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Multicenter Clinical Investigation of a New Active Osseointegrated Steady-State Implant System

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Objective: A new active transcutaneous bone conduction hearing implant system that uses piezoelectric technology has been developed: an active osseointegrated steady-state implant system (OSI). This was the first clinical investigation undertaken to demonstrate clinical performance, safety, and benefit of the new implant system.

Study Design and Setting: A multicenter prospective within-subject clinical investigation was conducted.

Patients: Fifty-one adult subjects with mixed and conductive hearing loss (MHL/CHL, $n=37$) and single-sided sensorineural deafness (SSD, $n=14$) were included.

Main Outcome Measure: Audiological evaluations included audiometric thresholds, speech recognition in noise, and quiet. Hearing and health-related patient-reported outcomes (PROs; health utilities index [HUI], abbreviated profile of hearing aid benefit [APHAB], and speech, spatial of qualities of hearing scale [SSQ]), daily use, surgical and safety parameters were collected.

Results: Intra- and postoperative complications were few. One implant was removed before activation due to post-

surgical infection. Compared with the preoperative softband tests, a significant improvement in speech recognition-in-noise was observed in the MHL/CHL group (-7.3 dB, $p \leq 0.0001$) and the SSD group (-8.1 dB, $p = 0.0008$). In quiet, word recognition improved in the MHL/CHL group, most markedly at lower intensity input of 50 dB SPL (26.7%, $p \leq 0.0001$). The results of all PROs showed a significant improvement with the new device compared with preoperative softband in the MHL/CHL group. In the SSD group significant improvements were observed in the APHAB and SSQ questionnaires.

Discussion: The results confirmed the clinical safety, performance, and benefit of this new treatment modality for subjects with CHL, MHL, and SSD. **Key Words:** Active transcutaneous bone conduction implant—Conductive and mixed hearing loss—Piezoelectric—Safety—Semi implantable hearing device—Single sided deafness—Speech recognition-in-noise—Speech recognition-in-quiet.

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Bone conduction hearing implants (BCHI) have been available for four decades and provide safe and effective aural rehabilitation for individuals with conductive (CHL) or mixed (MHL) hearing loss or single-sided sensorineural deafness (SSD). The original BCHI relied on percutaneous transmission of sound vibrations from an electromagnetic

transducer connected to a skin-penetrating abutment attached to an osseointegrated screw-shaped implant fixture. Thanks to the efficient transmission pathway and availability of a range of powerful sound processors, percutaneous implants still offer the broadest audiological fitting range and remain the most commonly used BCHI type. However, in recent years, there has been a rapid development of new implantable (1,2) and non-implantable (3,4) transcutaneous options for patients in need of a bone conduction hearing solution. Transcutaneous BCHIs have the benefit of reducing the risk of implant site infections compared with percutaneous ones and are perceived as a more esthetic option by some patients.

Available non-implantable and passive transcutaneous implantable systems all consist of a sound processor (SP) with an electromagnetic transducer that is retained on the skin using different methods. The efficiency of the sound

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vibrations to the skull bone in these systems is limited by attenuation in the intervening skin layer. The attenuation mainly affects high frequency sounds, parts of which can be compensated for by SP fitting algorithms. While transcutaneous passive systems provide satisfactory outcomes for many recipients (5), some patients require more amplification, e.g., to compensate for a greater sensorineural component of their hearing loss. An active transcutaneous BCI with an electromagnetic transducer implanted in the bone, thus avoiding the skin attenuation that is inherent to passive transcutaneous systems, has shown promising outcomes (6). However, due to the size of the electromagnetic transducer, a relatively large bone excavation is required to accommodate the implant (2), which may entail surgical challenges and/or anatomical restrictions.

A new active transcutaneous implant system has been developed that uses piezoelectric instead of electromagnetic stimulation: the active osseointegrated steady-state implant system (OSI). The piezoelectric element consists of a slim ceramic sandwich-structure, which is contained within a titanium casing that can be fixated on top of—instead of in—the bone, thus reducing surgical complexity. For efficient transmission of sound vibrations to the bone and the cochlea, the system uses the same osseointegrated platform as current percutaneous (7) and passive transcutaneous (8) BCIs.

This communication presents the results from the first clinical investigation conducted on the new piezoelectric system which aimed to demonstrate clinical safety, performance, and benefit in subjects with CHL, MHL, and SSD.

MATERIALS AND METHODS

This was an open, prospective, multicenter clinical investigation, conducted at five centers in Europe, Australia, and USA.

The investigation was approved by national competent authorities and local ethics committees as per local regulations and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (ISO14155:2011). The study was registered on ClinicalTrials.gov with identifier NCT03086135. Cochlear Bone Anchored Solutions AB (Mölnycke, Sweden) acted as study sponsor. Monitoring was performed by a contract research organization (Factory-CRO, Biltoven, The Netherlands) at European and Australian sites, and by Cochlear Americas (Denver, CO) at the US site. Study data management and statistical analyses were performed by independent data managers (Factory-CRO, Biltoven, The Netherlands) and biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden).

Inclusion and Exclusion Criteria

Adult subjects with CHL or MHL in the ear to be implanted (bone conduction thresholds with pure tone average [PTA4, mean of thresholds at 0.5, 1, 2, and 4 kHz] of ≤ 55 dB HL) or with SSD (air-conduction thresholds with PTA4 [mean of thresholds at 0.5, 1, 2, and 3 kHz] ≤ 20 dB HL in the contralateral ear) were included. Subject exclusion criteria were: uncontrolled diabetes; insufficient bone quality/quantity; use of ototoxic drugs that may affect hearing; previous/planned radiotherapy in the implant area; pregnancy or lactating; psychiatric/psychosomatic disorders; inability to follow investigational procedures; condition that could jeopardize osseointegration and/or wound healing (e.g., osteoporosis, psoriasis, long-term systemic use of corticosteroids) or may have an impact on the study outcome as judged by the investigator.

Investigational Device

The investigational device was the Cochlear™ Osia® System (Cochlear Ltd., Sydney, Australia). The system consists of an external SP (Osia Sound Processor) magnetically retained on the skin on top of an internal implant (OSI100 Implant) fixated to the temporal bone with an osseointegrated implant fixture (BI300 Implant, 3 mm or 4 mm) (Fig. 1). The SP was individually fitted

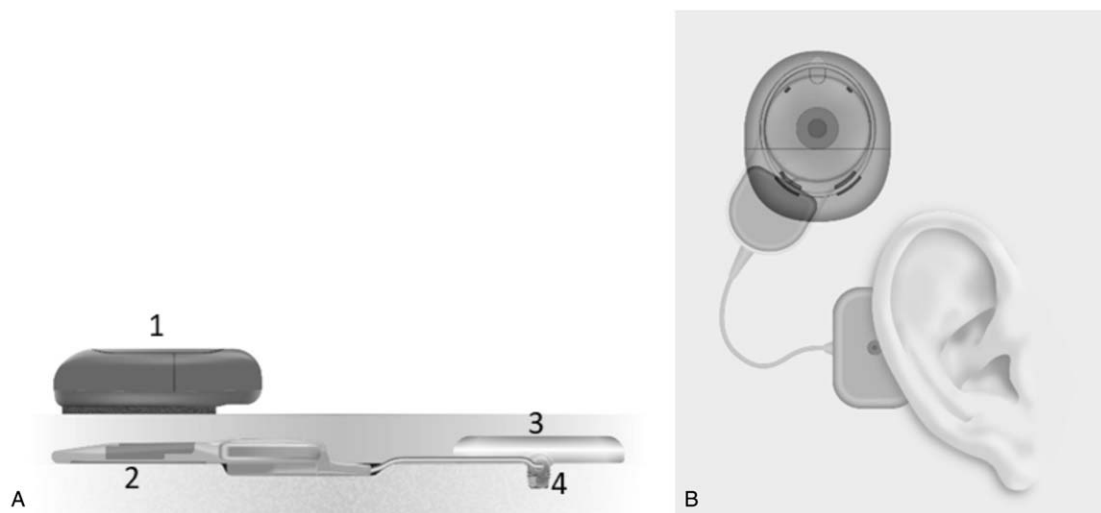


FIG. 1. A, Investigational device. An OTE (off-the-ear) button sound processor (1) captures and digitally processes sound and transmits power and digital information to the implant (2). The implant converts the digital information into an analogue electric signal, which is transmitted via a lead to the titanium-encased piezoelectric actuator located on the bone surface (3). The actuator converts the electric signal to vibrations that are transmitted to the mastoid bone through a small osseointegrated implant fixture (4). B, Position of the investigational device in relation to the outer ear.

to each subject's hearing loss using Osia Fitting Software 1.0 (Cochlear Ltd., Sydney, Australia). The implant was surgically implanted following the procedure described in the physician's guide provided by the manufacturer. Preoperative hearing evaluation was performed using a Cochlear™ Baha® BP110 Power SP on a Baha Softband fitted using Baha Fitting Software 4.0 (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden) to measure preoperative performance through bone conduction. The majority of the patients, especially the SSD patients, had had a default prolonged trial with a bone conduction transducer on a headband at home before, to experience bone conduction sound and to come to the decision to proceed for a bone conduction device.

Study Schedule and Assessments

At the screening and baseline visit, baseline characteristics and medical history were recorded, and complete audiograms were obtained. The subcutaneous parts of the investigational device were implanted unilaterally or bilaterally at a subsequent visit; for subjects implanted bilaterally, one side was preoperatively selected as test ear for efficacy evaluations. Postoperative visits were carried out 2 weeks (suture removal), 4 weeks (implant activation), 6 weeks, 3 months (primary efficacy evaluation), 6 months (primary safety evaluation), and 12 months (end of study) post-surgery.

Surgical study parameters included soft tissue thickness, soft tissue thinning at the SP location (mandated if thickness >6 mm), type of anesthesia, surgery time, any bone polishing/removal at the actuator site, and type/location of surgical incision.

Audiological assessments were performed unaided and with a SP on a softband at the baseline visit and with the investigational device at the time of activation (first fitting of SP on implant) and all subsequent visits. The tests were performed in a sound-insulated audiometric booth using calibrated equipment with the non-test ear double-blocked in case of normal or near-normal hearing or a large asymmetry between ears. During testing the SPs were set to omnidirectional mode. Thresholds audiometry was performed using narrow-band noise presented through a frontal speaker according to the so-called ascending or modified Hughson-Westlake method (9) at the following frequencies: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 kHz. Adaptive speech in noise tests were performed using the Matrix test in local language (10–14). Validated lists of phonetically balanced sentences were presented from the front and noise from behind. Noise was kept constant at presentation level of 65 dB SPL and speech level was adapted in predefined dB steps to establish the speech-to-noise ratio (SNR) providing 50% level of understanding. Speech recognition in quiet was measured using validated lists of monosyllabic words (15–19) presented from the front at 50, 65, and 80 dB SPL. Scores were recorded as % correctly repeated words for each presentation level.

Patient-reported outcomes (PROs) were collected at baseline, 3 and 12 months post-implantation using validated questionnaires: health utilities index (HUI3) (20), abbreviated profile of hearing aid benefit (APHAB) (21), and Speech, Spatial and Qualities of Hearing Scale (SSQ12) (22). HUI evaluates eight health-related quality of life (QoL) dimensions (vision, hearing, speech, walking/mobility, dexterity, self-care, emotion, cognition) and a comprehensive health state attribute. APHAB is a hearing-related PRO instrument, which includes four subscales (ease of communication, reverberation, background noise, aversiveness) and a global score. SSQ12 is a shorter (12-item) version of the original 49-item SSQ questionnaire (23) that measures the self-reported auditory disability in

everyday life across three subdomains (speech, spatial, and qualities of hearing).

Patient-reported daily usage and wearing comfort was collected at all study visits following activation. Daily use was reported as the average hours of daily SP use during the period preceding the visit. Comfort was assessed using a visual analog scale (0% no comfort at all, 100% most comfortable imaginable).

Safety parameters were recorded throughout the investigation.

The primary efficacy endpoints in the investigation were the improvements in 1) the mean free field thresholds (PTA4) and 2) speech reception threshold in noise (dB SNR) with the investigational device at 3 months compared with preoperative unaided hearing. Complete analysis of the primary and all secondary efficacy endpoints was performed with the data at 3 and 12 months. The primary safety endpoint was performed at 6 months and was repeated at the end of the study (12 mos).

Statistical Analyses

Statistical analyses were performed according to a predefined statistical analysis plan. Efficacy analyses were performed on the intention-to-treat (ITT) population (all implanted subjects) and per-protocol (PP) population (all subjects who completed the investigation without major protocol deviations). Safety analyses were performed on the safety population (all surgically treated subjects). The main efficacy analysis was performed on the whole subject cohort (total population). Primary and all secondary efficacy parameters were also analyzed for subjects with MHL/CHL and SSD, separately. Audiological results were analyzed against the subjects' unaided hearing and against the preoperative softband performance. Health-related QoL (HUI) with the investigational device was assessed against the subject's preoperative situation (with or without previous hearing amplification). Hearing-related PROs (APHAB, SSQ) were assessed against preoperative unaided hearing whether or not the subject used a hearing aid preoperatively.

All statistical analyses were paired and non-parametric. The Fisher's non-parametric permutation test for paired observations (24) was used for most of the paired analyses of continuous variables (when this test failed to approximate the *p*-value, Wilcoxon signed-rank test was used). The permutation tests used measured values and not only the ranks in the calculations. For paired analysis of dichotomous and ordered categorical variables the Sign test was used. All significance tests were two-sided and performed at the 0.05 significance level. Demographics, baseline characteristics, surgical variables, daily use, comfort, adverse events, and device deficiencies were only analyzed descriptively.

Sample size was calculated based on data from a pilot clinical investigation performed by the sponsor, where the investigational device was evaluated using a validated simulation model in subjects with CHL, MHL, and SSD currently using a percutaneous BCI. The within-subject standard deviations (SD) for the change from unaided to aided hearing for the primary efficacy variables PTA4 and SRT in noise were 9.5 and 11.3 dB SNR, respectively. Hence, to achieve 90% power to detect a clinically significant difference of 10 dB in the PTA4 and of 10 dB in the SRT in noise for the primary efficacy endpoints in the present investigation, 11 (PTA4) and 13 (SRT in noise) subjects were needed. For the primary safety endpoints 50 subjects, representing 25 patient-years at 6 months, was deemed acceptable (50 patient-years at 12 months). Hence, 50 evaluable subjects were needed in total, and each study arm (MHL/CHL and SSD) should include a minimum of 13 subjects.

RESULTS

Fifty-three (53) subjects were enrolled in the investigation. Fifty-one (51) subjects with CHL (n = 14), MHL (n = 23), or SSD (n = 14) were implanted with the investigational device (49 unilaterally, two bilaterally). Two subjects did not undergo surgery and were withdrawn from the investigation. All subjects were included in the ITT and safety populations and 43 in the PP population. Reasons for exclusion from the PP population were: early termination (n = 2), missed study visit (n = 1), audiological test not performed at one (n = 3) or more (n = 1) visits, audiological test incorrectly performed at one visit (n = 1). This report presents 3-month outcomes for the primary efficacy endpoint and 12-month outcomes for all safety and performance endpoints. Study results were similar for the ITT and PP population; hence, only results for the ITT population are presented. When considering multiplicity a False Discovery Rate (FDR) has been calculated and it is as low as 0.057 ($62 \times 0.05 / [62 - 8]$), which means that a fairly low number of 3.1 of the assumed 54 significances are false (unknown which ones). Therefore 50 to 51 out of the 54 significances are expected to be true significances (25).

Demographics and baseline characteristics are presented in Table 1 and Figure 2. Medical conditions and/or medication that may have a negative effect on healing and/or osseointegration were present during the study in 10 subjects: controlled diabetes (n = 5), HIV (n = 1), osteoporosis (n = 3), corticosteroid use (n = 1).

Surgery

All surgeries were performed under general anesthesia. The mean surgery time was 97.2 minutes (SD 27.8, range 60–197 min). Soft tissue thinning was performed in 10 subjects and (some degree of) bone polishing/removal in 42 subjects. C-shaped (n = 30), S-shaped (n = 19), curvilinear C-shaped (n = 1), or anterior slightly curved (n = 1) surgical incisions were used. A 4 mm implant fixture was used in 50 subjects and a 3 mm fixture in one subject.

Audiological Evaluation – Investigational Device Versus Unaided Hearing

Detailed audiometric results from the 12-month time-point are presented in Table 2 and Figure 3 for the total population and for the subgroups with MHL/CHL and SSD. The improvement in hearing thresholds at 12 months compared with the preoperative unaided hearing was statistically significant for the total population as well as for the two subgroups MHL/CHL and SSD at all tested frequencies (0.25–8 kHz) and PTA4, with the largest improvement at frequencies more than 3 kHz (Fig. 3A and B). Similarly, speech tests in quiet and noise showed statistically significant improvements compared with unaided hearing in all test conditions for the total population as well as for the two subgroups (Fig. 3C and D).

Investigational Device Versus Preoperative Device on Softband

Comparisons of the PTA4 in the aided condition with the investigational device at 12 months to preoperative performance with BP110 on softband also showed

TABLE 1. Demographics and baseline characteristics for the total subject population and for the subgroups of subjects with mixed (MHL) or conductive (CHL) hearing loss or single-sided sensorineural deafness (SSD)

Variable	Total (n = 51)	MHL/CHL (n = 37)	SSD (n = 14)
Age (yrs)	47.4 (SD 14.7, range 19.0–77.4)	47.7 (SD 15.0, range 19.0–77.4)	46.6 (SD 14.6, range 23.4–71.2)
Gender			
Male	27 (52.9%)	19 (51.4%)	8 (57.1%)
Female	24 (47.1%)	18 (48.6%)	6 (42.9%)
Nicotine use			
No	36 (70.6%)	26 (70.3%)	10 (71.4%)
Yes	15 (29.4%)	11 (29.7%)	4 (28.6%)
Type of hearing loss			
CHL	14 (27.5%)	14 (37.8%)	0 (0.0%)
MHL	23 (45.1%)	23 (62.2%)	0 (0.0%)
SSD	14 (27.5%)	0 (0.0%)	14 (100%)
Etiology			
(Chronic) ear infection	24 (47.1%)	24 (64.9%)	0 (0.0%)
Tumor	2 (3.9%)	0 (0.0%)	2 (14.3%)
Trauma	2 (3.9%)	0 (0.0%)	2 (14.3%)
Malformation	2 (3.9%)	2 (5.4%)	0 (0.0%)
Otosclerosis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	25 (49.0%)	15 (40.5%)	10 (71.4%)
Previous hearing aid use			
Yes	14 (27.5%)	13 (35.1%)	1 (7.1%)
No	37 (72.5%)	24 (64.9%)	13 (92.9%)

For categorical variables n (%) is presented. For continuous variables mean (SD, range) is presented.

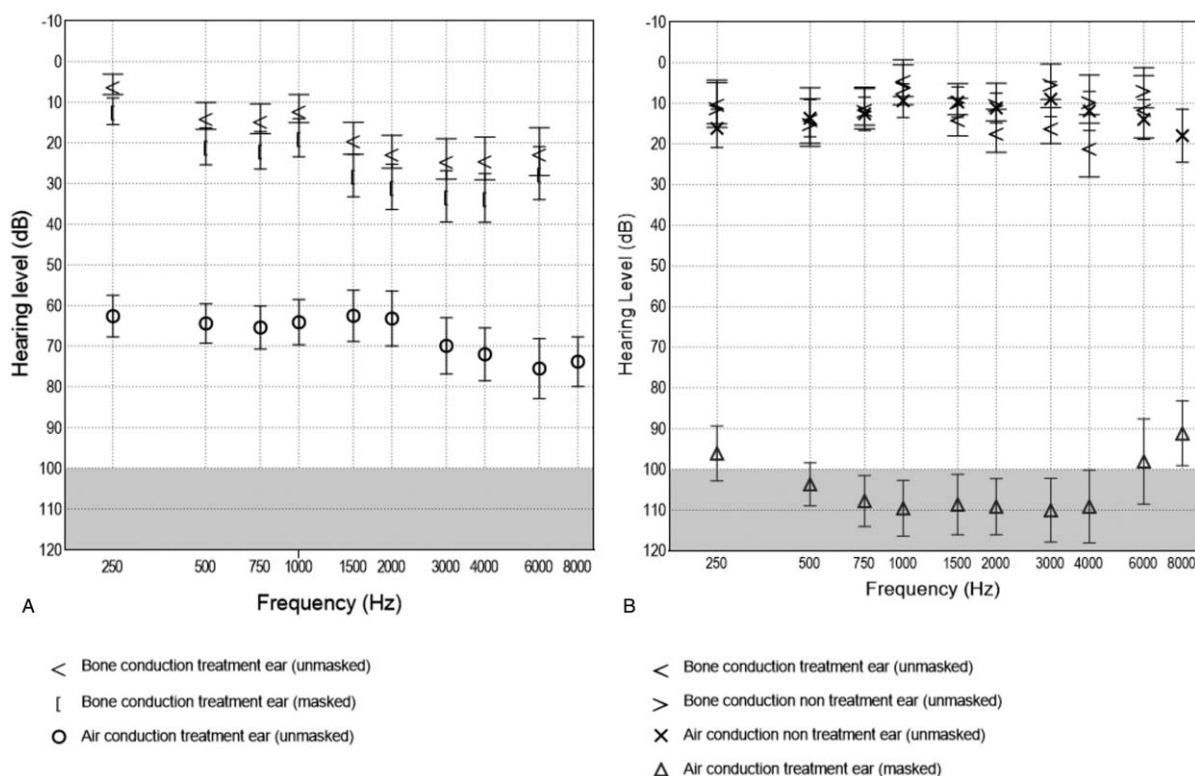


FIG. 2. Baseline audiograms for subjects with mixed or conductive hearing loss (A) or single-sided sensorineural deafness (B) (mean and 95% CI).

significant improvement for the total population (by – 7.9 dB [$p < 0.0001$]) as well as for the two subgroups. The differences were statistically significant at all individual frequencies except at 0.25 kHz for the total population and for subjects with MHL/CHL. Subjects with SSD experienced significantly improved free-field hearing thresholds compared with softband at frequencies from 1 kHz and above (Fig. 3A and B). At 12 months, the SRT in noise improved significantly compared with softband aided condition for the total population (–7.5 dB SNR, $p < 0.0001$) and for both subgroups; the results were numerically similar between groups (Fig. 3C). Out of the 14 patients previously using a conventional hearing aid, nine were tested for speech recognition in noise. Six out of these nine patients improved with the test device, whereas in three patients speech recognition in noise remained unchanged. The difference in word recognition in quiet compared with softband tests was not statistically significant for subjects with SSD. However, for the subjects with MHL/CHL the word recognition in quiet was significantly better with the test device (Fig. 3D).

Patient Reported Outcomes

The changes in the PRO results between the preoperative and 12 months postoperative conditions are presented in Table 3. HUI revealed statistically significant improvements in the hearing and speech attributes for the total population and for subjects with MHL/CHL. The changes

were not statistically significant in the SSD subgroup. Statistically significant improvements were obtained for the total population and for the two subgroups for all SSQ subdomains as well as for the APHAB global score and for all APHAB subscales except the aversiveness score. Although the number of patients previously using a conventional hearing aid was limited (14 out of 51), the results on the HUI and APHAB questionnaires within this subset of patients showed comparable benefit with the test device, compared with the other patients.

The mean daily use at the end of the study was 11.3 h/d (SD 3.6, range 4.0–18.0 h/d) for the total population and 12.2 h/d (SD 3.5, range 4.0–18.0 h/d) and 9.3 h/d (SD 3.0, range 4.0–15.0 h/d) for the subgroups MHL/CHL and SSD, respectively. The reported comfort level was 80.9% (SD: 16.2%, range 28.0–100.0%) for the total population, with no apparent differences between subgroups (MHL/CHL: 79.7%, SD: 15.0%, range 40.0–100.0%; SSD: 83.9%, SD: 19.2%, range 28.0–100.0%).

Evaluation of Safety

Postoperative healing was uneventful in all but one subject. Three days postoperatively, one subject developed an implant-site infection, which subsequently developed into skin necrosis and dehiscence. Despite attempts to salvage the implant through surgical debridement, rotational flap and antibiotic treatment, the implant had to be removed 55 days after implantation. This was the only procedure-related serious adverse event (SAE).

TABLE 2. Mean change in audiometric results from the preoperative unaided and softband test situation to the postoperative aided situation with the investigational device

Variable	Total Population		MHL/CHL		SSD	
	Mean Change from Unaided to 12 months Aided	Mean Change from Softband to 12 months Aided	Mean Change from Unaided to 12 months Aided	Mean Change from Softband to 12 months Aided	Mean Change from Unaided to 12 months Aided	Mean Change from Softband to 12 months Aided
Free-field hearing thresholds, PTA ^a (dB HL)	-30.4 (SD 8.9, range -58.5 to -11.3), n = 46, p ≤ 0.0001	-7.8 (SD 6.4, range -29.2 to 2.5), n = 46, p ≤ 0.0001	-30.9 (SD 10.2, range -58.5 to -11.3), n = 32, p ≤ 0.0001	-8.4 (SD 7.0, range -29.2 to 2.5), n = 32, p ≤ 0.0001	-29.3 (SD 5.2, range -36.3 to -20.0), n = 14, p ≤ 0.0001	-6.6 (SD 4.6, range -16.2 to -0.0), n = 14, p = 0.0001
Speech reception threshold in noise ^b (dB SNR)	-13.6 (SD 8.8, range -50.7 to 5.0), n = 45, p ≤ 0.0001	-7.5 (SD 8.0, range -25.3 to 18.2), n = 44, p ≤ 0.0001	-14.2 (SD 9.9, range -50.7 to 5.0), n = 31, p ≤ 0.0001	-7.3 (SD 8.7, range -25.3 to 18.2), n = 30, p ≤ 0.0001	-12.2 (SD 5.8, range -24.2 to -3.7), n = 14, p ≤ 0.0001	-8.1 (SD 6.3, range -20.7 to 6.3), n = 14, p = 0.0008
Word recognition score in quiet, 50 dB SPL (% correct)	57.8 (SD 24.9, range 5.0 to 92.0), n = 46, p ≤ 0.0001	20.7 (SD 29.5, range -42.0 to 90.0), n = 46, p ≤ 0.0001	54.1 (SD 25.4, range 5.0 to 90.0), n = 32, p ≤ 0.0001	26.7 (SD 28.4, range -13.0 to 90.0), n = 32, p ≤ 0.0001	66.4 (SD 22.3, range 20.0 to 92.0), n = 14, p ≤ 0.0001	6.86 (SD 28.2, range -42.0 to 44.0), n = 14, p = 0.37
Word recognition score in quiet, 65 dB SPL (% correct)	68.3 (SD 23.6, range 20.0 to 100.0), n = 46, p ≤ 0.0001	13.9 (SD 22.3, range -20.0 to 70.0), n = 46, p ≤ 0.0001	71.8 (SD 24.0, range 20.0 to 100.0), n = 32, p ≤ 0.0001	18.6 (SD 24.7, range -20.0 to 70.0), n = 32, p ≤ 0.0001	60.3 (SD 21.2, range 32.0 to 95.0), n = 14, p ≤ 0.0001	3.3 (SD 9.2, range -7.0 to 30.0), n = 14, p = 0.23
Word recognition score in quiet, 80 dB SPL (% correct)	32.7 (SD 32.4, range -6.0 to 100.0), n = 46, p ≤ 0.0001	3.6 (SD 10.4, range -10.0 to 45.0), n = 46, p = 0.041	41.9 (SD 33.4, range 0.0 to 100.0), n = 32, p ≤ 0.0001	5.66 (SD 11.8, range -10.0 to 45.0), n = 32, p = 0.0060	11.6 (SD 17.1, range -6.0 to 63.0), n = 14, p = 0.0068	-1.1 (SD 3.7, range -8.0 to 6.0), n = 14, p = 0.34

^aPure tone average, PTA4: Mean of hearing thresholds at 500, 1000, 2000 and 4000 Hz.

^bSpeech reception threshold (SRT) in noise, signal-to-noise ratio at which 50% of the words in a sentence are correctly repeated

The non-test ear double-blocked in case of normal or near-normal hearing or a large asymmetry between ears.

For PTA4 and SRT in noise, a negative value for the mean change indicates an improvement. MHL/CHL indicates mixed and conductive hearing loss; SSD, single-sided sensorineural deafness.

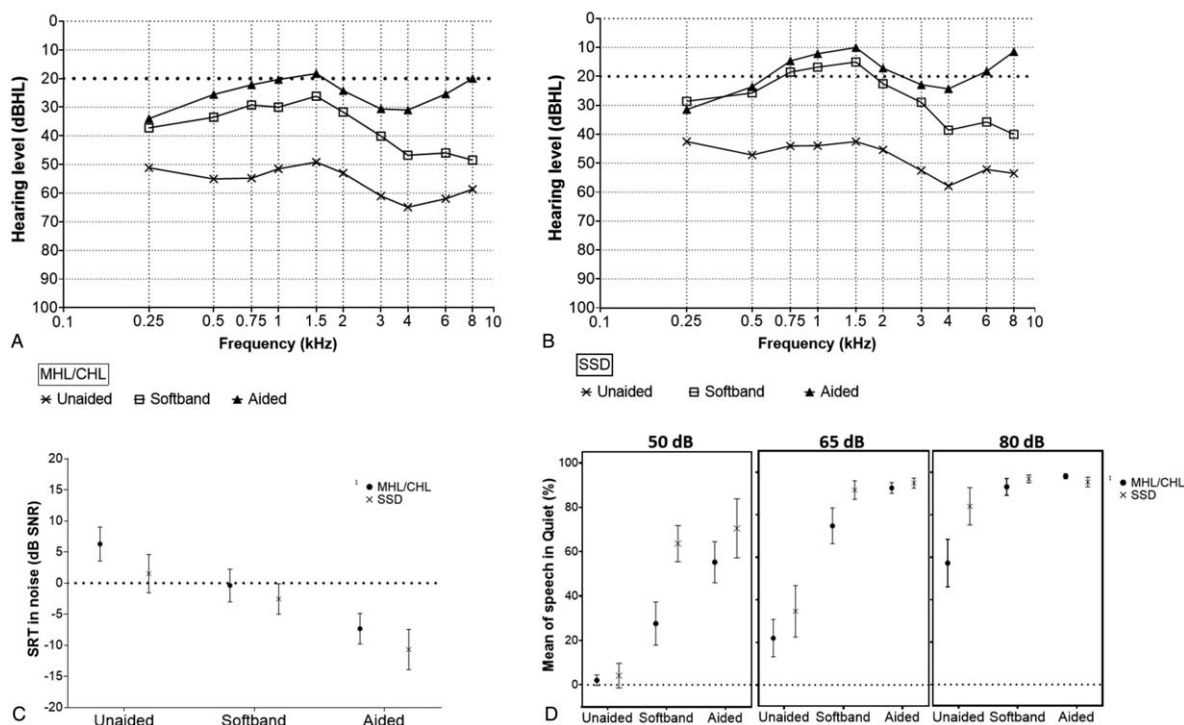


FIG. 3. Free-field thresholds measured preoperatively unaided (unaided) and with a sound processor on a softband (softband) and postoperatively with the investigational device 12 months after surgery (aided) for MHL/CHL subjects (A) and subjects with SSD (B). The dotted lines represent the upper limit for normal hearing. Speech reception threshold in noise displayed as signal-to-noise ratio (C) and word recognition score in quiet (D) for the three conditions for MHL/CHL and SSD subjects (mean and 95% CI). Note that the better hearing ear in asymmetric thresholds in MHL/CHL subjects and the normal hearing ear in SSD subjects was plugged and covered. MHL/CHL indicates mixed and conductive hearing loss; SSD, single-sided sensorineural deafness.

TABLE 3. Mean change in health utilities index (HUI3), abbreviated profile of hearing aid benefit (APHAB), and speech, spatial of qualities of hearing scale (SSQ) from the preoperative situation to the postoperative situation after 12 months

Variable	Total Population	MHL/CHL	SSD
HUI, hearing	0.149 (SD 0.300, range -0.290-0.710), n = 42, p = 0.0026	0.179 (SD 0.317, range -0.290-0.710), n = 30, p = 0.0046	0.073 (SD 0.248, range -0.290-0.540), n = 12, p = 0.31
HUI, speech	0.062 (SD 0.136, range -0.180-0.330), n = 48, p = 0.0024	0.073 (SD 0.137, range -0.180-0.330), n = 34, p = 0.0034	0.034 (SD 0.134, range -0.180-0.330), n = 14, p = 0.50
APHAB, ease of communication	24.0 (SD 19.1, range -12.8-65.7), n = 48, p ≤ 0.0001	29.8 (SD 18.0, range 1.8-65.7), n = 34, p ≤ 0.0001	9.80 (SD 13.9, range -12.8-37.7), n = 14, p = 0.022
APHAB, background noise	29.6 (SD 20.9, range -12.7-70.7), n = 48, p ≤ 0.0001	30.6 (SD 20.5, range -6.3-70.7), n = 34, p ≤ 0.0001	26.9 (SD 22.4, range -12.7-69.8), n = 14, p = 0.0009
APHAB, reverberation	25.4 (SD 25.8, range -33.5-74.8), n = 48, p ≤ 0.0001	30.6 (SD 26.0, range -33.5-74.8), n = 34, p ≤ 0.0001	12.8 (SD 21.2, range -23.0-54.2), n = 14, p = 0.040
APHAB, aversiveness	-3.58 (SD 24.6, range -82.2-43.2), n = 48, p = 0.32	-5.27 (SD 27.2, range -82.2; 43.2), n = 34, p = 0.27	0.533 (SD 16.8, range -18.5-41.3), n = 14, p = 0.92
APHAB, global	26.3 (SD 18.5, range -7.1-63.9), n = 48, p ≤ 0.0001	30.4 (SD 18.0, range 0.5-63.9), n = 34, p ≤ 0.0001	16.5 (SD 16.2, range -7.1-43.7), n = 14, p = 0.0032
SSQ, speech	2.94 (SD 1.94, range -2.00-6.44), n = 47, p ≤ 0.0001	3.17 (SD 1.95, range -2.00-5.94), n = 33, p ≤ 0.0001	2.42 (SD 1.89, range -0.12-6.44), n = 14, p = 0.0001
SSQ, spatial	2.95 (SD 2.52, range -2.70-8.23), n = 47, p ≤ 0.0001	2.85 (SD 2.50, range -2.70-8.23), n = 33, p ≤ 0.0001	3.18 (SD 2.66, range -1.37-7.67), n = 14, p = 0.0012
SSQ, qualities	2.13 (SD 2.30, range -2.85-6.78), n = 48 p ≤ 0.0001	2.36 (SD 2.26, range -2.85-6.78), n = 34, p ≤ 0.0001	1.57 (SD 2.37, range -2.75-6.00), n = 14, p = 0.030

Non-serious adverse events that were possibly, probably or causally related to the device or procedure were: pain (n=7), numbness (n=1), vertigo (n=3), swelling (n=3), tension implant site (n=1), warmth at the SP site (n=3), headache (n=3), hematoma/bleeding (n=2); all these events were resolved at the end of the investigation.

DISCUSSION

A new active transcutaneous BCHI for rehabilitation of patients with CHL or MHL and SSD was used and evaluated clinically for the first time in this international multicenter clinical investigation. Audiometry, patient-reported-outcomes, and safety analyses up to and including 12 months of follow-up suggest that the system is safe and performs as intended.

The investigational device introduces piezoelectric technology as a new way to deliver sound vibrations to the skull bone and to overcome the need for significant bone excavation that is associated with current implantable electromagnetic transducers (2). The flat piezoelectric actuator is placed on the bone surface, firmly attached to the same type of osseointegrated fixture used in percutaneous (7) and passive transcutaneous BCHIs (8). While no bone cavity is required, in the present investigation a certain degree of bone removal was performed in most subjects to create a flat bone surface underneath the actuator. Overall, surgical and postoperative complications were rare. Only one SAE related to the procedure was reported: implant explantation following a surgical site infection shortly after surgery.

Statistically significant and clinically relevant improvements were observed in psycho-acoustic assessments of hearing performance with the investigational device compared with the unaided condition and to a preoperative test situation with a SP on a softband. The softband test is a proxy for a passive transcutaneous BCHI, as previous studies have demonstrated similar audiological performance with the two systems (5,8). In the present study, improved audibility compared with softband was seen across the tested frequency range. While studies with passive transcutaneous systems have shown satisfactory outcomes in subjects with CHL, mild MHL, and SSD, the present study suggests that audibility can be improved further with an active system also for patients with a more moderate MHL. The difference in audibility compared with softband was greatest for the high frequencies, which confirms that more efficient high frequency sound transmission can be achieved with a transducer placed in direct contact with the bone compared with passive transcutaneous BCHIs that are limited by skin attenuation. Access to high frequency sounds is important for speech discrimination (26). SSD patients with a BCHI on the side of the deaf ear rely on transmission of sound vibrations to the contralateral functioning cochlea. Hence, for subjects with SSD, the BCHI needs to generate at least enough output to also compensate for the transcranial attenuation. This attenuation has been demonstrated to vary significantly between subjects and

between frequencies, and to be most prominent in the higher frequency range (27,28). In the present study, the improvement in audition was similar for subjects with MHL/CHL and SSD also in the high frequencies.

One listening situation that is known to be particularly challenging for hearing-impaired individuals is understanding speech in noisy environments (29). This study showed significant improvements in speech recognition in noise with the investigational device. The improvement was similar for subjects with MHL/CHL and SSD when compared with unaided hearing and to softband tests. It must be noted that for all the subjects the better hearing ear or normal hearing ear was plugged and covered. Therefore, especially for the SSD subjects the unaided condition does not reflect the daily situation. A comparison between the unaided and aided condition leaving the better or normal hearing ear open would lead to more improvement in the MHL/CHL subjects than in the SSD subjects. During the tests, the loudspeakers were configured to present speech from the front and noise from the back. Further tests should be considered to evaluate the performance of SSD patients in the more challenging situation where noise is presented to the side of the better ear and to the side of the active BCHI.

PROs showed clinically relevant subjective improvements in hearing benefit and hearing related QoL measures compared with the preoperative situation. In addition, in the MHL/CHL group of subjects an improvement in generic QoL was observed. The improvement in generic health-related QoL measured by HUI3 was primarily related to improved hearing; nine out of 10 subjects who were previously unable to hear what was said in a group conversation with at least three other people, were able to do so after implantation. An interesting observation was that the overall improvement in spatial hearing noted with the SSQ questionnaire was present also for subjects with SSD, whose ability to localize sounds is heavily impaired by their non-functioning cochlea.

The reported daily use and comfort level was high, suggesting good patient acceptance. At the end of the study the mean daily use in subjects with MHL/CHL and SSD was 12.2 and 9.3 h/d, respectively, which is significantly higher than the daily use reported in previous multicenter clinical investigations of a passive transcutaneous BCHI (5,8). A slightly lower daily use in subjects with SSD compared with MHL/CHL is expected, as subjects with SSD can benefit from normal hearing in one ear and thus may not require additional amplification in certain daily activities and/or (sound) environments.

While percutaneous BCHIs are highly effective, one drawback is that local adverse reactions and revision operations in the area of the skin-penetration may occur. Recent publications report a single mild skin reaction in 20 to 30% of the implants and no revision surgery in a 3 to 5 year follow-up (7,30). Transcutaneous systems have been shown to be associated with less skin complications (31). In this study, skin complications were rare. While the study was conducted in adults, it is anticipated that the

investigational device will be beneficial also in children who require a BCHI. Children appear to be more prone to skin-related problems with percutaneous devices and to implant loss due to trauma (32–34) compared with adults and, thus, may benefit greatly from a transcutaneous solution. Further investigations in the pediatric population would generate knowledge of clinical relevance.

In conclusion, the new active osseointegrated steady-state piezoelectric implant system showed significant improvements in hearing performance and subjective benefit both compared with unaided hearing and preoperative tests with a BCHI SP on a softband. The results confirm the clinical safety, performance, and benefit of this new treatment modality for subjects with CHL, MHL, and SSD.

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