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Premarket Approval Application

M040025/Module 3

Volume 2

Clinical Report

for

Esteem® Totally Implantable Hearing System

IDE G070162

August 1, 2009

October 21, 2009

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PMA Module 3 Volume 2

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Document Revision History

Revision	Date	Reason
Rev 01	August 1 2009	Original PMA Module 3 Submission
Rev 02	October 21, 2009	Update for Panel Briefing Pack

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1.0 Basic Information

IDE Number	G070162
Device Name	Esteem® Totally Implantable Hearing System
Indications for Use	The Esteem System is indicated for patients over the age of 18 with hearing loss that meets the following criteria: • Stable sensorineural hearing loss • Mild to severe hearing loss • Speech discrimination scores greater than or equal to 40%
Sponsor	Envoy Medical Corporation 5000 Township Parkway St Paul, MN 55110 Phone: (651) 361-8041 Fax: (651) 361-8001
Contacts:	Bud Horwath Regulatory Affairs

2.0 Study Progress

2.1 Overview

As reported here, there have been 60 subjects enrolled in the Esteem Pivotal Trial in the US, with 57 implanted and followed per the clinical protocol. (Note 5 additional subjects have been enrolled and implanted recently as part of the Continued Access Expansion approved by FDA, but have not reached any follow-up dates and are not included in this analysis.) Subject accountability and a current list of investigators and investigational sites for the Pivotal Trial are included in Table 1 and Table 2, respectively. Effectiveness and Safety objective results are presented in Section 4.

Overall, the Effectiveness metrics at 4 and 10-months post-activation indicate that the Esteem meets all Effectiveness Objectives by providing the same or better benefit as compared to the pre-implant aided condition (Hearing Aid). Esteem meets the superiority hypothesis over pre-implant aided condition for the primary effectiveness objective Speech Reception Threshold (SRT) at both the 4-month endpoint and 10-month follow-up.

The Safety metric of failures/revisions shows three failures/revisions for an incidence rate of 5.3%; two were caused by fibrotic tissue interference of the Driver-stapes movement and one was caused by fibrotic tissue interference of the Sensor-incus movement. The Safety

metric for cochlear function stability confirmed stable bone conduction for all subjects through the 4-month endpoint and 10-month follow-up. Six SADE were reported for an incidence rate of 10.5%.

Table 1: Pivotal Trial Subject Accountability-Single Procedure Outcomes*

Visit	Number of Subjects
Implanted	57
2 Months	57
4 Months	54[1]
10 Months	52[2]

Note 1: Three (3) subjects required revision prior to 4-month follow-up.

Note 2: Two additional subjects did not reach the 10-month follow-up: one was explanted due to incision breakdown and one had not yet reached the 10-month follow-up time interval.

*Single Procedure refers to all outcome endpoints reached for the original implant.

Table 2: Pivotal Trial Study Center Information

Site ID	Principal Investigator	Institution Address	Date of initial IRB Approval	Date 1st Subject Implanted	Number of Subjects Implanted
103	[redacted]	Southeastern ENT & Sinus Center, P.A. The Ear Center of Greensboro 1126 North Church Street, Suite 201 Greensboro, NC 27401	9 October 2007	30 January 2008	22
105	[redacted]	Shohet Ear Associates Medical Group, Inc. 446 Old Newport Blvd., Suite 100 Newport Beach, CA 92663	9 January 2008	14 April 2008	18
109	[redacted]	Lahey Clinic Department of Otolaryngology 41 Mall Road Burlington, MA 01805	9 January 2008	25 April 2008	17

2.2 Summary of Results

Table 3 summarizes the primary and secondary objectives for the Pivotal Trial to date. All data reported is current through July 27, 2009 and uses all subjects' single procedure outcomes.

Overall, the results of this trial through the 10-month follow-up indicate that the Esteem is safe and effective at treating subjects with sensorineural hearing loss. Audiological test results at the 4-month endpoint show Esteem is superior to the pre-implant aided condition in Speech Reception Threshold improvement and equal to or better than the pre-implant hearing aid in the other audiological test results. Safety and effectiveness results are stable and consistent through the 10-month follow-up.

Table 3: Summary of Clinical Results – Pivotal Trial

Clinical Protocol Objectives	4 Month Results	10 Month Results
Primary Performance Objective: • Speech Reception Threshold (SRT) at 4 months post-activation vs. pre-implanted aided condition	SRT • Average SRT improvement of 10.6 dB at 4 months compared to their baseline aided condition • SRT improvement met the Superiority hypotheses	SRT • Average SRT improvement of 11.4 dB at 10 months compared to their baseline aided condition • SRT improvement met the Superiority hypotheses
Primary Performance Objective • Word recognition score at 4 months post-activation vs. pre-implanted aided condition	Word Recognition Results at 50dB HL input condition • Average WRS was the same or better in 93% of subjects with the Esteem® at 4 months as compared to their pre-implant aided condition • Mean WRS improved a statistically significant 21.7% with Esteem over the pre-implant aided condition	Word Recognition Results at 50dB HL input condition • Average WRS was the same or better in 88% of subjects with the Esteem® at 10 months as compared to their pre-implant aided condition • Mean WRS improved a statistically significant 19.8% with Esteem over the pre-implant aided condition
Primary Safety Objective: • Serious Adverse Device Effects (SADE) • Incidence of Device Failures and Replacements	• SADE: 3 SADE for facial weakness/incision issues and 3 SADE for revision procedures have been reported/adjudicated to date. • Failures: Three (3) failures resulting in approved revisions were reported in 3 unique subjects prior to the 4-Month follow-up (5.3%).	• SADE: No additional SADE were reported between the 4-month and 10-month follow-up visits • Failures: No additional failures were reported between the 4-month and 10-month follow-up visits
Primary Safety Objective: • Bone conduction threshold at 4 months post-activation vs. pre-implant • Safety Algorithm for those that fail BC	Bone Conduction • Average 3 frequency (500, 1K, 2K) bone conduction change of 0.1 dB at 4 months vs. pre-implant. • Individually, no subjects (0) at 4 months had BC/SA change per the protocol criteria from pre-implant.	Bone Conduction • Average 3 frequency (500, 1K, 2K) bone conduction change of -0.8 dB at 10 months vs. pre-implant. • Individually, only one subject (1) at 10 months had BC/SA change per the protocol criteria from pre-implant at a single frequency (4 kHz).

Clinical Protocol Objectives	4 Month Results	10 Month Results
Secondary Performance Objective: • 3 frequency pure tone average (PTA) at 4 months post-activation vs. pre-implant unaided condition	Pure Tone Average • Average PTA was significantly better in 96% of subjects with the Esteem® at 4 months as compared to their pre-implant unaided condition. • Average PTA improved 27 dB at 4 months vs. pre-implant unaided condition.	Pure Tone Average • Average PTA was significantly better in 92% of subjects with the Esteem® at 10 months as compared to their pre-implant unaided condition. • Average PTA improved 27 dB at 10 months vs. pre-implant unaided condition.
Secondary Performance Objective: • Hearing in Noise Test QuickSIN results at 4 months post-activation vs. pre-implant aided	Average QuickSIN change vs. pre-implant aided condition: • Average QuickSIN change with Esteem vs. pre-implant aided condition was -1 at 4 months	Average QuickSIN change vs. pre-implant aided condition: • Average QuickSIN change with Esteem vs. pre-implant aided condition was 0 at 10 months
Secondary Performance Objective: • APHAB scores 4 months post-activation vs. pre-implant aided	APHAB: % Esteem of subjects equal to or better than the pre-implant HA • Total: 81% at 4 months • Esteem provided statistically significant mean benefit improvement in all APHAB subscales compared to the pre-implant conventional hearing aid	APHAB: % Esteem of subjects equal to or better than the pre-implant HA • Total: 79% at 10 months • Esteem provided statistically significant mean benefit improvement in all APHAB subscales compared to the pre-implant conventional hearing aid
Secondary Performance Objective: • Envoy Questionnaire scores 4 months post-activation vs. pre-implant aided	Envoy Questionnaire: % Esteem of subjects somewhat to much better than the pre-implant HA at 4 months • Clarity: 78% • Speech in Noise: 69% • Natural Voices: 76% • Understanding Conversation: 72% • More Active Lifestyle: 85%	Envoy Questionnaire: % Esteem of subjects somewhat to much better than the pre-implant HA at 10 months • Clarity: 79% • Speech in Noise: 71% • Natural Voices: 77% • Understanding Conversation: 67% • More Active Lifestyle: 87%

2.3 Device Accountability

A clinical implant kit is shipped for each scheduled implant. It typically includes 2 Sound Processors, 2 Sensors, 2 Drivers and multiple EnvoyCem and MedCem cements. Components not used are returned immediately after the implant, inspected and returned to inventory. Clinical sites do not inventory Esteem components. Currently there are no investigational devices at any of the clinical sites.

2.4 Study Protocol

The Clinical Trial Protocol is provided as Appendix 1 and summarized below:

2.4.1 Primary Objectives

1. Safety Objective – Serious Adverse Device Events

Objective: To determine the incidence of Serious Adverse Device Effects (SADE) and the incidence rate of device failures and replacements

Endpoint: The analysis of the incidence of SADE's and device failures and replacements through the 4–month and 10-month post-activation follow-up.

Hypotheses: This objective is to provide an accurate estimate of the SADE rate and device failure and replacement rate associated with the Esteem System. Therefore, no formal hypothesis tests will be conducted.

2. Efficacy Objective – Speech Reception Threshold

Objective: To demonstrate that the Esteem improves the speech threshold of sensitivity for hearing and identifying speech signals as well as or better than the pre-implant hearing aid (aided condition)

Endpoint: Comparison of the speech reception threshold (SRT) using the Esteem (4 months post-activation) as compared to the pre-implant aided condition.

Criterion for Non-Inferiority- The 95% Lower Confidence Bound (LBC) for the mean difference between the SRT at baseline versus four months ($\mu_{\text{Pre-implant aided} - \text{4 month}}$) is greater than or equal to -5 dB.

$$95\%\ \text{LCB for}\ \mu_{\text{Pre-implant aided} - \text{4 month}} \geq -5$$

Criterion for Superiority- The 95% Lower Confidence Bound (LCB) for the mean difference between the SRT at baseline versus four months ($\mu_{\text{Pre-implant aided} - \text{4 month}}$) is greater than +5 dB.

$$95\%\ \text{LCB for}\ \mu_{\text{Pre-implant aided} - \text{4 month}} > +5$$

3. Efficacy Objective – Word Recognition Score

Objective: To demonstrate that the Esteem at the 4 months post-activation visit is as effective as or better than the hearing aid for improving speech discrimination (intelligibility) as shown by the word recognition score at 50 dB.

Endpoint: Comparison of the word recognition score using the Esteem at 4 months post-activation compared to the pre-implant aided condition.

Hypotheses: This objective is to provide a comparison of the Word Recognition Scores at 50 dB associated with the Esteem versus the baseline aided condition. As a result, there is no formal hypothesis.

Statistical Analyses: The Word Recognition Scores will be compared using the Thornton and Raffin (1978) published upper and lower limits for various word lists based upon percentage scores. An analysis showing the % better than, % equal to, and % below the aided condition (HA) will be presented.

Reference: Thornton AR, Raffin MJ. Speech discrimination scores modeled as a binomial variable. J Speech Hear Res 1978; 21:507-18.

4. Safety Objective – Cochlear Stability

Objective: To demonstrate that the subject's cochlear function remains unchanged with the Esteem System as shown by comparison of the subject's pre-implant baseline Bone Conduction Threshold (BCT) vs. the subject's 4 and 10-months post-activation BCT.

Endpoint Analysis: Bone conduction will be measured with forehead probe placement. Stable results should be within ± 10 dB. The Safety Algorithm as described in the Clinical Protocol (Attachment C) will be used for any Bone Conduction results outside the stability range.

2.4.2 Secondary Objectives

1. Pure Tone Average (PTA)

Objective: To demonstrate that the Esteem System at the 4-month post-activation visit improves the 3-frequency (500, 1000, and 2000 Hz) pure tone average (PTA) when compared to the baseline unaided condition.

2. QuickSIN

Objective: To demonstrate that the Esteem System at the 4-months post-activation visit is as effective as or better than the hearing aid for improving speech discrimination (intelligibility) as shown by the QuickSIN (speech in noise) test results.

3. APHAB Quality of Life (QOL)

Objective: To show that the Esteem System improves Quality-of-Life when compared to the baseline aided condition as shown by APHAB scores

4. Esteem Questionnaire Quality of Life (QOL)

Objective: To gather subject feedback and comments on the use of the Esteem System relative to the pre-implant hearing aid (aided condition) as shown by the Esteem Questionnaire.

2.4.3 Inclusion/Exclusion Criteria

In order to be enrolled in this trial, the subjects had to meet all of the inclusion criteria and none of the exclusion criteria. The enrollment criteria are listed below.

2.4.3.1 Inclusion Criteria

- Subject is ≥ 18 years old
- Subject understands the nature of the procedure and has signed the Subject Informed Consent Form prior to the procedure
- Subject is willing and able to comply with specified follow-up evaluations and understands the audiological test procedures and use of the Esteem System.
- Subject has mild to severe sensorineural hearing loss between 500 and 4000 Hz in the ear to be implanted with pure tone air-conduction threshold levels within the limits of a Hearing Aid (HA) as follow:

Freq (Hz)	500	1000	2000	3000	4000
LL* (dB HL)	30	35	35	35	35
UL* (dB HL)	100	100	100	100	100

*LL = Lower Level; UL = Upper Level

- Subject's air-bone gap is no greater than 10 dB at 4 of the 5 following frequencies: 500, 1000, 2000, 3000 and 4000 Hz.
- Subject has an unaided maximum word recognition score of greater than or equal to 40% with recorded delivery using a phonetically balanced word list at SRT + 40 dB or at maximum tolerable presentation level.
- Subject is a current user of a properly functioning and appropriately fit hearing aid. This is defined as the subject has used this aid for at least four (4) hours (average) per day (in the ear to be implanted) for at least three (3) months for a new aid or one (1) month for an adjusted aid.
- Subject's hearing aid, in the ear to be implanted, shall appropriately fit optimally.

- Subject has normally functioning Eustachian tube
- Subject has normal tympanic membrane
- Subject has a normal middle ear anatomy
- Subject has adequate space for Esteem System implant determined via fine cut temporal bone CT scan
- Subject is a native speaker of the English language.
- Subject is a hearing aid user in the ear to be implanted.

2.4.3.2 Exclusion Criteria

- Subject has a history of post-adolescent chronic middle ear infections, inner ear disorders or recurring vertigo requiring treatment, disorders such as mastoiditis, Hydrops or Meniere's syndrome or disease
- Subject has a history of otitis externa or eczema for the outer ear canal and the investigator believes this will affect the Esteem System implantation
- Subject has cholesteatoma or destructive middle ear disease
- Subject has life expectancy of < two (2) years due to other medical conditions
- Subject has retrocochlear or central auditory disorders
- Subject is known to be suffering from any psychological, developmental, physical, or emotional disorder that the investigator feels would interfere with the surgery or follow-up testing
- Subject has a known history of fluctuating air conduction and/or bone conduction hearing loss over a one-year period of 15 dB in either direction at 2 or more frequencies (from 500 – 4000 Hz)
- Subject has sudden hearing loss due to unknown cause
- Subject has a history of disabling tinnitus, defined as tinnitus which required treatment.
- Subject is unable to adequately perform audiological testing
- Subject has a medical condition or undergoing a treatment that may affect healing and the investigator does not believe the subject is a good candidate for the trial.

- Subject has diabetes that is not well controlled with medication or diet and the investigator does not believe in his best medical judgment that the subject would be a good candidate for the trial
- Subject is pregnant at the time of device implant
- Subject has a history of keloid formation
- Subject has known hypersensitivity to silicone rubber, polyurethane, stainless steel, titanium and/or gold

2.4.4 Sample Size Statistical Considerations

Originally, a minimum sample size of 40 subjects was determined in order to provide adequate power for testing the primary effectiveness objective of Speech Reception Threshold (SRT). Calculations were based on a one-sample one-sided t-test for a mean in a non-inferiority framework and were performed with SAS version 9.2

Based on initial human data, it was assumed that the Esteem System has a true mean improvement of 5 dB over subject's hearing aid with a standard deviation of 10.5. A superiority margin of 5 dB was used as this is the limit of the testing method and is therefore considered the minimum clinically relevant difference. With these assumptions, and a one-sided 0.05 alpha level, a minimum of 40 subjects would provide greater than 80% power for acceptance of the hypothesis of superiority of the device, as recommended in the FDA Implantable Middle Ear Hearing Device Guidance (August 1, 2002) document.

After consultation with FDA, a minimum sample size of 50 subjects was agreed upon in order to increase confidence in the safety results of the clinical study, including device failure/revision rate and cochlear function stability.

2.4.5 Esteem Implant Procedure

All subjects were anesthetized. A standard mastoidectomy was performed followed by the opening of the facial recess to expose the middle ear. The incus bone was separated from the stapes bone and subsequently 2-3 mm of the long process of the incus was resected. A shallow cavity was drilled in the temporal bone for the Sound Processor to reside. The Driver and the Sensor were attached to the stapes and the incus respectively using cement. Intra-operative testing was performed to verify that the performance of the Driver and Sensor met the pre-determined requirements. The Driver and Sensor were attached to the Sound Processor and tested to verify the connection. The Sound Processor was turned off prior to the subject leaving the operating room. The device was turned on approximately 8 weeks later.

The only difference in the implant procedure for this study versus the previous Esteem clinical trial was that the Driver to stapes connection was made in two steps. First, after resection of the incus, the stapes was pre-coated with EnvoyCem. This pre-coating step allows proper and complete coverage of the EnvoyCem bond to the stapes. After a short curing time, the Driver tip is then bonded to the pre-coated stapes with a second application of EnvoyCem.

As mentioned above, a previous Esteem clinical trial was conducted under IDE G000321. The results of this previous trial included a relatively high revision rate due to Driver to stapes connection issues shortly after implant. This finding lead to the updated implant procedure described above that was used in this Pivotal Clinical Study. In addition, the Esteem design was enhanced with relatively minor feature and performance improvements. A summary comparison of the two clinical trials is provided as Appendix 2 for reference only. The most significant and relevant aspect of the ongoing previous G000321 clinical trial is that the clinical outcomes are consistent and stable over time through the 4-year follow-up.

3.0 Subject Population

3.1 Subject Demographics

Of the 57 implanted subjects with available baseline data, 98% (56) were Caucasian. At the time of study enrollment 25% (14) were retired, 9% (5) worked part time, and 51% (29) worked full time. Of the subjects implanted, 38 (67%) were male and 19 (33)% were female. The average age of the subjects was 52.9 years (SD=15.8).

Table 4 provides additional details on the subject demographics.

Table 4: Subject Demographics

Demographics	Mean ± sd n (min, max)
Age (years)	52.9 ± 15.8 57 (18.0, 77.2)
	N/Total (%)
Gender	
Male	38/57 (66.7%)
Female	19/57 (33.3%)
Race/Ethnicity	
White/Caucasian	56/57 (98.2%)
Black/Non-Hispanic	0/57 (0.0%)
Hispanic	0/57 (0.0%)
Asian	1/57 (1.8%)
Work Status	
Full Time Employee	29/57 (50.9%)
Part Time Employee	5/57 (8.8%)
Retired	14/57 (24.6%)
Unemployed	4/57 (7.0%)
Other	5/57 (8.8%)

3.2 Medical History

Investigators were requested to complete a medical history of each subject before enrollment into the study. Table 5 summarizes this information.

Table 5: Medical History

Condition	N/Total (%)	Ongoing at time of procedure N/Total(%)
Family History of Hearing Loss		
Yes	41/57 (71.9%)	NA
No	14/57 (24.6%)	
Unknown	2/57 (3.5%)	
Prior Ear Surgery		
Yes	2/57 (3.5%)	NA
No	55/57 (96.5%)	
Otitis Media		
Yes	17/57 (31.6%)	0/17 (0.0%)
No	39/57 (68.4%)	17/17 (100.0%)
External Otitis		
Yes	4/57 (7.0%)	0/4 (0.0%)
No	53/57 (93.0%)	4/4 (100.0%)
Ototoxicity		
Yes	1/57 (1.8%)	0/1 (0.0%)
No	56/57 (98.2%)	1/1 (100.0%)
Head Trauma		
Yes	4/57 (7.0%)	0/4 (0.0%)
No	53/57 (93.0%)	4/4 (100.0%)
Labyrinthitis		
Yes	0/57 (0.0%)	NA
No	57/57 (100.0%)	
Mastoiditis		
Yes	0/57 (0.0%)	NA
No	57/57 (100.0%)	
Post-adolescent chronic middle ear infections		
Yes	0/57 (0.0%)	NA
No	57/57 (100.0%)	
Vertigo, requiring treatment		
Yes	2/57 (3.5%)	0/2 (0.0%)
No	55/57 (96.5%)	2/2 (100.0%)
Tinnitus, requiring treatment		
Yes	1/57 (1.8%)	1/1 (100.0%)
No	56/57 (98.2%)	0/1 (0.0%)

Condition	N/Total (%)	Ongoing at time of procedure N/Total(%)
Tinnitus, not requiring treatment		
Yes	30/57 (54.4%)	16/30 (53.3%)
No	26/57 (45.6%)	14/30 (46.7%)
Fullness or plugging of ear(s)		
Yes	9/57 (15.8%)	4/9 (44.4%)
No	48/57 (84.2%)	5/9 (55.6%)
Otosclerosis		
Yes	0/57 (0.0%)	NA
No	57/57 (100.0%)	
Cholesteatoma		
Yes	0/57 (0.0%)	NA
No	57/57 (100.0%)	
Eczema / Psoriasis (head or neck)		
Yes	0/57 (0.0%)	NA
No	57/57 (100.0%)	
Circulation Disorder		
Yes	4/57 (7.0%)	2/4 (50.0%)
No	53/57 (93.0%)	2/4 (50.0%)
Diabetes Mellitus		
Yes	5/57 (8.8%)	4/5 (80.0%)
No	52/57 (91.2%)	1/5 (20.0%)
Blood/Bleeding Disorder (anemia)		
Yes	2/57 (3.5%)	1/2 (50.0%)
No	55/57 (96.5%)	1/2 (50.0%)
Speech impediment / Impairment		
Yes	2/57 (3.5%)	1/2 (50.0%)
No	55/57 (96.5%)	1/2 (50.0%)
Depression		
Yes	11/57 (19.3%)	10/11 (90.9%)
No	46/57 (80.7%)	1/11 (9.1%)
Nasal Surgery		
Yes	12/57 (21.1%)	0/12 (0.0%)
No	45/57 (78.9%)	12/12 (100.0%)
Seasonal Allergies, requiring treatment		
Yes	13/57 (22.8%)	9/13 (69.2%)
No	44/57 (77.2%)	4/13 (30.8%)

3.3 Audiological History

The great majority of the subjects (54, 95%) suffered a gradual hearing loss that was diagnosed at an average age of 32.5 years. The degree of hearing loss (based on PTA) was mild in 3 subjects, moderate in 18 subjects, moderately severe in 26 subjects and severe in 10 subjects. Table 6 summarizes the subjects' audiological history.

Table 6: Audiological History

Audiological History	Mean ± sd n (min, max)
Age (years) of hearing loss realization	30.0 ± 20.0 57 (0.0, 67.0)
Age (years) of hearing loss diagnosis	32.5 ± 21.0 57 (1.0, 66.0)
	N/Total (%)
Onset of hearing loss:	
Sudden	3/57 (5.3%)
Gradual	54/57 (94.7%)
Cause of hearing loss[1]:	
Unknown	29/57 (50.9%)
Familial/Genetic	11/57 (19.3%)
Noise exposure	11/57 (19.3%)
Infection	3/57 (5.3%)
Congenital	2/57 (3.5%)
Fever	2/57 (3.5%)
Drug toxicity	1/57 (1.8%)
Usher's Syndrome	1/57 (1.8%)
Degree of hearing loss (implanted ear):	
Mild (PTA ≤ 40 dB)	3/57 (5.3%)
Moderate (41 dB < PTA ≤ 55 dB)	18/57 (31.6%)
Moderate Severe (56 dB < PTA ≤ 70 dB)	26/57 (45.6%)
Severe (PTA > 71 dB)	10/57 (17.6%)

[1]Causes listed are not mutually exclusive. Subjects may report more than one possible cause.

3.4 Hearing Aid Use

All 57 (100%) subjects were current users of a hearing aid with average usage time over 13 years. Of the subjects implanted, 49 (86%) subjects used hearing aids in both ears. General information regarding the subjects' hearing aid use is summarized in Table 7.

Table 7: Hearing Aid Use

Condition	Implanted Ear mean ± sd n (min, max)	Non-implanted Ear mean ± sd n (min, max)
Time using a hearing aid (years)	13.7 ± 10.1 57 (0.4, 37.8)	12.7 ± 9.6 50 (0.2, 34.9)
Time using this particular hearing aid (years)	3.7 ± 3.8 57 (-0.1, 22.8)	3.4 ± 3.8 49 (-0.1, 22.8)
	Implanted Ear N/Total (%)	Non-implanted Ear N/Total (%)
Style of hearing aid		
Behind-the-ear	23/57 (40.4%)	21/49 (42.9%)
In-the-ear	7/57 (12.3%)	7/49 (14.3%)
In-the-canal	14/57 (24.6%)	11/49 (22.4%)
Completely-in-the-canal	13/57 (22.8%)	10/49 (20.4%)

4.0 Discussion of Results

4.1 Reporting Formats

Data are reported in Sections 4.2 and 4.3 in the following format:

- All subjects: Single Procedure Outcomes for the 4-month and 10-month endpoints with mean difference and standard error ($\mu \pm SE$) and 95% confidence interval range (x, y) as appropriate.
- Revised subjects are included in the reports of primary outcomes up to the time of revision. After revision, they are reported separately from the single-procedure subjects. For this report, only one revision subject has post-revision follow-up data as discussed in Section 4.3.

Data analyses by cohort are discussed in Section 4.4 and provided in Appendix 3. Cohorts include Protocol Deviation Subjects, Balance of Subjects and All Subjects. In addition, a pooling analysis is included that supports the inclusion of all subjects in the analyses of safety and effectiveness data.

A detailed listing of Subject Status is provided in Appendix 4.

4.2 Effectiveness Endpoints

4.2.1 SRT

Objective: A Primary Effectiveness Objective identified in the clinical protocol is that the Esteem System would improve the speech threshold of sensitivity for hearing and identifying speech signals as well as or better than the pre-implant hearing aid (aided condition).

Endpoint: The endpoint is a comparison of the speech reception threshold (SRT) using the Esteem System at 4-months post activation as compared to the pre-implant aided condition.

Hypotheses: Both non-inferiority and superiority hypotheses will be evaluated.

Criterion for Non-Inferiority- The 95% Lower Confidence Bound (LBC) for the mean difference between the SRT at baseline versus four months ($\mu_{\text{Pre-implant aided} - \text{4 month}}$) is greater than or equal to -5 dB.

$$95\%\ \text{LCB for}\ \mu_{\text{Pre-implant aided} - \text{4 month}} > -5$$

Criterion for Superiority- The 95% Lower Confidence Bound (LCB) for the mean difference between the SRT at baseline versus four months ($\mu_{\text{Pre-implant aided} - \text{4 month}}$) is greater than +5 dB.

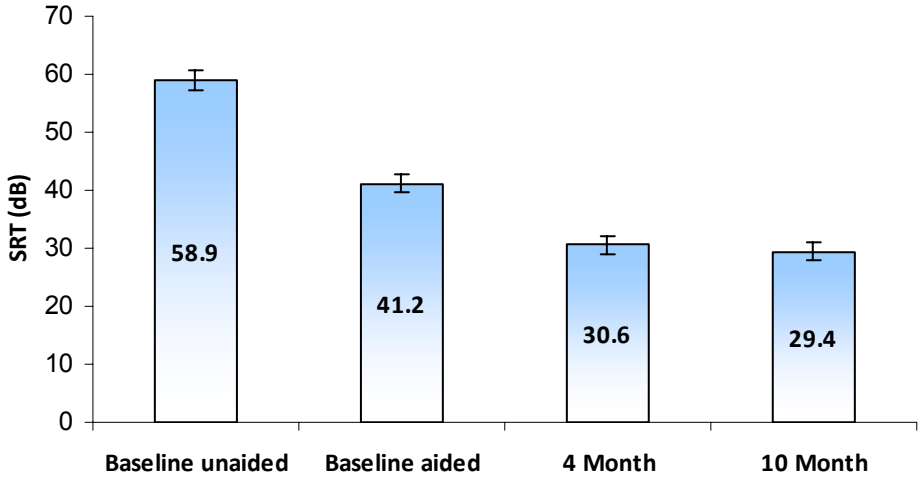
$$95\%\ \text{LCB for}\ \mu_{\text{Pre-implant aided} - \text{4 month}} > +5$$

Data: All Subjects, Single Procedure Outcomes
Overall mean SRT scores showed significant improvement compared with pre-implant baseline aided, as follows.

- 4 Months: 10.6 ± 1.8 dB (CI 7.1, 14.2)
- 10 Months: 11.4 ± 1.8 dB (CI 7.7, 15.2)

Table 8: Speech Reception Thresholds

Follow-up Period	SRT (in dB) mean ± se n (min, max)		
	Pre-Implant Aided	4-Month	10-Month
	41.2 ± 1.5 57 (38.3, 44.1)	30.6 ± 1.6 54 (27.4, 33.7)	29.4 ± 1.6 52 (26.1, 32.7)
Mean Improvement (95% CI)	NA	10.6 ± 1.8 (7.1, 14.2)	11.4 ± 1.8 (7.7, 15.2)



SRT in dB (mean ± se)

Analysis: The analysis of the non-inferiority and superiority hypotheses verifies that the Esteem is superior to the pre-implant aided condition (hearing aid). The 95% Lower Confidence Bound for the mean difference between Esteem and baseline aided condition as shown above is greater than 5 dB for both 4-month and 10-month follow-up (7.1 and 7.7 dB, respectively) meeting the superiority criteria ($p \leq 0.001$).

4.2.2 Word Recognition Score (WRS) at 50 dB versus pre-implant aided hearing

Objective: A Primary Effectiveness Objective identified in the IDE protocol is that the Esteem System would improve speech discrimination (intelligibility) as effectively as or better than the pre-implant hearing aid (aided condition).

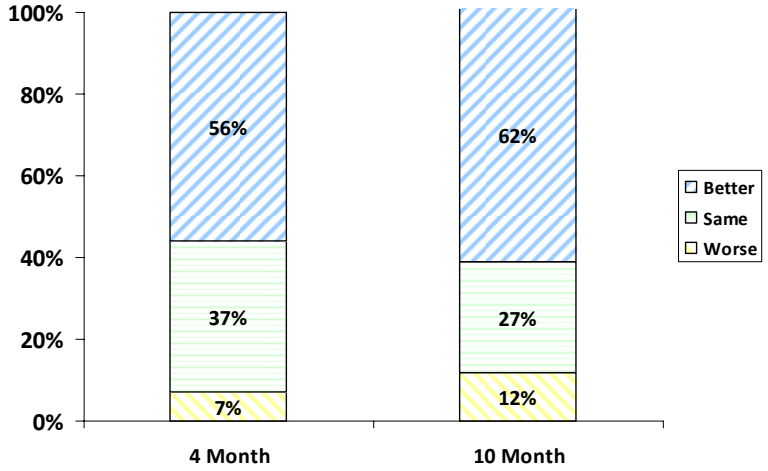
Endpoint: The endpoint is a comparison of the WRS at 50 dB results using the Esteem System as compared to the pre-implant aided condition.

Statistical Analyses: The Word Recognition Scores will be compared using the Thornton and Raffin (1978) published upper and lower limits for various word lists based upon percentage scores. An analysis showing the % better than, % equal to, and % below the aided condition (HA) will be presented. Reference: Thornton AR, Raffin MJ. Speech discrimination scores modeled as a binomial variable. J Speech Hear Res 1978; 21:507-18.

Data: Word Recognition Scores were measured prior to the Esteem implant procedure and at each of the follow-up evaluations after implantation of the device. Table 9 below displays the results of the 4 and 10-month follow-up endpoint. The Esteem improves word recognition scores in 56% of the subjects at 4-month follow-up and 62% at 10 months as compared to the pre-implant aided condition.

Table 9: Word Recognition Scores (WRS) at 50 dB

	All Subjects	
	4 Month N=54	10 Month N=52
% Better HA	30/54 (56%)	32/52 (62%)
% = HA	20/54 (37%)	14/52 (27%)
% Below HA	4/54 (7%)	6/52 (12%)



In addition, the mean individual change in WRS was calculated comparing the Esteem to the pre-implant aided condition on a per subject basis. The results shown below indicate an increased improvement in WRS with Esteem. Since the lower bound of the 95% confidence interval is far above zero, this individual subject analysis of WRS mean change demonstrates that the Esteem is statistically superior to the pre-implant hearing aid ($p<0.05$).

WRS Mean Improvement with Esteem versus Pre-implant Aided

Follow-up	Mean ± SE (95% CI)
4-Month	21.7 ± 4.2 (13.3, 30.1)
10-Month	19.8 ± 4.3 (11.1, 28.4)

Analysis: In accordance with the Thornton and Raffin model analysis, at 4 months Esteem is superior to the pre-implant hearing aid in 56% of the subjects and is better than or equal to the hearing aid in 93% of subjects. The 10-month follow-up data demonstrated similar improvement with Esteem with 62% of subjects having WRS superior to the pre-implant hearing aid and 88% of subjects having WRS better than or equal to the pre-implant hearing aid. In addition, the improvement in mean WRS with Esteem further demonstrates that the Esteem is statistically superior to the pre-implant hearing aid at 4 and 10-month follow-up.

4.2.3 Pure Tone Average (PTA) Compared to Baseline Unaided Condition

Objective: A Secondary Effectiveness Objective identified in the IDE protocol is that the Esteem System will improve the pre-implant unaided condition for the 3-frequency (500, 1000 and 2000 Hz) PTA.

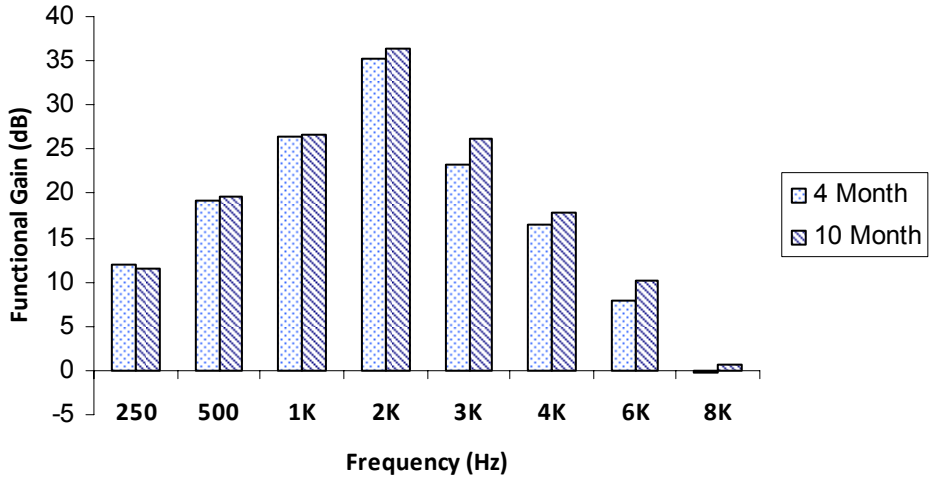
Endpoint: The endpoint is a comparison of the PTA using the Esteem System to the pre-implant unaided condition.

Data: For each subject, the 4-month and 10-month post-activation Air Conduction endpoint data was compared to the baseline unaided data at various frequencies (Hz). The difference between this data is the amount of functional benefit provided by the Esteem. Table 10 below details the mean AC change and the number of subjects in each functional benefit group at each frequency.

Table 10: Air Conduction Threshold Change at 4 & 10 Months

	Air Conduction Thresholds 4 Months N=54								
	250	500	1000	2000	3000	4000	6000	8000	PTA
Mean delta from Baseline ± SE (CI range)	12 ± 2 (16, 8)	19 ± 2 (22, 16)	26 ± 2 (30, 23)	35 ± 2 (39, 32)	23 ± 2 (27, 19)	17 ± 2 (21, 12)	8 ± 2 (12, 4)	0 ± 2 (5, -5)	27 ± 1 (30, 24)
% Greater than +10 dB	25/54 (46%)	38/54 (70%)	49/54 (91%)	51/54 (94%)	44/54 (81%)	35/54 (65%)	23/54 (43%)	8/54 (15%)	52/54 (96%)
% Stable (±10 dB)	28/54 (52%)	16/54 (30%)	5/54 (9%)	3/54 (6%)	8/54 (15%)	16/54 (30%)	20/54 (37%)	23/54 (43%)	2/54 (4%)
% Less than -10 dB	1/54 (2%)	0/54 (0%)	0/54 (0%)	0/54 (0%)	1/54 (2%)	2/54 (4%)	6/54 (11%)	7/54 (13%)	0/54 (0%)
% No Response	0/54 (0%)	0/54 (0%)	0/54 (0%)	0/54 (0%)	1/54 (2%)	1/54 (2%)	5/54 (9%)	16/54 (30%)	0/54 (0%)

	Air Conduction Thresholds 10 Months N=52								
	250	500	1000	2000	3000	4000	6000	8000	PTA
Mean delta from Baseline ± SE (CI range)	11 ± 2 (15, 8)	20 ± 1 (23, 17)	27 ± 2 (30, 23)	36 ± 2 (40, 33)	26 ± 2 (30, 22)	18 ± 2 (22, 14)	10 ± 2 (15, 5)	1 ± 3 (6, -5)	27 ± 1 (30, 25)
% Greater than +10 dB	23/52 (44%)	40/52 (77%)	46/52 (88%)	49/52 (94%)	43/52 (83%)	35/52 (67%)	25/52 (48%)	10/52 (19%)	48/52 (92%)
% Stable (±10 dB)	29/52 (56%)	12/52 (23%)	5/52 (10%)	3/52 (6%)	6/52 (12%)	13/52 (25%)	16/52 (31%)	20/52 (38%)	4/52 (8%)
% Less than -10 dB	0/52 (0%)	0/52 (0%)	1/52 (2%)	0/52 (0%)	1/52 (2%)	3/52 (6%)	6/52 (12%)	6/52 (12%)	0/52 (0%)
% No Response	0/52 (0%)	0/52 (0%)	0/52 (0%)	0/52 (0%)	2/52 (4%)	1/52 (2%)	5/52 (10%)	16/52 (31%)	0/52 (0%)



Analysis: The data presented in Table 10 above demonstrates that 96% (52/54) of subjects at 4-month and 92% (48/52) at 10-month follow-up received significant functional benefit from the Esteem compared to their pre-implant unaided condition as measured by PTA and that the mean average gain in PTA was 27 dB at both 4 and 10 months, representing functional gain benefit from the device when compared to their pre-implant unaided condition.

4.2.4 QuickSIN

Objective: A Secondary Effectiveness Objective identified in the IDE protocol is that the Esteem System is as effective as or better than the pre-implant hearing aid (aided condition) for improving speech discrimination (intelligibility).

Endpoint: The endpoint is a comparison of the Hearing-in-Noise Test (QuickSIN) results using the Esteem System as compared to the pre-implant aided condition.

Data: The speech in noise test using QuickSIN was compared with Esteem at 4-month and 10-month endpoints to the pre-implant aided condition. The change with Esteem from aided baseline was -1 ± 1 (CI -2, 0) at 4-month and 0 ± 0 (CI -1, 1) at 10-month follow-up.

Analysis: The small change from the aided baseline condition indicates that the Esteem is equivalent to the hearing aid in improving speech discrimination (intelligibility) as shown by the QuickSIN (speech in noise) test results.

In summary, a qualitative comparison of the QuickSIN testing data supports an informal conclusion of equivalent improvement when comparing the Esteem System to the aided baseline condition in the subjects' ability to understand speech in noise at 4 months and 10 months post-activation. Relative to baseline aided condition, at 4 months the change in QuickSIN score with Esteem was -1 ± 1 and at 10 months 0 ±0.

4.2.5 APHAB versus baseline aided condition

Objective: A Secondary Effectiveness Objective is to show that the Esteem System improves Quality of Life when compared to the baseline aided condition. Results are reported using the Abbreviated Profile of Hearing Aid Benefit (APHAB) Questionnaire.

Endpoint: The endpoint is a comparison of the APHAB results using the Esteem System as compared to the pre-implant aided condition.

Data: The mean benefit scores over the unaided condition were collected for the pre-implant aided condition (hearing aid) and at the 4-month and 10-month Esteem follow-up visits as shown below. The APHAB score is broken down into sub-categories of Easy Communication Situations (EC), Background Noise Situations (BN), Reverberate Environments (RV) and Aversiveness (AV) as shown below. The benefit provided by the acoustic hearing aid and the Esteem System is also compared by showing the mean difference in benefit score in Table 11.

Table 11: APHAB: Mean Benefit Score (%)

	Global Score mean ± se n (95% CI)	EC Scale mean ± se n (95% CI)	BN Scale mean ± se n (95% CI)	RV Scale mean ± se n (95% CI)	AV Scale mean ± se n (95% CI)
Baseline Aided	18.7±1.7 59 (15.4, 22.0)	38.9±2.9 59 (33.1, 44.7)	29.8±2.2 59 (25.4, 34.3)	34.7±2.6 59 (29.6, 39.9)	-28.9±2.9 59 (-34.8, -23.0)
Esteem 4-Month	28.3±2.5 53 (23.3, 33.3)	50.5±3.1 53 (44.3, 56.7)	39.5±3.3 53 (32.8, 46.2)	42.0±3.5 53 (35.0, 49.0)	-19.0±3.8 53 (-26.6, -11.4)
Mean Difference in Benefit Score	10.9±2.5 53 (5.9, 15.8)	13.5±3.2 53 (7.1, 20.0)	10.2±3.1 53 (4.1, 16.3)	8.4±3.1 53 (2.1, 14.6)	11.4±4.0 53 (3.3, 19.5)
Esteem 10-Month	26.3±2.8 51 (20.7, 31.8)	48.1±3.4 51 (41.2, 55.0)	36.0±3.6 51 (28.7, 43.3)	38.5±3.9 51 (30.6, 46.4)	-17.9±3.9 51 (-25.7, -10.2)
Mean Difference in Benefit Score	8.9±2.6 51 (3.8, 14.1)	11.4±3.4 51 (4.5, 18.3)	7.1±3.2 51 (0.7, 13.4)	5.0±3.1 51 (-1.3, 11.3)	12.2±4.0 51 (4.1, 20.2)

Table 12 provides the individual subject APHAB scores in percentage steps for Esteem at 4-months and 10-months follow-up compared to baseline hearing aid. The number and percent of subjects meeting each comparison step are provided for each APHAB score. For Total APHAB 60% of the subjects had improved benefit scores compared to the pre-implant hearing aid at 4-months and 63% had improved hearing benefit at 10-months.

Table 12: APHAB Comparison by Subject: Esteem vs Hearing Aid

	4 Month APHAB Comparison Results N=53				
	Total	EC	BN	RV	AV
% Better HA > +22%	13/53 (25%)	15/53 (28%)	18/53 (34%)	14/53 (26%)	17/53 (32%)
% Better HA +10 to 21%	14/53 (26%)	12/53 (23%)	10/53 (19%)	9/53 (17%)	11/53 (21%)
% Better HA +5 to 9%	5/53 (9%)	10/53 (19%)	4/53 (8%)	5/53 (9%)	4/53 (8%)
% Equal HA (±4%)	11/53 (21%)	6/53 (11%)	7/53 (13%)	9/53 (17%)	9/53 (17%)
% Below HA -5 to -9%	3/53 (6%)	1/53 (2%)	7/53 (13%)	6/53 (11%)	1/53 (2%)
% Below HA -10 to -21%	4/53 (8%)	6/53 (11%)	4/53 (8%)	8/53 (15%)	4/53 (8%)
% Below HA < -22%	3/53 (6%)	3/53 (6%)	3/53 (6%)	2/53 (4%)	7/53 (13%)

	10 Month APHAB Comparison Results N=51				
	Total	EC	BN	RV	AV
% Better HA > +22%	9/51 (18%)	13/51 (25%)	13/51 (25%)	11/51 (22%)	16/51 (31%)
% Better HA +10 to 21%	16/51 (31%)	16/51 (31%)	10/51 (20%)	13/51 (25%)	11/51 (22%)
% Better HA +5 to 9%	7/51 (14%)	6/51 (12%)	3/51 (6%)	1/51 (2%)	3/51 (6%)
% Equal HA (±4%)	8/51 (16%)	8/51 (16%)	10/51 (20%)	8/51 (16%)	7/51 (14%)
% Below HA -5 to -9%	6/51 (12%)	3/51 (6%)	5/51 (10%)	5/51 (10%)	5/51 (10%)
% Below HA -10 to -21%	2/51 (4%)	3/51 (6%)	6/51 (12%)	9/51 (18%)	7/51 (14%)
% Below HA < -22%	3/51 (6%)	2/51 (4%)	4/51 (8%)	4/51 (8%)	2/51 (4%)

Analysis: Mean Benefit Comparison: As shown in Table 11, when comparing the mean benefit for Esteem versus the hearing aid, Esteem provides significantly more benefit than the hearing aid at each of the four environmental subscales: EC (easy listening); BN (background noise); RV (reverberant); and AV (Aversiveness loud sounds). Each of the APHAB scales showed a statistically significant difference in mean benefit score between the Esteem and the hearing aid at the 4-month endpoint (all $p<0.01$).

Individual Benefit Comparison: According to the *Instructions for Manual Scoring of the APHAB*, a significant benefit has occurred if a difference of ≥ 22% is obtained for the EC, RV or BN score. If all three scores improve by ≥ 10%, there is a 96% probability that a true benefit has occurred. If all three scores improve by ≥ 5%, there is an 89% probability that a true benefit has occurred.

Scoring of the benefit scores for the baseline hearing aid and the Esteem at 4 and 10-month follow-up was calculated versus unaided baseline. In addition, the Esteem at the 4 and 10-month evaluation was compared to the baseline Hearing Aid for each subject according to these same criteria. The number of subjects meeting each of the above scoring criteria is presented in Table 13.

Table 13: APHAB – Benefit Categories

Benefit Categories	Esteem vs Hearing Aid n/N (%) 4-Month	Esteem vs Hearing Aid n/N (%) 10-Month
Significant Benefit Subjects with a ≥ 22% improvement in EC, RV, or BN	25/53 (47.2%)	21/51 (41.2%)
96% Probability of a Significant Benefit Subjects with a ≥ 10% improvement in EC, RV, and BN	16/53 (30.2%)	13/51 (25.5%)
89% Probability of a Significant Benefit Subjects with a ≥ 5% improvement in EC, RV, and BN	23/53 (43.4%)	19/51 (37.3%)

Both the hearing aid and the Esteem provided statistically significant benefit over the baseline unaided condition in over 90% of the subjects. However, Esteem was statistically superior to the hearing in providing significant benefit. Esteem had twenty-five subjects (47%) at 4-month follow-up and twenty-one subjects (41%) at 10-month follow-up that showed significant benefit improvement over the Hearing Aid by achieving a greater than 22% change in EC, RV or BN per the APHAB scoring guidelines.

The APHAB benefit comparison between Esteem and the baseline Hearing Aid clearly demonstrates that the Esteem is statistically superior to the hearing aid by significantly improving the mean benefit in all environmental categories and by providing significantly more benefit to nearly half (47%) of the subjects in this study at the 4-month endpoint.

4.2.6 Envoy Questionnaire versus baseline aided condition

Objective: A Secondary Effectiveness Objective is to show through subject feedback and comments how the Esteem System improves Quality of Life when compared to the baseline aided condition. Results are reported using the Envoy Quality of Life Questionnaire.

Endpoint: The endpoint is a comparison of the APHAB results using the Esteem System (4 months post-activation) as compared to the pre-implant aided condition.

Data: At the 4-month and 10-month follow-up, subjects completed a questionnaire rating various subjective attributes concerning their experience with Esteem as compared to their previous hearing aid. Ratings were on a scale of 1 to 5 where 1 is much worse, 3 is the same and 5 is much better. The questions and responses are provided in Table 14 below:

Table 14: Esteem Questionnaire Results

Question	4 Month Response				
	1	**2**	**3**	**4**	**5**
How do you rate the clarity of the sound you hear with the *Esteem* compared to your hearing aid?	3/54 (6%)	5/54 (9%)	4/54 (7%)	13/54 (24%)	29/54 (54%)
How do you rate your ability to understand speech in background noise or street noise with the *Esteem* as compared to your hearing aid?	3/54 (6%)	7/54 (13%)	7/54 (13%)	17/54 (31%)	20/54 (37%)
How natural sounding are voices and other sounds compared to your hearing aid?	1/54 (2%)	6/54 (11%)	6/54 (11%)	13/54 (24%)	28/54 (52%)
How do you rate the benefit of the entire system being invisible to the onlooker compared to your hearing aid?	9/54 (17%)	0/54 (0%)	9/54 (17%)	12/54 (22%)	24/54 (44%)
How well do you understand conversation with your *Esteem* even when several people are talking compared to your hearing aid?	3/54 (6%)	3/54 (6%)	9/54 (17%)	18/54 (33%)	21/54 (39%)
How confident do you feel with the *Esteem* compared to your hearing aid?	2/53 (4%)	2/53 (4%)	4/53 (8%)	13/53 (25%)	32/53 (60%)
Does the Esteem allow you to live a more active lifestyle?	1/54 (2%)	1/54 (2%)	6/54 (11%)	13/54 (24%)	33/54 (61%)

Question	10 Month Response				
	1	**2**	**3**	**4**	**5**
How do you rate the clarity of the sound you hear with the *Esteem* compared to your hearing aid?	3/52 (6%)	5/52 (10%)	3/52 (6%)	7/52 (13%)	34/52 (65%)
How do you rate your ability to understand speech in background noise or street noise with the *Esteem* as compared to your hearing aid?	5/52 (10%)	3/52 (6%)	7/52 (13%)	14/52 (27%)	23/52 (44%)
How natural sounding are voices and other sounds compared to your hearing aid?	3/52 (6%)	5/52 (10%)	4/52 (8%)	14/52 (27%)	26/52 (50%)
How do you rate the benefit of the entire system being invisible to the onlooker compared to your hearing aid?	5/52 (10%)	0/52 (0%)	11/52 (21%)	15/52 (29%)	21/52 (40%)
How well do you understand conversation with your *Esteem* even when several people are talking compared to your hearing aid?	3/52 (6%)	4/52 (8%)	10/52 (19%)	12/52 (23%)	23/52 (44%)
How confident do you feel with the *Esteem* compared to your hearing aid?	4/52 (8%)	3/52 (6%)	3/52 (6%)	12/52 (23%)	30/52 (58%)
Does the Esteem allow you to live a more active lifestyle?	1/52 (2%)	3/52 (6%)	3/52 (6%)	10/52 (19%)	35/52 (67%)

Where the responses represent the following experience: 1 is much worse
2 is somewhat worse
3 is about the same
4 is somewhat better
5 is much better

Analysis: The results of the questionnaire at 4-months indicate that a large number of the subjects consider the Esteem somewhat or much better that their baseline hearing aid.

- 78% rated the Clarity of Sound as somewhat or much better
- 69% rated the Ability to Understand Speech in background noise as somewhat or much better
- 76% reported Voices Sounding Natural as somewhat or much better
- 72% reported Understanding Conversation when several people are talking as somewhat or much better
- 85% said their Activity level was somewhat or much better

4. 3 Safety Endpoints

4.3.1 Bone Conduction

Objective: A Primary Safety Objective of the clinical study is to demonstrate that the subject's cochlear function remains unchanged with the Esteem system as shown by a comparison of the subject's pre-implant baseline Bone Conduction Threshold (BCT) versus the subject's BCT at the 4 and 10 month endpoints. Average and individual changes were evaluated per the protocol.

Endpoint Analysis: Bone conduction will be measured with forehead probe placement. Stable results should be within ± 10 dB. The Safety Algorithm as described in the Clinical Protocol, Appendix A, will be used for any Bone Conduction results outside the stability range.

Data: Bone conduction data is presented below both as group average change and as individual subject change from baseline.

Average: Change in Bone Conduction was used to determine whether the Esteem implant caused damage to residual cochlear function. Average 3-frequency (500, 1000, 2000 Hz) bone conduction change from baseline for all subjects was 0.1 ± 0.9 dB at 4 months and -0.8 ± 1.1 dB at 10 months. This small change is indicative of no systemic cochlear damage being caused by either the implant or the therapy. Results are similar across frequencies tested as shown in Table 15 below.

Table 15: Average Bone Conduction Threshold Results

	500 Hz mean ± se (CI range)	1000 Hz mean ± se (CI range)	2000 Hz mean ± se (CI range)	4000 Hz mean ± se (CI range)	PTA mean ± se (CI range)
Pre-Implant	45.0±1.9 (41.3, 48.7)	57.5±1.7 (54.1, 60.8)	66.6±1.4 (63.7, 69.4)	65.0±1.7 (61.5, 68.5)	56.3±1.3 (53.7, 58.9)
4-Month	45.4±1.9 (41.7, 49.1)	57.9±1.6 (54.6, 61.1)	67.4±1.3 (64.8, 70.0)	65.6±1.5 (62.6, 68.6)	56.4±1.3 (53.7, 59.0)
Mean Difference	0.0 ± 0.9 (-1.8, 1.8)	0.0 ± 1.0 (-2.0, 2.0)	2.2 ± 1.3 (-0.4, 4.8)	1.2 ± 1.2 (-1.3, 3.7)	0.1 ± 0.9 (-1.7, 2.0)
10-Month	42.6±2.0 (38.7, 46.5)	56.9±1.6 (53.8, 60.1)	68.0±1.4 (65.2, 70.7)	66.3±1.5 (63.4, 69.3)	55.3±1.5 (52.3, 58.3)
Mean Difference	-2.3±1.0 (-4.4, -0.3)	-0.3±1.2 (-2.7, 2.0)	1.3±1.4 (-1.5, 4.1)	2.2±1.3 (-0.5, 4.8)	-0.8±1.1 (-3.1, 1.5)

Individual Subjects: All subjects with 4-month and 10-month follow up data in the database as of July 27, 2009, were analyzed according to the Bone Conduction/EnvoyGram Safety Algorithm in accordance with the clinical protocol. No (0) subjects had a bone conduction/EnvoyGram threshold shift at the 4-month endpoint greater than the protocol criteria. At the 10-month follow-up, one subject (--------- had a bone conduction/EnvoyGram threshold shift greater than the protocol criteria at the 4 kHz frequency but a stable response at all other frequencies. It is likely that the more consistent and stable bone conduction measurements in this study compared to the previous 0203 Esteem clinical study are due to the forehead probe placement versus the mastoid probe placement.

Analysis: Bone conduction was shown to be stable through the 4-month end point and 10-month follow-up. Both the group average and the individual subject bone conduction change verified stable readings, thus confirming that there were no changes to the subject's cochlear function following the implant of the Esteem due to the implant procedure or therapy delivered.

4.3.2 SADE

Objective: To determine the incidence of Serious Adverse Device Effects (SADE) and the incidence rate of device failures and replacements.

Endpoint: The analysis of the incidence of SADE's and device failures and replacements through the 10-month post-activation follow-up.
Serious Adverse Device Effects (SADE's) include device revisions and explants.

Data: There have been 6 SADE's reported in 6 unique subjects. Three of the SADE's were due to limited benefit which resulted in revision procedures; two involved the surgical implant incision; and one was severe pain and facial weakness due to the mastoidectomy procedure.

- -------- ---------: Limited Benefit
- ---------- ----: Pain and Facial Weakness
- ----------: Incision Breakdown
- ----------: Limited Benefit
- ----------: Limited Benefit
- -------- ----------: Incision Infection

The three (3) limited benefit subjects have undergone a revision procedure to correct the limited benefit condition. The cause of the limited benefit was determined to be fibrous adhesions which formed after implant and inhibited either the Sensor-incus or the Driver-stapes from moving. The subjects are receiving appropriate benefit post revision. Subject -------- has passed the 4-month endpoint post-revision; Subject -------- and Subject -------- have both passed the 2-month follow-up post-revision. The two incision SADEs were incision breakdown and incision infection. Both subjects have been treated. The incision infection was treated with amoxicillin and incision cleaning/re-suturing which resolved the SADE with no residual effects; and the other incision breakdown was treated with Neosporin and redoing the incision closure; however, the treatment was not successful and

the subject required explant of the device. The pain and facial weakness required medication that subsequently resolved with no residual effects.

Analysis: For 6 subjects with SADEs among 57 implants, the exact 95% confidence interval for the proportion of subjects with an SADE is (4.0%, 21.5%).
Reasons for device explantation or surgical revision due to limited or no benefit include device failure or medical reasons.

- Device failures include hardware and software defects that prevent the device from providing clinical benefit.
- Medical reasons include infection, surgical implant technique, electrode misplacement, or biological issues.

There were three (3) revisions due to medical reasons. Zero (0) device failures were reported for the 57 subjects implanted, resulting in 95% confidence of greater than 94% reliability.

4.3.3 Device Failures

Another safety objective of the clinical study is to determine the rate of device failures and revisions. Since the beginning of this clinical trial, there have been three (3) limited benefit failures requiring revision procedures to correct. All three occurred prior to the 2-month post-activation follow-up visit. One limited benefit was caused by low Sensor output due to fibrotic tissue interference and the other two (2) were caused by low Driver output due to fibrotic tissue interference. The overall rate of failure occurrence is 5.3% (3/57) through the 2 month follow-up visit. No failures have occurred between the 4-month and 10-month follow-up visits.

One of the revision subjects, [redacted], has reached the 4-month follow-up after the revision procedure and is receiving very good benefit (ΔSRT= +10dB and ΔWRS@50dB= +38%, both compared to baseline aided condition). The other two revision subjects have been through the 2-month follow-up post-revision with similar results that are better than baseline aided, but have not yet reached 4-month follow-up.

The Failure Summary that follows provides details on each failure cause to date.

Failure Summary:

Fibrosis/Tissue Bridging:
Subject [redacted] reported a decrease in benefit shortly after Activation, continuing through the 2-month follow-up visit. Diagnostic testing indicated that the Sensor output was lower than normal. The revision procedure found extensive dense fibrous adhesions filling the facial recess. The fibrous adhesions had fixed the Sensor to the incus and the Driver to the malleus. In order to remove the fibrous adhesions, [redacted] had to remove the Sensor and Driver and replace them with new components. During this process, [redacted] noticed some MedCem butted against the short process of the incus, restricting its movement. He removed this obstruction in order to restore mobility of the incus. The new Sensor, Driver and System tests were conducted with acceptable results. [redacted] conclusion was that the dense fibrous adhesions that formed after implant prevented the Sensor and incus from moving properly causing the poor performance. The MedCem attached to the incus likely was the cause of lower than expected Sensor and System ISA test performance at implant but as indicated by

the positive benefit data at Activation the fibrous adhesions that developed after Activation were the cause of the decrease in benefit.

Subject [redacted] reported limited benefit at Activation that progressively worsened through the 2-month follow-up. Diagnostic testing indicated that the Driver output was lower than normal. The revision procedure showed extensive fibrous adhesions in the facial recess surrounding the Driver and stapes, which was difficult to remove. The Sensor was functioning properly and not affected by the adhesions. After removal of the fibrotic tissue with a pick and some excess MedCem cement between the Sensor and Driver with a burr, [redacted] found that the Driver tip had been laterally pulled away from the stapes EnvoyCem connection and that an unusually small amount of EnvoyCem was present to form the Driver-stapes connection. This subject had a small facial recess opening that could have affected visibility and the original application of EnvoyCem. [redacted] implanted a new Driver and used EnvoyCem to complete the connection to the stapes. The new Driver, Sensor and System tests were conducted with acceptable results. The conclusion was that the fibrous adhesions that formed after implant likely prevented the Driver and stapes from functioning properly causing the limited benefit. The extensive disruption caused by the difficult removal of the fibrous adhesions and excess MedCem cement caused the Driver to move from its original position and had nothing to do with the limited benefit.

Subject [redacted] reported limited benefit at Activation that progressively worsened through the 2-month follow-up. Diagnostic testing indicated that the Driver output was lower than normal. The revision procedure showed extensive fibrous adhesions in the facial recess surrounding the Driver and stapes, which was difficult to remove. The Sensor was functioning properly and not affected by the adhesions. During removal of the fibrotic tissue with a pick, [redacted] found that an unusually small amount of EnvoyCem was present to form the Driver-stapes connection. This subject had a small facial recess opening that could have affected visibility and the original application of EnvoyCem. [redacted] implanted a new Driver and used EnvoyCem to complete the connection to the stapes. The new Driver, Sensor and System tests were conducted with acceptable results. The conclusion was that the fibrous adhesions that formed after implant likely prevented the Driver and stapes from functioning properly causing the limited benefit. The partial EnvoyCem coverage observed was not considered to have contributed to the cause of the decreased benefit.

4.4 Supporting Analyses

4.4.1 Protocol Deviations

As requested by FDA, a statistical analysis was conducted on the primary effectiveness and safety objectives of the clinical protocol to determine whether there were differences in these outcomes between the Protocol Deviation Subjects and the other study subjects, and whether or not they affect the study conclusions. The clinical status was also evaluated using the audiological testing and questionnaire results.

As detailed in Appendix 3, based upon the statistical analysis of the primary clinical objectives and the clinical evaluation of the audiological test results, it is clear that all three cohorts meet the clinical study objectives and that the inclusion of the Protocol Deviation Subjects do not substantially change the conclusions of the study.

4.4.2 Other Analyses

Warble Tone Average: Although Warble Tone performance was not a protocol objective, data was collected and analyzed. As compared to the pre-implant aided condition, 93% of subjects at 4-month follow-up and 92% at 10-month follow-up had WTA equal to or better than their hearing aid. 43% and 44% of subjects at 4-month and 10-month follow-up, respectively, had WTA better than (>10 dB) their pre-implant hearing aid.

Table 16: Warble Tones

	4 Month N=54						10 Month N=52					
	500	1000	2000	3000	4000	PTA	500	1000	2000	3000	4000	PTA
% Above HA > +10 dB	15/54 (28%)	22/54 (41%)	22/54 (41%)	17/54 (31%)	9/54 (17%)	23/54 (43%)	18/52 (35%)	23/52 (44%)	24/52 (46%)	21/52 (40%)	12/52 (23%)	23/52 (44%)
% Equal HA (±10 dB)	35/54 (65%)	26/54 (48%)	31/54 (57%)	26/54 (48%)	27/54 (50%)	27/54 (50%)	31/52 (60%)	25/52 (48%)	25/52 (48%)	23/52 (44%)	24/52 (46%)	25/52 (48%)
% Below HA < -10 dB	4/54 (7%)	6/54 (11%)	1/54 (2%)	10/54 (19%)	12/54 (22%)	4/54 (7%)	3/52 (6%)	4/52 (8%)	3/52 (6%)	8/52 (15%)	13/52 (25%)	4/52 (8%)
% NR	0/54 (0%)	0/54 (0%)	0/54 (0%)	1/54 (2%)	6/54 (11%)	0/54 (0%)	0/52 (0%)	0/52 (0%)	0/52 (0%)	0/52 (0%)	3/52 (6%)	0/52 (0%)

Several other data analyses were conducted to evaluate the effects of the subjects' baseline hearing loss and speech discrimination on the audiological benefits of Esteem.

Baseline Hearing Loss: For baseline hearing loss, the subject data was analyzed for the following cohorts: mild (≤ 40 dB), moderate (41 – 55 dB), moderately severe (56 – 70 dB) and severe (≥ 71 dB).

Baseline Speech Discrimination: For speech discrimination, the subject data was analyzed for the following cohorts: SD > 60% and SD < 60%. The details of the analyses are provided in Appendix 3.

In summary, the following conclusions can be drawn:

- For baseline hearing loss, the Esteem provides the greatest benefit improvement over the baseline unaided and aided conditions (hearing aid) for the moderately-severe hearing loss cohort. This improvement is consistently seen in SRT, WTA, PTA and WRS.
- For baseline speech discrimination, the Esteem benefit improvements over the baseline unaided and aided conditions (hearing aid) are very similar between the cohorts with no apparent differences in SRT, WTA, PTA and WRS.

Most Comfortable Loudness (MCL): Although MCL performance was not a protocol objective, data was collected and analyzed. The MCL was also the presentation level at which Speech Discrimination testing was conducted. As compared to the pre-implant aided

condition, 96% of subjects at 4-month follow-up and 94% at 10-month follow-up had MCL equal to or better than their hearing aid. Additionally, 41% and 46% of subjects at 4-month and 10-month follow-up, respectively, had MCL at least 10 dB better than their pre-implant hearing aid. Lastly, with pre-implant hearing aid, 48% of subjects had MCL levels at or below a normal conversation level of 65 dB HL, compared with 74% of subjects at 4-month follow-up and 75% of subjects at 10-month follow-up.

4.4.3 Additional Analyses

The following additional analyses were conducted at FDA's request during the PMA review process and are added here for completeness.

Demographic Associations: To examine correlates of results with patient demographics and baseline characteristics, we examined whether or not these factors were associated with the primary outcome variable. P-values in the table below are from linear models for the association of change in SRT at 4 months from baseline with the demographic variable of interest. Values less than 0.05 are considered statistically significant. "NA" indicates variables for which there were an insufficient patients to assess the association. For example, none of the 57 enrolled subjects had labyrinthitis and so no p-value could be calculated for the association of labyrinthitis.

Association of Results With Patient Demographics

Variable	P-value
Age in years	0.15
Gender	0.09
Work status	0.75
Family history	0.26
Prior ear surgery	0.94
Otitis Media	0.28
External Otitis	0.38
Ototoxicity	0.67
Head Trauma	0.38
Labyrinthitis	NA
Mastoiditis	NA
Post-adolescent chronic middle ear infections	NA

Vertigo	0.64
Tinnitus requiring treatment	0.67
Tinnitus not requiring treatment	0.66
Fullness or plugging of ear(s)	0.35
Otosclerosis	NA
Cholesteatoma	NA
Eczema/Psoriasis (head or neck)	NA
Circulation disorder	0.28
Diabetes Mellitus	0.55
Blood/Bleeding Disorder (anemia)	0.20
Speech impediment/Impairment	0.94
Depression	0.33
Nasal Surgery	0.66
Seasonal Allergies, requiring treatment	0.30
Age of hearing loss realization	0.66
Age of hearing loss diagnosis	0.32
Onset of hearing loss	0.42
Cause of hearing loss	0.32
Degree of hearing loss (SRT)	0.04

The only variable that was significantly associated with the primary efficacy outcome of SRT was baseline degree of hearing loss. With 26 demographic comparisons used to calculate the p-values listed above, one would expect at least one to be statistically significant at the 0.05 level by chance alone. Nonetheless, a thorough analysis of this factor was provided in Section 4.4.2 and Appendix 3 of the Clinical study report, Volume 2 of the PMA.

Stratification Analyses: Below we present results for outcomes stratified on the requested factors of age, severity of baseline hearing loss, baseline unaided WRS at max, and the length of hearing aid experience. For age and length of hearing aid experience, patients were divided into three equal sized groups (i.e. tertiles). For WRS, the division into three groups was based on commonly used clinical cutoff values of 60% and 80%. P-values were calculated from a linear model of the outcome as a function of the stratification factor and are two-sided.

Stratified Results

Stratification Factor	Strata	N	SRT Change at 4 months		WRS @ 50 dB Change at 4 months	
			Mean±SE	P-value For Strata Differences	Mean±SE	P-value For Strata Differences
Age	**< 47 years**	18	6.4±3.4		16.9±7.9	
	47 - 60.3 years	18	13.1±3.4	0.242	25.2±8.1	0.708
	> 60.3 years	18	12.5±2.2		23.0±5.8	
Baseline Hearing Loss Severity (PTA)	**Mild**	3	10.0±5.0		20.7±6.6	
	Moderate	41	11.2±2.1	0.843	19.8±4.1	0.659
	Severe	10	8.5±4.2		29.8±15.2	
Baseline unaided WRS (at MCL)	**< 60%**	10	15.0±5.3		22.4±8.5	
	60% – 80%	23	11.1±2.4	0.389	28.4±7.1	0.300
	> 80%	21	8.1±2.9		14.0±6.0	
Length of hearing aid experience	**<8 years**	18	10.6±2.3		17.6±4.1	
	8 – 16 years	18	14.4±3.8	0.232	29.8±7.3	0.399
	>16 years	18	6.9±2.9		17.8±9.3	

Results were consistent among subgroups of patients; each showed a benefit of the Esteem System over hearing aid. The overall mean changes were positive in every subset, of a similar magnitude, and there were no statistically significant differences between the subgroups (all $p>0.20$). This provides further evidence that the Esteem System is effective for a broad patient base.

Clinical Site Analyses: The Esteem 0204 study recruited subjects from three investigative sites to ensure timely enrollment of the trial and to gather data on a diverse set of patients under the care of different investigators. Including patients from multiple sites provides a more representative sample of patients than those from only one site.

This was pre-planned and a single protocol was developed for use at all three sites (and approved by each site's IRB) to help ensure consistent application of the technology. The analysis of study data was to be performed on all implanted subjects.

Some variation between investigative sites is not unexpected in multicenter clinical trials. Even though the same protocol was reviewed and applied at all sites, differences in subject baseline characteristics between sites may exist and result in some site variability in the overall study results.

Because the subjects' baseline hearing condition (e.g. baseline SRT and baseline hearing loss) are related to the primary efficacy outcome, SRT change, we performed an analysis that examined differences between investigative sites accounting for these patient-level factors. The table below displays these results for least-square (model adjusted) means for each site from linear models for the change in SRT at 4 months.

SRT Change by Site

Analysis	Site 103 Mean ± SE	Site 105 Mean ± SE	Site 109 Mean ± SE	P-value for Site Differences
Unadjusted	11.9±2.6	16.9±2.8	1.3±3.0	<0.01
Adjusted for Baseline SRT, and baseline hearing loss	9.6±2.0	14.6±2.4	7.0±2.4	0.06

When adjusted for subjects' baseline hearing condition, the differences between the sites are small, not clinically relevant, and not statistically significant. All three sites show significant benefit relative to the pre-implant hearing aid as the site-level adjusted mean changes in SRT are greater than or equal to 7.0 dB.

This analysis shows that differences in subjects' baseline hearing levels do cause some variability in the improvement outcome with Esteem as would be expected. As a result, some clinical outcome variability between investigative sites is to be expected due to the relatively small subject sample size at each site but does not change the overall conclusions of the clinical study based upon the more representative combined subject data base.

5.0 Adverse Events

Adverse Events are continuing to be collected throughout the Pivotal Trial. All adverse events that have been reported and adjudicated for the subjects enrolled in the trial as of July 2009 will be reported here.

A Clinical Events Committee (CEC) has been established in order to adjudicate all adverse events reported in the Pivotal Trial. The CEC defined specific categories for causal relationships to which the adverse events were adjudicated. These categories are as follows:

- **Device:** Related to the electronic functioning of the device.
- **Envoy Medical Device Implant Procedure:** Related to the specific surgical technique that is used for implanting the Esteem System.
- **Mastoidectomy w/facial recess:** Related to any Tympanum / Mastoidectomy Procedure

- **Peri-operative Surgery Related:** Related in general to non-otological aspects of surgery as occurring before, during or after the surgery.
- **Underlying or concomitant illness:** Related to a different medical condition / illness.
- **Concomitant Medication:** Related to a medication.
- **Other:** Does not fall into any of the other categories, a comment is required to describe what the "other" cause is.

If a subject experienced an event following his or her initial Esteem System implant which resolved but then the subject experienced it again either at a later date or following a revision procedure, both events are being counted independently and are therefore noted as two events.

The protocol used the following definitions of adverse events:

Adverse Event (AE): An Adverse Event is any undesirable clinical event occurring to a subject, during a clinical trial, whether or not it is considered related to the investigational product. This includes a change in a subject's condition or laboratory results, which has or could have a deleterious effect on the subject's health or well-being.

Adverse Device Effect (ADE): An Adverse Device Effect is an Adverse Event related to the investigational device.

Unanticipated Adverse Device Effect (UADE): An Unanticipated Adverse Device Effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious Adverse Event (SAE) or Serious Adverse Device Effect (SADE): A Serious Adverse Event (SAE) or a Serious Adverse Device Effect (SADE) are events which:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment/damage

The protocol specified the following reporting of AE's:

- All AE's, ADE's, UADE's, SAE's, and SADE's will be documented on an Adverse Event Form
- The Investigator shall report all SAE's, SADE's and UADE's to Monitor/Sponsor within 10 days of knowledge of event.
- Sponsor is responsible for informing the FDA, all reviewing IRBs and other investigators of any UADE that has occurred.
- The Investigator is responsible for reporting AE's to his or her IRB in accordance to his or her IRB procedures.

5.1 Results

UADE: Using these definitions, there have been no UADE's reported during this clinical investigation.

A complete list of the adjudicated Adverse Events reported during this clinical investigation is reported in Appendix 5.

SADE: 6 events in 6 subjects were reported which were classified as Serious Adverse Device Effects (SADE). Four (4) of the events were classified as mild intensity, one moderate and one severe.

Table 17: **SADE's: A total of 6 events in 6 subjects**

Event	Mild	Moderate	Severe	Total
Severe Pain and Facial Weakness	1	0	0	1
Incision Breakdown	0	0	1	1
Incision Infection	0	1	0	1
Limited Benefit	3	0	0	3
TOTAL	**4**	**1**	**1**	**6**

Events were reported in this table as Serious if they were determined to be Serious by CEC adjudication. Events were classified as SADE's if they were found to be caused by the mastoidectomy w/facial recess, device, peri-operative surgery related, or EMC device implant procedure related.

In the case of the SADE for severe pain and facial weakness, the subject, who is otherwise considered to be a successful case, required medication to treat severe pain and facial weakness that subsequently has resolved with no residual effect. Two SADEs involved the surgical implant incision, one breakdown and one infection. Both subjects have been treated. The incision infection subject has recovered with no residual effect; the other subject had a severe incision breakdown that required device explant due to a smoking habit that inhibited healing. Of the 3 limited benefit SADEs, all have been successfully revised to resolve the benefit issue with no residual effects.

SAE: A total of 2 events have been reported which were classified as SAE's. Both events were classified as severe.

Table 18: SAE's: A total of 2 events in 2 subjects

Event	Mild	Moderate	Severe	Total
Broken Leg	0	0	1	1
Transient Ischemic Attack	0	0	1	1
TOTAL	**0**	**0**	**2**	**2**

Events were reported in this table as Serious if they were determined to be Serious by CEC adjudication. Events were classified as SAE's if they were found during CEC adjudication to be caused by underlying or concomitant illness, concomitant medications, or other causes.

One subject severely broke a leg, requiring hospitalization and has since recovered. The other subject suffered a transient ischemic attack (TIA) and has recovered with no residual effects.

ADE: A total of 96 events in 43 subjects were reported which where classified as Adverse Device Effects (ADE). The majority of the events were classified as mild; eleven (11) events were classified as moderate. The ADE's are as follows:

Table 19: ADE's: A total of 96 events in 43 subjects are reported.

Event	Mild	Moderate	Severe	Total
Aural Fullness	2	0	0	2
Blistering TM	1	0	0	1
Chest Pain	1	0	0	1
Discomfort above Incision	1	1	0	2
Dizziness	1	0	0	1
Dry Eye	1	0	0	1
Disequilibrium	3	0	0	3
Ear Cracking	2	0	0	2
Ear Pain	4	0	0	4
Ear Roaring	1	0	0	1
Eye Irritation	1	0	0	1
Eye Squint	1	0	0	1
Facial Weakness/Paralysis	2	1	0	3
Feedback	1	0	0	1
Fluid	3	6	0	9
Headache	1	1	0	2
Imbalance	1	0	0	1
Incision Discomfort	3	0	0	3
Incision Drainage	1	0	0	1
Limited Benefit	1	0	0	1
Metallic Taste	1	0	0	1
Middle Ear Effusion	8	0	0	8
Moist Debris	1	0	0	1
Nasal Drainage	1	0	0	1
Noise	1	0	0	1
Numbness	1	0	0	1
Otitis Externa	2	0	0	2

Otalgia	2	0	0	2
Pain	2	0	0	2
Taste Disturbance	23	1	0	24
Tinnitus	8	0	0	8
TM Perforation	1	0	0	1
Tongue Numbness	1	0	0	1
Unsteadiness	1	0	0	1
Vertigo	0	1	0	1
TOTAL	**85**	**11**	**0**	**96**

Events were reported in this table as ADE's if they were found during CEC adjudication to be not serious and were found to be caused by the mastoidectomy w/facial recess, device, peri-operative surgery related, or device implant procedure related. Of the 96 ADE's reported, 67 (70%) have recovered with no residual effects while 29 (30%) were ongoing at the time of the report, including taste disturbance (11), ear pain (3) and tinnitus (3).

AE: A total of 29 events in 25 subjects were reported which were classified as Adverse Events (AE). 17 events were classified as mild, 4 as moderate and 1 severe. The AE's are as follows:

Table 20: AE's: A total of 29 events in 25 subjects are reported

Event	Mild	Moderate	Severe	Total
Apnea	1	0	0	1
Dizziness	1	0	0	1
Ear Canal Wound (non-implant ear)	0	0	1	1
Eustachian Tube Dysfunction	1	0	0	1
Headache	1	0	0	1
Imbalance	1	0	0	1
Knee Pain	1	0	0	1
Light Headedness	1	0	0	1
ME Effusion	1	0	0	1
ME Fluid	1	0	0	1
Motor Vehicle Accident	1	0	0	1
Mucosal Inflammation	0	1	0	1
Nose bleed	2	0	0	2
Pain	0	1	0	1
Post Nasal Drainage	1	0	0	1
Rapid Heart Rate	1	0	0	1
Rash Abdominal	1	0	0	1
Root Canal	1	0	0	1
Sinus Infection	2	0	0	2
Sprained Ankle	0	1	0	1
Touch Sensation	1	0	0	1
Tinnitus	0	1	0	1
URI	2	0	0	2
Vertigo	2	0	0	2
Yeast infection	1	0	0	1
TOTAL	**24**	**4**	**1**	**29**

By definition, the AE's reported in this table were not serious. Events were classified as AE's if they were found during CEC adjudication to be caused by underlying or concomitant illness, concomitant medications, or other causes. Of the 29 AE's reported, 21 (72%) have recovered with no residual effects while 8 (28%) were ongoing at the time of the report, including Apnea, Imbalance, Knee pain, Light headedness, tinnitus, touch sensation and URI (2).

AE First Occurrence Timing: Another way to depict the occurrence of adverse events is by time of occurrence. Table 21 provides a summary of the first reported occurrence for the various adverse events experienced by more than one subject in this trial. Overall, the occurrence of adverse events goes down dramatically from the implant-14 day post-op time frame to the post 2-month follow-up time frame.

Table 21: AE First Occurrence Timing Reported by More than One Subject

Time Period	Adverse Event	Number
Pre-Implant		
Implant to 14 Days Post-Op	Taste Disturbance	18
	Ear Effusion	16
	Dizziness/Imbalance/Vertigo	10
	Tinnitus	7
	Ear Pain/Pressure/Incision Discomfort	5
	Facial Weakness	3
	Feedback	2
	Headache	2
Healing Period 2 to 10 weeks	Ear Effusion	5
	Taste Disturbance	4
	Ear Pain/Pressure/Incision Discomfort	3
	Tinnitus	2
	Ear Cracking	2
	Incision Discomfort/Infection	2
Activation	Incision Breakdown	1
Post-Activation (0 to 2 Months)	Taste Disturbance	1
	Mild pain in head	1
Post-Activation (2 to 10 Months)	Imbalance	2
	Taste Disturbance	2
	Congestion/Sinus Infection	2
	Vertigo/Unsteadiness/Imbalance	1
	Pain in temporal bone	1
	Ear Effusion	1

There were 78 adverse events reported during the implant to 14 days post-implant time period. The most frequently reported AE's were Taste disturbance (18), ear effusion (16), dizziness/vertigo (10) and tinnitus (7). During the healing period 2 to 10 weeks post-implant, 33 adverse events were reported with the most frequent being ear effusion (5), taste disturbance (4) and ear/incision pain (3). After Activation, taste disturbance is the most frequently reported adverse event.

Top 10 Device/Procedure related AE: Overall, 102 device/procedure related AE's were reported. The top ten (10) reported device/procedure related adverse events are shown in Table 22 below. Taste disturbance is the most frequent device/procedure related ADE; the majority of the top ten occurring ADE's are typical of the mastoidectomy with facial recess surgical procedure.

Table 22: Top 10 Device/Procedure related AE

Event Type	N Events	% of Events	N Pts With Events	% of Patients
Chorda Tympani/Taste Disturbance	24	24%	23	40%
Ear Effusion/Fluid	17	17%	17	30%
Tinnitus	9	9%	8	14%
Dizziness/Vertigo	7	7%	7	12%
Incision Discomfort/Breakdown	6	6%	6	10%
Ear Pain	4	4%	4	7%
Facial Weakness/Paralysis	4	4%	4	7%
Headache/Pain (post-op)	4	4%	4	7%
Ear Cracking/Roaring	3	3%	3	5%
Otitis Externa/TM	3	3%	3	5%

6.0 Protocol Deviations

The term protocol deviation is used to describe instances where the investigational protocol was not followed: A summary of the protocol deviations are listed in Table 23.

Table 23: Protocol Deviations

Deviation	N	N Patients
Inclusion / Exclusion criteria not met	12	9
Informed consent not completed correctly	0	0
Subject missed visit	0	0
Visit completed outside the allotted window	17	11
Required Test not performed	17	10
Other deviation	6	6
Total	52	28*

***** Some subjects have more than one protocol deviation.

Protocol deviations included in the above categories are:

- Inclusion/Exclusion criteria not met: minor threshold deviations; speech discrimination scores < 60% before FDA approved protocol change to Inclusion Criteria (SD > 40%)
- Visit outside window: scheduling problems resulting in minor deviations
- Required test not performed: Questionnaire delays, calibration issues or tester error
- Other deviations: Transducer capacitance out of spec due to OR temperature; Driver attach done in second procedure

All the protocol deviations are considered minor and have no effect on subject safety or the scientific validity of the data as demonstrated by the analyses included in Appendix 3.

Complete details of the Protocol Deviations are provided in Appendix 6.

7.0 Conclusion

As demonstrated by the results of this clinical trial through 10-months post-activation, Esteem is safe and effective in treating sensorineural hearing loss. Concerning safety, the Esteem implant had a 5% revision rate prior to the 4-month follow-up visit due to fibrotic tissue growth/interference and no revisions between 4 and 10-month follow-up. None of the revisions were due to Esteem device malfunctions. The Esteem implant procedure and therapy had no significant effect on cochlear function stability as measured by bone conduction. The Esteem and the implant procedure resulted in no unanticipated adverse events and the occurrence of expected adverse events was similar to a normal mastoidectomy procedure. Concerning effectiveness, Esteem was statistically superior to the pre-implant hearing aid in Speech Reception Threshold and Word Recognition Scores. In addition, Esteem outcomes were better than or equal to the pre-implant hearing aid condition in several other standard audiological measures, including Abbreviated Profile of Hearing Aid Benefit and the hearing in noise test as measured by QuickSIN.

8.0 Risk analysis

8.1 Out-of-Service Explanted Devices

Since the beginning of this clinical trial, there have been four (4) surgical revision procedures conducted that resulted in the explant of one or more components of the Esteem System. The revision of subject [redacted] was due to limited benefit caused by a low Sensor output restricted by fibrotic tissue interference. Subject [redacted] was revised due to low Driver output restricted by fibrotic tissue interference. Subject [redacted] was revised due to low Driver output restricted by fibrotic tissue interference. In addition, one subject [redacted] had an infection at the surgical implant incision that would not heal and required explant of the entire Esteem system. A summary of the post-explant analysis of these components is provided in Table 24 below.

Table 24: Out-of-Service Explanted Device Analysis

Subject Number	Date of Revision	Reason for Revision	Explanted Component	Out of Service Reason	Analysis Conclusion
[redacted]	10/16/08	Low Sensor Output due to Fibrotic Tissue	Sound Processor (Model/Serial 2001/200168) Sensor (Model/Serial 7002/130286) Driver (Model/Serial 7502/160243)	Removed due to extensive fibrotic tissue growth	SP, Sensor and Driver met all functional specifications
[redacted]	5/29/09	Low Driver Output due to Fibrotic Tissue	Sound Processor (Model/Serial 2001/200326) Driver (Model/Serial 7502/160047)	Removed due to extensive fibrotic tissue growth	SP and Driver met all functional specifications
[redacted]	5/01/09	Low Driver Output due to Fibrotic Tissue	Sound Processor (Model/Serial 2001/200300) Driver (Model/Serial 7502/160042)	Removed due to extensive fibrotic tissue growth	SP and Driver met all functional specifications
[redacted]	2/27/09	Incision Infection	Sound Processor (Model/Serial 2001/200373) Sensor (Model/Serial 7002/130187) Driver (Model/Serial 7502/160020)	Removed due to incision infection that wouldn't heal due to subject smoking.	SP, Sensor and Driver met all functional specifications

8.2 Risk Benefit Analysis

The subjects enrolled in this study were adults suffering from sensorineural hearing loss. All were utilizing hearing aids, which are the most common treatment prescribed for this type of hearing impairment. External hearing aids, whether behind the ear or in the ear canal, utilize microphones and are prone to feedback, poor sound quality, fitting problems and other limitations that generally lead to user dissatisfaction, limited interaction with others and a degradation of quality of life.

This clinical trial validated the effectiveness of the fully-implantable Esteem in several audiological measures by demonstrating superior or similar hearing benefit as compared to the subjects' pre-implant hearing aid. In addition, quality of life questionnaire results showed that a majority of subjects found the Esteem to be somewhat to much better than the hearing aid for sound clarity, natural sounding, and ability to hear conversations in crowds and with background noise. The Esteem greatly improved the majority of subjects' self confidence and allowed them to live much more active lifestyles.

The risks associated with the Esteem implant include those adverse events that are associated with mastoid operative procedures, which are typically transient in nature, and those that result in limited or no hearing benefit, which may require a second surgical procedure to correct. The most frequent adverse events reported in this clinical study included taste disturbance (40%), ear effusion (30%), and tinnitus (14%). Causes of limited or no benefit include surgical or medical complications, improper implant technique or defective components. Typically these can be revised and hearing benefit can be restored. There were 3 subjects (5%) revised in this study. However, there is a risk that the device may need to be explanted and the ossicular chain reconstructed to restore hearing to pre-implant condition.

In this study, nearly 90% of the subjects responded that they would be likely to very likely to do the Esteem implant again. This testimonial from the clinical subjects together with the positive audiological effectiveness and safety results provide a strong supportive conclusion that the benefits of the Esteem do outweigh the associated risks.

8.3 Published Articles

No new published articles or conference presentations concerning Esteem have been authored since the last Annual Progress Report.

9.0 Other Changes

9.1 Summary of IDE Supplements

The table below outlines the progress of the Esteem System Pivotal Trial through submissions and approvals related to the IDE, Protocol 0204 and informed consent since the approval of the IDE.

Table 25: FDA Submissions

Date	Supplement	Subject
1/11/08	S001	Response to Conditional Approval Letter
1/23/08	S002	Submission of IRB Approval Certifications
2/19/08	S003	5 Day Notice of Change: Inclusion Criteria for SD > 40%
3/28/08	S004	Response to Conditional Approval Letter
6/03/08	S005	5 Day Notice of Change: Manufacturing Site Changes
7/16/08	S006	Request for Revision: [redacted]
9/09/08	S007	Request for Revision: [redacted]
9/24/08	S008	Response to [redacted] Conditional Approval Letter
11/07/08	S009	Request for Revision: [redacted]
11/10/08	S010	Response to [redacted] Conditional Approval Letter
11/10/08	S011	Response to [redacted] Conditional Approval Letter
11/14/08	S012	IDE Annual Report 2008
12/19/08	S013	Withdrawal of [redacted] Request for Revision
12/31/08	S014	Response to Annual Report Questions
1/12/09	S015	Request for Continued Access Expansion
2/09/09	S016	Response to Annual Report Questions
2/13/09	S017	Request for [redacted]
2/18/09	S018	Response to Conditional Approval for Continued Access Expansion
2/19/09	S019	Request for Revision: [redacted]
3/18/09	S020	Response to Annual Report Questions
6/05/09	S021	Response to ISA Questions

9.2 Summary of Minor Design Changes Implemented

Other than the changes made via IDE Supplement listed above, no additional design or manufacturing changes were made during the clinical study.

Concerning the Clinical Protocol, in addition to the supplement listed above concerning the Protocol Inclusion Criteria, the ISA test criteria at implant has been refined and modified from the Protocol. The ISA test criteria change has been discussed in S008, S011 and S021.

10.0 Future Plans

10.1 Pivotal Trial

Enrollment in the original Pivotal Trial has been completed. Subjects will continue to be followed per protocol until the trial is completed.

10.2 Continued Access

Continued Access Expansion has been granted and five (5) subjects have been enrolled and implanted to date. While no issues were reported at these additional implants, none of the subjects has reached a follow-up point for data collection per protocol. Subjects will continue to be followed per protocol until the trial is completed.

10.3 Post-approval Study

A post-approval study has been requested by FDA. An extension of this clinical trial is being proposed, which will continue the follow-up of the implanted subjects through 5 years. It is not anticipated that any additional subjects will be enrolled or implanted.

11.0 Appendices for Esteem Clinical Report

Appendix	Title
1	Clinical Study Protocol
2	Previous Study Comparison: IDE G000321 and IDE G070162
3	Pivotal Trial Data
4	Subject Status
5	Adverse Events
6	Protocol Deviations