 12 (34.3%)
		18 mo hearing age: 34 (97.1%)	18 mo: 19 (54.3%)
		24 mo hearing age: 35 (100%)	24 mo: 20 (57.2%)

Study	Preoperative score Mean (% correct)	Postoperative score Mean (% correct)	Change pre- to postoperative score Mean (% correct)
Connix et al. (2009) Normative values	NA	8 mo hearing age: 10-18 (28.6-51.4%)	NA
		9 mo hearing age: 12-20 (34.3-57.1%)	
		12 mo hearing age: 16-24 (45.7-68.6%)	
		6 mo hearing age: 8-9 (22.9%-25.7%)	
		18 mo hearing age: 23-30 (65.7%-85.7%)	
		24 mo hearing age: 26-34 (74.2%-97.1%)	

Table 9: *LittlEARS questionnaire pre- to postoperative change scores reported as a standard score and percent correct*

Study	Preoperative score Mean (% correct)	Postoperative score Mean (% correct)	Change pre- to postoperative score Mean (% correct)
PAS Intent to Treat 9.0 mo-11.99 mo	6.7 (16.8%)	7.7 mo postop: 30.7 (76.9%)	7.7 mo: 23.4 (58.5%)
PAS Per Protocol 9.0 mo-11.99 mo	6.3 (15.8%)	6.8 mo postop: 29.7 (74.3%)	6.8 mo: 23.4 (58.5%)
Waltzman & Roland (2005) CI under 12 mo	0.7 (1.8%)	6 mo hearing age: 30.4 (76%) (~25% above the mean for NH children at 6 mo)	6 mo: 29.7 (74.2%)
		12 mo hearing age: 34.8 (87%) (~7% above mean for NH children at 12 mo)	12 mo: 34.1 (85.3%)
Robbins et al (2004) CI Group 1: (12 mo-18 mo at implant)	~10%	3 mo hearing age: ~65% (outside normative range)	3 mo: 55%
		6 mo hearing age: ~80% (within normative range)	6 mo: 70%
		12 mo hearing age: ~85% (within normative range)	12 mo: 75%
Robbins et al (2004) CI Group 2: (19 mo-23 mo at implant)	~10%	3 mo hearing age: ~55% (outside normative range)	3 mo: 45%
		6 mo hearing age: ~65% (outside normative range)	6 mo: 55%
		12 mo hearing age: ~75% (within normative range)	12 mo: 65%
Zimmerman-Phillips, Robbins, & Osberger (2000) CI at 18 mo-20 mo	Average 1.4%	3 mo hearing age: 49.2%	3 mo: 47.8%

Study	Preoperative score Mean (% correct)	Postoperative score Mean (% correct)	Change pre- to postoperative score Mean (% correct)
Robbins et al (2004) Normative Values	NA	6 mo hearing age: ~20-50%	NA
		8 mo hearing age: ~40-65%	
		9 mo hearing age: ~45-70%	
		12 mo hearing age: ~50-75%	
		18 mo hearing age: ~70-85%	
		24 mo hearing age: ~75-95%	

Table 10: *: IT-MAIS questionnaire pre- to postoperative change scores reported as a standard score and percent correct*

A review of the post-approval study data collected reveals that IT-MAIS questionnaire data was obtained between 3 months and 17 months postoperatively, and LittlEARS questionnaire data was obtained between 3 months and 21 months postoperatively.

Neither questionnaire had data out to the 24 month postoperative time point. However, the available data still shows that children who receive a cochlear implant between 9 months and 12 months of age demonstrated improved auditory skill development, which is likely due to improved access to sound through their cochlear implant.

The numbers provided in *Table 9* on page 27 and *Table 10* on page 29 reflect the mean postoperative time point for each test and condition (Intent to Treat and Per Protocol) for ease of reporting purposes due to the number of available data points and the need to compare results of this study to the published literature.

Results of this study reveal IT-MAIS scores of:

- 76.9% at a mean of 7.7 months postoperatively for Intent to Treat
- 74.3% at a mean of 6.8 months postoperatively for Per Protocol.

These outcomes are aligned with reported scores:

- at 6 months hearing age for children implanted under age 12 months (76%) Waltzman & Roland (2005)
- at 6 months hearing age for children implanted at 12 months to 18 months (approximately 80%) Robbins et al. (2004).

Data for slightly older children implanted beyond 12 months of age are poorer compared to this dataset. Specifically, reported scores:

- at 6 months hearing age for children implanted between 19 months and 23 months (approximately 65%) Robbins et al. (2004)
- at 3 months hearing age for children implanted between 18 months and 20 months (approximately 49%) Zimmerman-Phillips, Robbins, & Osberger (2000).

When reviewing LittlEARS data, children in this study demonstrated a mean score of:

- 81.6% at a mean of 9.9 months postoperatively for Intent to Treat
- 77.1% at a mean of 9.0 months postoperatively for Per Protocol.

This data is slightly higher than scores reported by May-Mederake et al. (2010) who reported scores of approximately 65.7% and approximately 68% for children implanted under 12 months and over 12 months respectively, at a hearing age of 9 months.

Scores in this post-approval dataset better align with 12 month hearing age outcomes reported by May-Mederake et al. (2010), which demonstrated scores of approximately 80% for children implanted under 12 months of age, and approximately 77.1% for children implanted over 12 months of age.

Results of May-Mederake (2010) also showed that children who were implanted before 12 months of age had lower baseline scores, but demonstrated steeper trajectories, such as faster improvement and/or development, compared to children who were older at time of implantation (that is, over 12 months of age).

Data from this study showed that children who receive a cochlear implant between 9 and 12 months of age demonstrated improved auditory skill development as evidenced through these clinically relevant parental questionnaires.

Secondary effectiveness endpoint

The secondary effectiveness endpoint of this study was to evaluate the performance of the cochlear implant on aided audiometric thresholds.

Data collected demonstrated a significant improvement in audiometric thresholds following cochlear implantation. This demonstrates that use of the device provides improved access to auditory information.

In summary, this post-approval study provides a dataset of over 100 patients who received a Cochlear Nucleus cochlear implant between 9 months and 12 months of age. Data was collected preoperatively and postoperatively out to two years or date of final protocol approval.

The data provided continues to support the effectiveness of cochlear implantation with the Cochlear Nucleus device in infants as young as 9 months of age. Findings of this post-approval study demonstrate agreement with previously published literature (Connix et al., 2019; May-Mederake et al., 2010; Robbins et al., 2004; Waltzman & Roland, 2005; Zimmerman-Phillips, Robbins, & Osberger, 2000) for both effectiveness endpoints.

Study strengths and weaknesses

Strengths of the post-approval study include the use of data from multiple implanting centres over an 8-year period, which resulted in a large cohort of eligible participants and ears receiving treatment with a cochlear implant.

Weaknesses of this study include the retrospective nature of the study, which can limit the amount of data that is available for review in comparison to a prospective study. An additional limitation to consider is the selection of sites who participated in this study. Sites were specifically chosen to participate in the post-approval study due to their known use of cochlear implantation in children under 12 months of age.

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