UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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EAR, NOSE AND THROAT DEVICES PANEL

+ + +

December 18, 2009
8:00 a.m.

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PANEL MEMBERS:

DONALD A. LEOPOLD, M.D.	Chairman
JOSEPH W. HALL III, Ph.D.	Voting Member
MARGARET A. KENNA, M.D.	Voting Member
AKIRA ISHIYAMA, M.D.	Temporary Voting Member
ANIL K. LALWANI, M.D.	Temporary Voting Member
BARRY ELIOT HIRSCH, M.D.	Temporary Voting Member
BRENDA LONSBURY-MARTIN, Ph.D.	Temporary Voting Member
JASON CONNOR, Ph.D.	Temporary Voting Member
JOHN J. ROSOWSKI, Ph.D.	Temporary Voting Member
KATHLEEN C. SIE, M.D.	Temporary Voting Member
LINDA J. HOOD, Ph.D.	Temporary Voting Member
PAUL R. KILENY, Ph.D.	Temporary Voting Member
ROBERTO A. CUEVA, M.D.	Temporary Voting Member
STEVEN W. CHEUNG, M.D.	Temporary Voting Member
SUSAN J. NORTON, Ph.D.	Temporary Voting Member
YVONNE S. SININGER, Ph.D.	Temporary Voting Member
TERRY D. PORTIS	Consumer Representative
DAVID M. TIMLIN	Industry Representative
JAMES K. KANE, Ph.D.	Designated Federal Officer
JAMES P. SWINK	Designated Federal Officer

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JACK SHOHET, M.D.
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OPEN PUBLIC HEARING SPEAKERS:

AMANDA PAJULA
MICHAEL E. GLASSCOCK III, M.D., F.A.C.S.
ANDREA STINE
SUZANNE MERICLE BISHOP, D.M.D., P.C.
MANDY TAYLOR
CRAIG B. ARNOLD
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M E E T I N G

(8:00 a.m.)

DR. LEOPOLD: I'd like to call this meeting of the Ear, Nose and Throat P090018 Devices Advisory Panel to order. I'm Dr. Don Leopold, and I'm the chair of this Panel. I'm an otolaryngologist and professor at the University of Nebraska Medical Center in Omaha, Nebraska.

At this meeting, the Panel will be making a recommendation to the Food and Drug Administration on the pre-market approval application P090018 for the Esteem Totally Implantable Hearing System. This device is indicated to alleviate hearing loss in adults by replicating ossicular chain and providing additional gain.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this Panel during one of the open sessions, please provide your name to Ms. AnnMarie Williams at the registration table. Also, if anyone requires sign language interpreting, please see Ms. Williams for this.

If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to

the FDA, please arrange to do so with Ms. Williams.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R., Part 14, and I would like to add that the Panel participating in the meeting today has received training in FDA device law and regulations. To be fair to everyone concerned, I would like to stay as close as possible to our agenda today.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And let's start to my left here.

DR. KANE: I'm Dr. James Kane. I'm the designated -- Dr. James Kane, Designated Federal Official for the ENT Advisory Panel. I'm also an audiologist and scientific reviewer in the Ear, Nose and Throat Branch, FDA.

MR. SWINK: My name is James Swink. I'm the Designated Federal Officer for the Office of Device Evaluation.

DR. CUEVA: My name is Dr. Roberto Cueva. I'm an otologist/neurotologist in practice at Southern California Permanente Medical Group and also an associate professor at UC San Diego.

DR. HALL: My name is Joe Hall. I am a professor at the University of North Carolina, Chapel Hill, and I'm in audiology and cycloacoustics.

DR. CHEUNG: Steven Cheung at University of California, San Francisco, clinical otologist and research interest in auditory physiology.

DR. SININGER: I'm Yvonne Sininger. I'm a professor at the medical school at UCLA. And I'm an audiologist and a hearing scientist.

DR. NORTON: I'm Susan Norton. I'm a professor at the University of Washington, School of Medicine, in otolaryngology and also an audiologist at Seattle Children's Hospital.

DR. CONNOR: Hi. My name is Jason Connor. I work for Barry Consultants, and I'm a statistician with expertise in clinical trial design.

DR. LONSBURY-MARTIN: I'm Brenda Lonsbury-Martin. My expertise is cochlear physiology, and I'm a professor at Loma Linda University Medical Center.

DR. PORTIS: I'm Dr. Terry Portis. I'm an administrator with Anne Arundel Community College and a psychologist.

MR. TIMLIN: I'm Dave Timlin. I'm the industry representative on the Panel. I work for Medtronic XOMED ENT, and that's it.

DR. EYDELMAN: Good morning. I'm Malvina Eydelman. I'm Director of the Division of Ophthalmic Neurological and ENT Devices.

DR. SIE: I'm Kathy Sie, a professor of otolaryngology at the University of Washington and an appointment at Seattle Children's Hospital.

DR. ROSOWSKI: I'm John Rosowski. I'm from the Massachusetts Eye and Ear Infirmary, where I work on middle ear function and disease, and I'm also a professor of otology and laryngology at Harvard.

DR. LALWANI: Anil Lalwani from New York University. I'm a professor of otolaryngology. My clinical interest is in otology/neurotology, and my research interest is in molecular biology of hearing loss.

DR. KILENY: Good morning. I'm Paul Kileny. I'm a professor of otolaryngology at the University of Michigan and the director of Division of Audiology, and I'm a audiologist, licensed to practice in the states of Michigan and Indiana.

DR. KENNA: I'm Marly Kenna, and I'm a pediatric otolaryngologist at Children's Hospital in Boston with a specialized interest in deaf and hard of hearing children. I'm also a professor of otology and laryngology at Harvard Medical School.

DR. ISHIYAMA: I'm Akira Ishiyama from UCLA School of Medicine, and I'm an otologist/neurotologist. My research interests include molecular biology of Ménière's disease and anatomy of the human temporal bones.

DR. HOOD: I'm Linda Hood. I'm a professor at Vanderbilt University. I'm an audiologist with research interests in auditory physiology.

DR. HIRSCH: I'm Barry Hirsch. I'm a neurotologist, Director of Neurotology at the University of Pittsburgh Medical Center.

DR. LEOPOLD: Dr. Kane, our Designated Federal Officer of this Panel, will now make some introductory remarks.

DR. KANE: Good morning. I will now read into the record two Agency statements prepared for this meeting: The Conflict of Interest Statement and the Appointment of Temporary Voting Members Statement. First, I'll read the Conflict of Interest statement.

The Food and Drug Administration is convening today's meeting of the Ear, Nose and Throat Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the

industry representative, all members and consultants of the Panel are special government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Part 208 and Part 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Part 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Part 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to

afford the committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose of 18 U.S.C. Part 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves a discussion on a pre-market approval application, or PMA, for the Esteem Totally Implantable Hearing System, sponsored by Envoy Medical Corporation. The Esteem is a totally implantable hearing device that is implanted in the middle ear to help hearing in patients suffering from mild to severe hearing loss that is sensorineural in origin. The intended use of the Esteem is to alleviate hearing loss in adults by replicating the ossicular chain and by providing additional gain.

This is a particular matters meeting during which specific matters related to the PMA will be

discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Part 208 and Part 712 of the Food Drug & Cosmetic Act.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Mr. David Timlin is serving as the industry representative, acting on behalf of all related industry, and he is employed by Medtronic XOMED ENT.

We would like to remind members and consultants that if the discussions involve any other products and firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

I will now read the Temporary Voting Statement. Pursuant to the authority granted under

1 the Medical Devices Advisory Committee charter of the
2 Center for Devices and Radiological Health, dated
3 October 27, 1990, and as amended August 18, 2006, I
4 appoint the following individuals as voting members
5 of the Ear, Nose and Throat Devices Panel for the
6 duration of this meeting on December 18, 2009:
7 Dr. Akira Ishiyama, Dr. Anil Lalwani, Dr. Barry
8 Hirsch, Dr. Brenda Lonsbury-Martin, Dr. Jason Connor,
9 Dr. John Rosowski, Dr. Kathleen Sie, Dr. Linda Hood,
10 Dr. Paul Kileny, Dr. Roberto Cueva, Dr. Steven
11 Cheung, Dr. Susan Norton, and Dr. Yvonne Sininger.
12 For the record, these individuals are
13 special government employees who have undergone the
14 customary conflict of interest review and have
15 reviewed the materials to be considered at this
16 meeting.
17 Before I turn the meeting back over to
18 Dr. Leopold, I'd like to make a few general
19 announcements, which will be followed by an
20 announcement by Ms. Geretta Wood, Panel Coordinator.
21 You should make note of the following announcements:
22 Transcripts of today's meeting will be
23 available from Free State Court Reporting, Inc.
24 Their telephone number is (410) 974-0947.
25 Information on purchasing videos of today's meeting

can be found on the table outside the meeting room.

I would like to introduce our FDA press contact, Ms. Peper Long. If she's here, she can stand.

I would like to remind everyone that members of the public and press are not permitted in the Panel area at any time during the meeting, including breaks. If you are a reporter and you wish to speak to FDA officials, please wait until after the Panel meeting has ended.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, as a courtesy around you, please silence your electronic devices if you have not already done so. Thank you very much.

Geretta?

MS. WOOD: Good morning. First of all, I'd like to thank the Panel members for being here today to participate in this ENT Advisory Panel meeting. Secondly, I would like to take a few moments to recognize Dr. James Kane.

Dr. Kane is first and foremost a leading scientific reviewer for ENT products. But in addition, he has also served as Executive Secretary

or Designated Federal Officer for the ENT Panel since 2006. Due to the centralization of the Designated Federal Officers who serve as executive secretaries to the ODE Advisory Panels, Jim will dedicate his efforts full-time as a scientific reviewer.

James, I want to personally thank you for your dedication and say I've enjoyed working with you over the past few years.

Mr. James Swink will be taking over as the Designated Federal Officer for the ENT Panel. He graduated from the University of Maryland in 2003 with a degree in neurobiology and physiology. Prior to coming to the Advisory Committee staff, James has served as a reviewer for the Interventional Cardiology Devices Panel and a project manager for the Division of Cardiovascular Devices. James was responsible for the Circulatory System Devices Panel from 2006 to 2009, where he organized over 19 Panel topics across three divisions.

James, I want to welcome you as the new Designated Federal Officer. Thank you.

(Applause.)

DR. LEOPOLD: There will now be a brief presentation before the main agenda topic by Dr. Malvina Eydelman, Director of the Division of

1 Ophthalmic, Neurological and Ear, Nose and Throat
2 Devices. Dr. Eydelman, you may now proceed with your
3 FDA update presentation.
4 DR. EYDELMAN: Thank you. Actually,
5 Dr. Danica Marinac-Dabic will be presenting first,
6 and I will follow. She will now be presenting a
7 post-approval studies update.
8 DR. MARINAC-DABIC: Good morning, ladies
9 and gentlemen, Dr. Leopold, Dr. Eydelman,
10 distinguished members of the Panel. My name is
11 Danica Marinac-Dabic, and I'm the Director of CDRH's
12 Division of Epidemiology. Division of Epidemiology
13 resides in the CDRH's Office of Surveillance and
14 Biometrics and is in charge of oversight for mandated
15 post-approval studies for medical devices and also in
16 charge of conducting FDA-sponsored original research
17 studies that are designed to address overarching
18 epidemiologic issues related to medical device
19 performance post-market.
20 Before I begin, I would like to introduce
21 two members of my division who are here today and
22 working on ENT devices. The first, I would like to
23 introduce Dr. Federico Soldani, who is the reviewer
24 for this PMA from the epidemiologic perspective, and
25 also, Dr. Cara Krulewitch who is a team leader

1 overseeing the ENT epidemiologic work in my division.
2 Let me first begin with a brief overview of
3 FDA mandate, as far as the post-approval study goes.
4 As you know, at the time of the approval for some PMA
5 devices, FDA has the authority to ask for continuing
6 collection of data that will confirm the safety and
7 effectiveness and reliability in the post-market
8 setting for PMA products. And this authority is
9 outlined on this slide.
10 I also would like to put this in post-
11 market context. As you can see, the CDRH certainly
12 endorses the concept of shared responsibility for the
13 safety and effectiveness of medical devices in the
14 post-market setting. On the last slide, you will see
15 that there is one component of our post-market
16 science responsibility that certainly resides in our
17 regulated industry arena. Those are the studies that
18 are mandated by the FDA at the time of the approval.
19 We call them post-approval or condition of approval
20 studies that are presented in red on this slide.
21 On the right side, you will see that the
22 FDA also sponsors our original studies that are
23 designed to independently look into specific safety
24 and effectiveness or use issues in the post-market
25 setting of medical devices. That's represented on

the right side. But we also have, as you probably already know, evolving sentinel initiative that is led by the FDA but also involves a lot of networks outside of the FDA, that will have a lot of potential to change the way how FDA designs these post-market studies and also how we take advantage of the distributed networks across the country that collect the information on safety and effectiveness of medical devices.

So under this initiative, we will also have the opportunity to improve the post-market infrastructure for studying medical devices in the post-market setting and also developing the methodologies, hopefully helping also our colleagues from industry to be able to utilize more diverse tools to address the FDA questions for the post-market performance of devices.

Then I would like to say a couple words about the public health value of post-approval studies and why we are asking for those. The post-approval studies really have a lot of utility in evaluating medical devices as they enter the real-world utilization beyond the arena of very heavily controlled, randomized, controlled trials that are primarily done in the pre-market setting. And then

our goal is really to feed back the information that we learn in the post-market setting back to our pre-market colleagues. And, hopefully, these post-approval studies will be able to contribute to better design of future pre-market studies.

Post-approval studies also can provide the very meaningful infrastructure for nesting pre-market clinical trials, and we have a lot of examples. For example, in cardiovascular arena, where we have the registries developed to address specific post-market questions, and then the industry is also using this infrastructure to nest the pre-market trials.

But also, post-approval studies can be also very useful to detect real-time signals as the study continues to progress. We do not wait until study is over. We review reports every six months, and if there is a signal that we identify, then it's potentially actionable, and we certainly act on those.

And, finally, these individual post-approval studies help us identify overarching regulatory science needs that are not related to a specific PMA, but rather to a specific class of devices. And this is where, then, the FDA dollars come in, and we fund our own research to address

1 those and not to put that burden on our colleagues
2 from industry.
3 What we can get from post-approval studies.
4 We can certainly gather essential post-market
5 information on long-term performance of medical
6 devices because pre-market trials are typically
7 short-term. And we would like, especially for
8 implantable devices, to know how these devices
9 perform long-term.
10 We're also learning about real-world device
11 performance once the device is being used by
12 community types of hospitals, physicians outside of
13 the clinical sites utilizing the pre-market settings.
14 We can also assess the effectiveness of the training
15 programs and learning curves in the post-market
16 setting. We can study the subgroup performance for
17 those vulnerable populations that have not been
18 represented in the pre-market clinical trials, and
19 certainly, if there are outcomes that concerns both
20 safety and effectiveness that can be further studied
21 in the post-market setting, provided that they're not
22 essential for the establishment of safety and
23 effectiveness of medical devices, which decision has
24 to be made at the time of the approval.
25 For those of you who are new to this Panel,

I would like just briefly to go over some of the major recent developments at CDRH. In 2005 we transferred the post-approval studies program to the post-market Office of Surveillance and Biometrics. And at that time, we started -- you started, actually, I'm sure, seeing a lot of changes in the way -- how these presentations are being given to the Panel.

Also, you will see that the epidemiologist is added to the pre-market review teams. We started raising scientific rigor of post-approval studies, asking for hypothesis, for clear objectives, for sample size for those post-approval studies, that they're based on the objectives of the study. And we tried to work very closely with our pre-market colleagues. And with their help, we hope that we are continuing raising the bar for these post-approval studies.

In 2006 we developed and instituted tracking system that automatically tracks the progress of all post-approval studies asked by the CDRH. In 2007 we created the public website and database that is accessible on that website. In 2006 we issued the guidance documents for the industry and the FDA staff and updated that guidance twice since

then. In 2007 we started Advisory Panel updates, as this -- as such is the one that I'm giving today -- just to give you an overview of what the current developments are.

In 2008 we initiated BIMO inspections of post-approval studies. And, finally, in 2008, we increased the focus on building the post-market research infrastructure, in terms of facilitating the development of registries and other data sources that will then help the industry to nest their studies in those infrastructures.

And in 2009, this year, we have increased our focus on the development of methodologies, again, with the goal to also help the colleagues from industry to design better post-approval studies.

And I would like now to just say couple words about the volume of the studies that we have here in CDRH. And if you look at this slide, since 1995 to present, the CDRH asks for over 300 post-approval studies; actually, exactly 305 post-approval studies. And you can see that most of these studies, more than half, are certainly already -- actually 54% of these studies are still in progress, and 46% of the studies had been completed so far.

On this slide, very briefly, just to

illustrate how the number of post-approval studies that we ask at the time of the approval in relation to the number of approved PMAs and Panel track supplements -- for example, if we look for the year 2007, the CDRH approved 30 original PMAs and Panel track supplements, and for 12 of those, we ask -- we had conditions of approval. And for those 12 PMAs, we actually asked for 19 post-approval studies to address specific questions that had been identified either by the PMA review team or by the Panel.

CDRH staff is very carefully and very diligently looking into progress of these post-approval studies. So post-2005, as you can see, we have a total of 126 ongoing studies that had been initiated post-2005 when we transferred the program to OSB. Most of these studies are progressing well, but you can still see that there are 27, approximately 20% of these studies that we mark as progress inadequate. And for those, we have worked very hard with our colleagues from industry to make sure -- that address whether the obstacles have to do with enrollment issues or loss to follow-up, trying to help move these studies forward.

And this is the website that I was talking about. This is linked to our PMA database, and the

information that we can share with the public is on this website, and it can be accessed.

In our quest to -- more transparency, we have sponsored two workshops that have been very well attended this year. One was conducted in June and focused on implementation strategies for post-approval studies, received huge compliments from our colleagues from industry, which was very well attended. We had over 100 participants on site and almost as many attending as a Webinar.

In September, we have sponsored methodological approaches to post-approval when we brought leading experts from academia and also presented various aspects on how one can approach methodologically the post-approval study design. And as I said, in our increased focus on infrastructure building, we would like to point out that we certainly see the value of registries. We would like to use them more in the future. And, you know, as Panel members, you have a really critical role to play as you give us your update on the way -- as you give us your recommendation on the way -- what should be done in the post-market setting for medical devices.

And I have only two more slides just to

1 give you a couple of examples of CDRH ongoing
2 registry efforts. They are not from the ENT arena,
3 but I thought for your reference just including those
4 on the slides, you can see that we actually use
5 existing registries for post-approval studies,
6 INTERMACS being one of them. We also facilitate new
7 registry development, and these are some examples.
8 We are working with the ACC, HRS, STS on the
9 establishing of atrial fibrillation registry. We
10 also work with the American Association of Orthopedic
11 Surgeons on establishing American Joint Replacement
12 Registry. And there is also listed on this slides,
13 which show that we do -- we would like to see the
14 national infrastructure for medical device studies.
15 We also use these registries for our
16 discretionary studies, and we establish contracts
17 with the American College of Cardiology, for example,
18 to study ICD registries. I'm not going to go down
19 the list, but you will see also that we have
20 contracts outside of U.S. registries, such as
21 Orthopedic Registries of Australia and Denmark, where
22 we would like to have the information about how
23 devices perform post-market.
24 And this is the last slide. I have chosen
25 this to showcase one of the very innovative

methodological approaches that we are working currently on with our colleagues from Harvard on creating and quantifying the prognostic ability of models that pool multiple data sources to predict device long-term performance. As we are facing every day with the silos of information in the pre-market setting, post-approval studies, registry data, billing data coming from CMS and other databases outside of U.S. data, we have not utilized them, really, in a systematic way. So what we are doing now, we are putting together a model that will pool that data, and we will be able to help our colleagues from industry as well to utilize this as we ask for post-approval studies.

And highlights for 2010, the CDRH is establishing the formal relationship with ten academic centers that will work with us on these methodological advances. And we will be integrating into sentinel initiative and are committed to continue to be very transparent and to give you these updates at very Panel meeting.

I wish you a very successful day, and thank you very much for your attention.

DR. LEOPOLD: Thank you.

(Applause.)

DR. EYDELMAN: Good morning once again. I would like to take a few minutes to give you a division update. The last time ENT Panel meeting was held was in October 6 of 2004. That meeting was held by the Division of Ophthalmic and Ear, Nose and Throat Devices. Since 2004, this division has grown and expanded quite significantly. As a matter of fact, we have hired 36 new outstanding members to our team. I will now just read their names in alphabetical order: Patrick Axtell, Bernard Berne, Alexander Beylin, Kristen Bowscher, Jennifer Brown, Shelly Buchen, Daniel Clupper, Peter Quomo, Ann Costello, Sami Dahr, Vasant Dasika, Sarah Doll, John Doucet, Natalie Getzoff, Molly Ghosh, Margot Goodkin, Angelo Greene, Denise Hampton, David Heydrick, Michael Hoffmann, Tina Kiang, Robert Kramm, Alex Leder, Marisol Lendor, Ryan Kretzer, Timothy Marjenin, Sanjay Misra, Attallah Page, Lawrence Park, Shu-Chen Peng, Anna Postell, Marc Robboy, Susan Rudy, Michelle Tarver-Carr, Evella Washington, and Andrew Yang.

Additionally, since 2004, the Office of Device Evaluation has undergone significant transformation. The last time the Panel met, the Office of Device Evaluation structure looked like

this. It was the two divisions, DOD and DGRND, respectively, being the Division of Ophthalmic and Ear, Nose, Throat Devices and Division of General Restorative Neurological Devices. In February of 2009, all of the neurological devices from the Division of General Restorative and Neurological Devices were transferred to the Division of Ophthalmic and Ear, Nose and Throat Devices. As a result, our name has changed from DOD to DONED, and we're now Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices.

As you can guess, as a result, there have been quite significant reorganization of the division internally. And I would like just to take a few minutes to summarize current structure of our division. As you can see, I am very lucky to have two outstanding deputy directors, Dr. Kesia Alexander and Dr. Eric Mann, who is probably well known to most of you. Deborah Falls is our associate director, and all of the scientific reviewers are placed in four branches. Neurodiagnostic and Neurotherapeutic Devices Branch is led by Quynh Hoang. Kwame Ulmer is the branch chief of Ophthalmic Lasers, Neurostimulators and Diagnostic Branch. Tina Kiang leads the Intraocular, Cornea and Neuromaterials

1 Branch. And Dr. Srinivas Nandkumar is leading the
2 ENT Branch.
3 Each branch is responsible for a particular
4 kind of device. And while they're too numerous to
5 list on the slides, I just put highlights, or the
6 biggest buckets of the devices. So our NNDB branch
7 reviews neuromanual surgical instruments, VP, EEG
8 electrodes, and most of the neural implant
9 stimulators. Our ONDB branch reviews ophthalmic,
10 diagnostic, and surgical devices, brachial therapy
11 and retinal implants, cutaneous stimulation, RF
12 lesion, and neurolaser devices. Our ICNB is
13 responsible for IOLs, corneal implants,
14 viscoelastics, corneal storage media adhesives,
15 contact lenses, cranioplasty, dural sealants and
16 dural -- substitutes.
17 And last but not least, the ENTB, the
18 branch that is leading this Panel presentation today,
19 is responsible, obviously, for ENT devices, but
20 additionally is currently reviewing peripheral and
21 vagal nerve stimulators, neural endoscopes, auditory
22 evoked response, stereotaxis, and drills and burrs.
23 As I said, all of the reviewers are placed
24 in branches. And unfortunately, this slide cannot be
25 well seen, but it just demonstrates that the division

has grown, and we do have a lot of people in the division reviewing the devices. Last July, the whole office undergone a move to White Oak facility. As a result, we have a new phone number, which is now up on the screen, and I would like to encourage all of you to call us, e-mail us, just ask, and we're ready to answer any question that you might have.

Now, I would like to ask Nandu to continue with ENT Branch update.

DR. NANDKUMAR: Good morning, distinguished Panel members. My name is Srinivas Nandu Nandkumar, Branch Chief of the Ear, Nose and Throat Devices Branch.

All right. Okay. As mentioned by Dr. Eydelman in her division update, the ENT branch now also reviews neurological devices, such as vagals, neural stimulators, other peripheral stimulators and stereotaxic systems for neurosurgery. The scientific expertise in the branch reflects these neurological devices that we now review in addition to the ENT devices. As I introduce the branch members, I request that they stand up.

We have two audiologists, who are also hearing scientists, Dr. Jim Kane and Dr. Shu-Chen Peng. We have a board-certified toxicologist,

Dr. Vasant Malshet. We have a head and neck surgeon as our ENT medical officer, Dr. Angie Khan. We have two additional medical officers, a neurologist, Dr. David Hadrick, and a psychiatrist, Dr. Lawrence Park. Susan Rudy is a family nurse practitioner and serves as a nurse consultant and stability reviewer. Dr. Daniel Clupper has a Ph.D. in material science and engineering. Dr. John Doucet is a neuroscientist and a biomedical engineer. Lieutenant Andrew Yang has a master's in mechanical engineering and serves as an engineering and software reviewer. Mike Hoffmann has a master's in biomedical engineering. And Dr. Vasant Dasika has a Ph.D. in biomedical engineering with a hearing science specialization.

I'm going to present a few noteworthy approval submissions that were approved or cleared since the last ENT Panel meeting in October 2004. PMA supplement, P960058, Supplement 49, by Advanced Bionics, was approved on August 17th, 2006. A key aspect of this cochlear implant submission is the HiRes Fidelity 120 speech coding strategy. Fidelity 120 implements active current steering through rated simultaneous stimulation of an electrode pair during each processing cycle. It has the potential to choose from 120 unique spectral bands for stimulation

if all 16 electrodes are enabled. This strategy is limited for use in adults with post-lingual onset of severe or profound hearing loss; two, a minimum of three months experience with standard HiRes; and, three, who have the cognitive ability to choose between the sound processing options.

Another PMA submission, from Med-El Corporation, P00025, Supplement 23, was approved on September 24th, 2007. Supplement 25 was approved on December 19th, 2008. A key aspect of these cochlear implant submissions is the Maestro programming software with fine structure processing, approved for adults with six months experience and the cognitive ability to choose between speech processing options. This was approved in Supplement 23. And then the restriction regarding use of fine structure processing by inexperienced adult user was removed, and FSP was approved for all adults in Supplement 35. FSP aims to facilitate better encoding of patient lower frequencies.

A PMA supplement by Cochlear Corporation, Supplement 28, P970051, Supplement 28, was approved on March 1st, 2005. The Nucleus Freedom System was approved in this supplement, key aspects of which were higher stimulation rates and faster sampling

rates for telemetry. The CI-500 Series Implant, where a key aspect is reduced thickness of the implant case, was approved in Supplement 48, on August 28th, 2009.

The PROVENT Professional Sleep Apnea Therapy by Ventus Medical, Incorporated, submitted to the FDA in a 510(k), numbers K071560 and K090398, were cleared on February 8, 2008, and April 3rd, 2009, respectively. The device is indicated for the treatment of obstructive sleep apnea. The PROVENT device is placed just inside the nostrils. It directs expiratory flow through selected pathways, which increases intranasal pressure. The device is similar to the expiratory portion of the breathing cycle during CPAP use.

The HealthCheck Home Test for the loss of sense of smell, submitted to the FDA in a 510(k) submission, K051653, was cleared on March 27th, 2006. This device is intended for over-the-counter use to determine if a loss of olfactory function is present or has occurred in the patient. One or more odorants are presented to the patient's nose to detect an olfactory loss.

The branch has also been involved in several significant outreach activities since the

last Panel meeting, which I'll summarize in the next few slides. This is a snapshot of the FDA cochlear implant website. The ENT branch played a key role in the development of this website in January 2005. The purpose of this website is to describe cochlear implants linked to FDA-approved implants, tell the benefits and risks of cochlear implants, and provide news about cochlear implant recalls and safety issues. You can find information here on what educators of implant users need to know, what happens before, during, and after surgery, and where to report problems.

This is a snapshot of the FDA hearing aid website. The ENT branch also played a key role in the development of this website in October 2009. This site provides general information on hearing aids, types of hearing loss, different types and styles of hearing aids, how to get a hearing aid, benefits and safety of hearing aids, hearing aids and cell phones, other products and procedures to improve hearing, and a checklist of steps to remember and consider before purchasing a hearing aid. This site also includes information on the difference between hearing aids and sound amplifiers that amplify environmental sounds for consumers with no hearing

loss.

FDA issued a guidance for industry and FDA staff, entitled Regulatory Requirements for Hearing Aid Devices and Personal Sound Amplification Products, also known as PSAPs. This document was primarily written by the ENT branch and issued on February 25th, 2009. FDA regulate hearing aids as Class I medical devices, which are intended to compensate for hearing loss. On the other hand, PSAPs are intended to amplify environmental sound for non-hearing-impaired consumers. FDA does not consider sound amplifiers to be medical devices, as defined in the Food, Drug and Cosmetic act, when labeled for recreational or other use by individuals with normal hearing. However, certain safety regulations related to sound output levels still apply to these products. PSAPs are subject to applicable provisions of the Radiation Control For Health and Safety Act of 1968 under which FDA regulates electronic products that emit sound vibrations.

The ENT Branch was involved in a tinnitus masker guidance document, which was issued on November 8th, 2005. This document provides regulatory guidance regarding pre-clinical testing,

clinical studies, and labeling for tinnitus masker devices.

FDA played an active role in the development of an ASTM standard on implantable middle ear hearing devices, also known as IMEHDs, adopted in 2005. This standard defines means for the description of system performance ex vivo. In particular, the standard describes system output of an IMED by measuring a physical quantity that is relevant to the insertion gain and output level of the IMED when implanted in the patient. Measurements defined in this standard should be useful for patients, clinicians, manufacturers, investigators, and regulatory agencies in making comparative evaluations of IMEHDs.

This concludes the ENT Branch update. Thank you.

DR. LEOPOLD: Thank you very much. We'd now like to move on to our Sponsor presentation for the Esteem Totally Implantable Hearing System. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel. Mr. Michael Spearman, Vice Chairman, Envoy Medical

Corporation will speak. You have up to 75 minutes for this presentation, and we have reserved approximately 15 minutes afterwards for questions. And I will let Mr. Spearman speak or introduce any speakers. Thank you.

MR. SPEARMAN: Good morning. As Dr. Leopold said, I am Mike Spearman. I'm the vice chairman of Envoy Medical, and on behalf of the entire Envoy team, we'd like to -- we're extremely happy and pleased to be here today to share the presentation of the Esteem implant and the results of the pivotal clinical trial.

Joining me today will be our three clinical investigators, Dr. Shohet, Kraus, and Catalano, Dr. Stach and Dr. Brown, who will also be doing parts of this presentation. In addition, we have Dr. Glasscock, Peter Schiller, Bud Horwath, and Chris Mullin, who will be available during the Q and A session to answer questions as well.

And just to give you a little idea of how we have this set up, I'll do a little bit of the introduction or the background of the Esteem. Dr. Shohet will take us through the surgery. Dr. Kraus will speak to the battery processor replacement surgery, as well as reversing and

reconstructing the ossicular chain. Dr. Catalano will talk about the adverse events in the clinical study as well as revisions. Dr. Stach will speak to the ideological perspective of the Esteem. And Dr. Brown will speak to statistics in a couple of areas.

This represents an important milestone in hearing loss treatment. There have been two previous middle ear implants which have been approved, the Soundtec and the Soundbridge, both in 2001, as well as several cochlear implants. But these were all partially implantable devices. The Esteem is the first totally implantable middle ear device for sensorineural hearing loss and, in fact, the first totally implantable hearing device for sensorineural hearing loss.

And if we think about partially implantable versus totally, they all share very similar concepts with respect to the way that they take sound and input it to the processor in the system. You're all familiar with hearing aids, a microphone and a processor, and then they use a speaker to deliver acoustic energy into the ear canal to drive the TM and the ossicles.

But, of course, we're all familiar with,

also, the difficulties that hearing aids create, collusion effects, distortion, and feedback, because the acoustic energy leaking back through around the ear molds or through the vent systems, and that feedback actually prevents a certain amount of functional gain once the system gets to that point.

Middle ear implants get rid of the acoustic energy, and in the case of Soundbridge and Soundtec, use a similar concept of using an electromagnetic technology to drive a small, rare earth magnet that's been implanted on the ossicles at the IS joint, and to directly drive the stapes and the cochlea. They share the internal processing system, similar to a hearing aid, where there is a microphone and a processor that takes the sound in, processes it, and then delivers it in one form or another to the -- in a couple different forms to those magnets to vibrate the ossicles, and both of them have external devices like a hearing aid. And, of course, your cochlear implant, similar in concept to the processing, like a hearing aid, microphone processor, and then delivering the electronic signals transdermally to the receiver to the cochlea.

If we think about how our natural anatomy works, it's really quite elegant, in the sense of how

normal people hear. For one, we have the pinna, which collects sounds. And in doing so and transferring those and focusing them on the concha and into the canal, there is what we call the pinna effect in which it tends to amplify high frequency sounds, peaking at about 4K and, in effect, filtering out background noise, or lower frequency sounds, which is typically background noise.

In addition, the ear canal, being a long tube, acts as a resonator, and it resonates higher frequencies, and in a sense, filtering out lower frequency sounds. The interesting part, the combination of these two amplifies all these important high frequency sounds, which is where the contents, the major contents of speech is located, and filters out background noise. So this helps people in environments, noisy environments, restaurants, et cetera, in the real world, be able to better understand speech in real-world conditions.

And that's really where the difficulty lies in an external processing device like this because they don't take advantage of the pinna and the canal and utilize all that natural processing coming in. Instead, they have to try doing it within the processor itself. And that's really the elegant

beauty of the Esteem.

The first thing that one will notice about the Esteem is there is no microphone. Instead, we utilize a couple -- there is a piezo electric transducer called a sensor and a piezo electric transducer called a driver. And I'm holding a sample of the implant in front of me here, and we'll pass it around after this so you can look at it.

These are connected to the sound processor, which contains the battery by a couple of leads, which are removable and to be able to put back in. That enables this battery and processor to be changed out when it comes to the end of battery life in a simple process, as Dr. Kraus will explain, and then to be put back together and put back into the patient.

The sound processor is basically similar in construction to a pacemaker. It's an all titanium case, hermetically sealed, and we use the same manufacturing techniques that are used in the pacing industry. So it's a very robust design. It houses the electronics, the processing electronics, and everything, to process sound, as well as primary battery. When we say a primary battery in the pacing industry and neurostim industries and now ours, it

means a non-rechargeable battery. It's used one time and discarded.

The beauty of the Esteem system is the technology and design of these sensors and transducers, as well as the processor has such a low power consumption, this battery will last for four and a half to nine years without being recharged in a patient. And that's a pretty amazing milestone, too.

As you've probably seen, the way in which this is implanted in the patient is the processor is placed behind here under the skin in the mastoid and the sensor is attached to -- excuse me -- to the incus. And the driver is attached to the stapes.

That allows sound to be naturally captured by the pinna through the canal the same way a normal hearing person listens to sound and, indeed, the ossicles to vibrate in the same way. So we have the processed sound the same way that a normal person hears.

The sensor then picks up those sounds, those vibrations, I should say, and converts them into an electric signal, back to the processor, which then takes and adjusts those signals for the specific loss of the patient, not unlike a hearing aid, and then sends the process signals back to the driver,

where they're converted to mechanical energy to directly drive the stapes to the cochlea.

Now, as you can imagine, we have a driver connect -- we're driving the ossicular chain at the stapes, we're sensing at the incus. There would be feedback between those systems if we did that, so what we do is we resect about a 1 to 2 mm section of the long process of the incus in order to prevent feedback in the system.

One of the benefits of all middle ear devices which have come to this industry, including the two previous and the Esteem, is that we've gotten rid of the acoustic energy requirement to drive the chain. And in doing so, we've eliminated that feedback loop. So what that does is offers the ability to provide increased gain without going into feedback. The other thing, of course, is without something in the ear, we get rid of the occlusion effect, the direct driving has less distortion, and this whole concept of this natural ear has a much more natural sounding quality, natural sound quality to a patient.

But the additional benefits that come from the Esteem have to do with the fact that we do have this natural hearing effect that we're using and a

much more natural input to the processor, to the patient. Of course, it leaves the canal totally open for patients, which they love. And, in addition, because it's totally implantable, it's invisible to others.

But it also becomes somewhat invisible to the patient. They're no longer having to maintain or clean hearing aids. They're no longer reminded that they have to change batteries every week. They're able to use this in all types of environments, including swimming, sleeping, showering, and sporting activities, times in which they've not been able to use hearing aids in the past. In essence, it decouples them more and more from their handicap and allows them to live a much more normal and natural life.

Having said that, I'll turn this over to Dr. Shohet, and he'll take us through the surgery.

DR. SHOHET: Thank you, Mike. Good morning, everyone. I have to point out. I am not an F.A.C.S., so I apologize for that slide. My name is Jack Shohet. I am an M.D. I work in Orange County, California. I am a principal investigator on this project since 2004. I do not have an equity interest in the company. I am a surgical consultant. And I

am compensated for my time and travel expenses.

I'm going to give you an overview of the surgery involved in doing the Envoy. I liken it most similarly to a cochlear implant in that we make an L-shaped or a lazy-S type of postauricular incision. We then complete a mastoidectomy and identify the facial nerve, and a large facial recess approach is needed. We do intact chain testing to assess the mobility of the ossicular chain. We then resect a small portion of the incus, about 1 to 2 mms, with a laser. We clean the soft tissue off of the stapes. We then insert the sensor and driver into the system and cement it in place with bone cement. Intraoperative system testing is then performed, and we then close the wound.

Here, you can see a projection of the implant over the skull. The well is drilled to accommodate the implant to help stabilize it. You can see the two transducers, the sensor and the driver, coming out of the header portion of the sound processor and their position within the mastoid cavity.

This is the L-shaped incision, which hugs the hairline, and an S-shaped incision.

We use a speaker/microphone assembly that's

positioned in the ear canal and held in place with a foam ear mold. This speaker/microphone assembly helps with later postoperative testing, or intraoperative testing. I'm sorry.

After the incision is made, we then do a mastoidectomy. We identify the facial nerve, and a trapezoidal-shaped facial recess is done. We thin out the incudal buttress so as to allow the maximum exposure of the incus and lower the nerve over the facial ridge so as to identify the stapes crura.

Intraoperative testing with a laser Doppler vibrometry is then done to assess the intact chain mobility. And this helps us calibrate for further intraoperative testing.

A diode laser is then used in a non-contact mode, where we will then cut the incus. About 1 to 2 mms is removed to allow room for the driver.

In our best practices module, we identified that it was very important to remove soft tissue from the capitulum of the stapes. And here you can see the capitulum of the stapes with a cuff of mucosa around it. This allows and facilitates the maximum adhesion of the bone cements to the stapes capitulum.

A pre-coat with EnvoyCem is then done over the stapes capitulum after it's been completely

cleaned off of soft tissue.

Here you can see the Glasscock stabilizer bars, and these help stabilize the transducers as we position them into the mastoid cavity. They hold them in place so they don't move once you have them in the proper position before you cement them.

This is a image of the sensor properly placed, hugging the tegmen, with the tip of the sensor over the head of the incus. And here is the driver projecting through the facial recess.

This is a graphic of the driver going through the facial recess. And here you can see the tip of the driver adjacent to the stapes capitulum. It will be later cemented right there.

This is the transducers now positioned properly in the mastoid cavity, and we apply MedCem to stabilize them in place.

After they've been stabilized, we can then cement the tips of the sensor right here to the head of the incus and the driver to the stapes capitulum. A thin coat of EnvoyCem is used to accomplish this step.

After these have been positioned and cemented in place, we then do intraoperative testing. And once we've found out that the sensor and driver

are working appropriately, we can then put the sound processor into its surgical bed in the well. It can be fixated to the bone. And then we can do testing, intraoperative testing. And one of the unique things that we do is we can tell at the end of the operation if this system is actually working appropriately as it should. Here, you can see the sound processor anchored to the bone and the leads going into the mastoid cavity where the transducers have been cemented into the mastoid. Here is the postoperative incision.

In the recovery room, we'll then go ahead and do a lateral skull film to ensure that the leads have been projected past the most distal terminal on the header, and that way, we know that it's properly placed.

And that's all I have. Thank you very much.

DR. KRAUS: Good morning. My name is Dr. Eric Kraus. I'm an otologist from Greensboro, North Carolina. I've been a principal investigator with Envoy Medical since 2004. I have no equity position in the company. I am compensated for time and travel, and I'm an inventor for Grace Medical, a manufacturer of the K-Helix Crown prosthesis that

you'll be seeing in a few minutes.

I'm going to lead you through our battery replacement. As you heard from Mike Spearman, the battery is housed within the sound processor. The battery is not rechargeable. The system has very low power requirements, and the battery is changed after four and a half to nine years. The patients are very happy about this because they're used to changing their hearing aid batteries every one to two weeks.

So this is a very infrequent procedure. Again, the battery lasts four and a half to nine years. We consider it to be low risk, and it's very well accepted by the patients. It's a minor procedure, and it's very similar to changing your cardiac pacemaker. Patients have a major benefit because the battery and the electronics are all housed within one component. When the sound processor is removed to change the battery, the patient automatically gets updated technology four and a half to nine years later. And the transducers are -- and the sound processors are backwards compatible.

This procedure takes about 30 to 40 minutes in the outpatient world. I've done a number of these in our first study group, and we do them under local

anesthesia with some sedation. Basically, the patient is taken to an outpatient center. An IV is started. They're sedated with IV versed, fentanyl, and a small amount of Alfenta.

Then an incision is drawn. We use the same postauricular incision, although smaller, to do the battery replacements. We infiltrate 1% Xylocaine with 1 to 100,000 epinephrin, usually 6 to 8 ccs, and we prep and -- we then start the incision superiorly. We identify the sound processor. We follow it to the header. We identify the leads, which you can see here, the sensor and driver. We rotate the sound processor out of a capsule pocket that is formed around the device.

We then test the electrodes, the leads, with a capacitance meter to make sure that the sensor and driver are functioning. We then clean the leads with deionized water, as you see here. We reconnect the new, updated sound processor and battery. We then slide it back into the pocket, and we do intraoperative testing using a personal programmer. We activate the device. This is the reason that we like to have the patients under local anesthesia so that we can voice test them in the operating room. As soon as the device is activated, the patients

generally report immediately that they're hearing from their ear. We then apply a dressing. The patient is then sent to a recovery room for a half an hour and then returned to our office in the afternoon for programming of the device.

So now I'd like to address the issue of ossicular chain reconstruction. As you've heard from the previous presenters, we do resect a small portion of the distal long process of the incus. This is done because we are attaching a sensor and driver, and if we didn't detach the incus, we would have a automatic feedback, as the driver would be driving the sensor, and the sensor would be feeding right back to the driver.

Now, even though this ossicular chain is anatomically normal, the ear is not physiologically functioning well, and we have many areas in surgery where we disturb intact anatomy to try to restore function, such as in total joints and LASIK procedures.

You can do this procedure -- usually, I do it transcanal or it can be done transfacial recess. The components that are used are the K-Helix Crown titanium prosthesis and EnvoyCem glass ionomeric cement. Both of these have received clearance from

the FDA. And I'd like to pass around to the Panel one of the K-Helix prosthesis. This is the 10X model, and then you'll see the actual model -- the actual prosthesis in this case.

Okay. The conventional ways to reconstruct the distal portion of the incus is with the hydroxyl apatite Applebaum prosthesis, as you see here, or a Kurz prosthesis. These are for any small gaps.

So I developed the Kraus K-Helix prosthesis in 2007 in order to solve this problem. We attach it to the incus with these adjustable coils, and then the crown rests on the stapes capitulum. I call this endoskeletal ossicular reconstruction. We coat the prosthesis with glass ionomeric cement proximally and add a microdot of cement to the crown for stabilization. So, in other words, we're restoring the anatomy back to its regular configuration.

The prosthesis is made out of lightweight porous titanium. It's adjustable in these dimensions. It was designed to be optimized with cement so that the cement grabs these coils and just the coils direct the cement around the incus. This avoids using a cartilage graft as you would use in the standard partial ossicular replacement PORP-type prosthesis so we avoid contact with the tympanic

membrane and all the tension problems with standard PORPs. It is MRI compatible, and this prosthesis has received FDA clearance and a CE mark.

This is what the K-Helix prosthesis looks like in place. This is the left ear, looking through the facial recess. But, again, most of these we do transcanal. This shows the coils wrapping around the incus and the crown resting on the stapes capitulum. We had proximal cement, and then one microdot here at the crown for stability.

This is the very first patient that underwent the incudoplasty technique. This is a patient from the first study. This is a left ear. This is the stapes superstructure and tendon, facial nerve, and this is the distal incus. This is the reconstruction with the technique.

This is the patient's audiogram. Now, a little explanation. This patient had an infection, had to have her device explanted, and then she -- we waited until the infection was totally gone before reconstructing her. So this is with the Envoy Esteem middle ear device removed and then prior to the K-Helix incudoplasty. You can see here what she has is her sensorineural loss and then her conductive loss down here at the bottom. Looks like she has a

pretty definite loss.

This is her baseline audiogram when she first -- on the left -- when she first presented, prior to being implanted with the Esteem, and this is one-year postop results, and you can see we've completely closed the ear bone gap and restored her to her baseline condition. And this is her two-year result, so it's similar.

So, in summary, we have had -- we can explant patients and successfully reconstruct them using the K-Helix incudoplasty technique or a standard PORP. There have been four patients that have been reconstructed, three in the first study, and one in this study. Three of them have received a K-Helix prosthesis in the incudoplasty, and one of them from one of our other sites in the first study underwent a PORP reconstruction and was returned to acceptable levels.

I'd also like to say that as a spin-off of this, I have used this prosthesis in chronic ear surgery, and I've been able to restore the ear bone gap to within 10 dB. And so this actually -- the K-Helix incudoplasty technique with this prosthesis is actually a benefit to the general otolaryngology community, to our American patients, and to patients

worldwide.

DR. CATALANO: Good morning, Panel members. I'm Peter Catalano. I'm the chief of otolaryngology at the Lahey Clinic in Boston. I'm also an associate professor of otolaryngology at Boston University. I've been a member of the '03 and '04 Esteem trials, and I'm a member of the advisory board for Envoy and paid for my time and travel. I am not a shareholder in the company in any way.

I'm going to talk about adverse events in the revision patients. Adverse events in this particular study are seen to be similar to those in middle ear surgery, cochlear implants, and other implantable middle ear devices.

If we look here at some of the more common adverse events, you can see we've tried to group them by neurologic. In the first group, you have taste, dizziness, vertigo, tinnitus, facial paresis, and then some postoperative wound issues, those who had failure or limited benefits, and then some miscellaneous categories at the bottom. The first -- the second column, the middle column is the number of reported in this trial, and the last column is the number that have resolved as of the last data submission to the FDA.

1 So if we look at tinnitus, for example, you
2 can see that, you know, we had a significant
3 resolution of tinnitus. But what's important to note
4 is that of the 57 patients in the trial, 30 entered
5 the trial with a history of tinnitus. At the time of
6 surgery, 16 of the patients had active tinnitus.
7 After surgery, there were two patients who had new
8 onset tinnitus. Both of those had resolved within
9 the ten months after surgery. And there were only
10 two patients who had unresolved tinnitus, but these
11 patients both had a history of prior tinnitus. They
12 were in the 30 of the 57 with a history of tinnitus
13 previously. Middle ear effusions are very common
14 after any mastoid surgery and completely resolved, et
15 cetera. We'll talk about some of the others in
16 subsequent slides.
17 If we look at the facial paresis group, for
18 reporting purposes, you'll see four patients reported
19 with either paresis or paralysis. However, there is
20 one error that I have to share with you. This is an
21 adverse event form from the study signed by one of
22 the doctors. And it lists here facial numbness.
23 Because there is no category for facial paresis -- I
24 mean for facial numbness in the reporting, it was put
25 into the facial paresis category. So it's actually a

numbness. It's not a paresis. So there's actually only two pareses and one paralysis. But for the purpose of reporting, it had to be reported, and it was put into that category.

Of the two patients that had paresis -- actually, of all three patients, all three of these developed their facial nerve process between three and seven days post-surgery. They were delayed in all cases. One of mine was at seven days. She was a diabetic patient, and they were all partial. Of the two partials, rather -- so take one paresis off because it was a numbness. There were two other pareses. Both of those have completely resolved to normal facial nerves at this time.

At the time of reporting, however, you'll see that there are only two of the patients that seem to have repaired to normal facial function. The patient with the total paralysis was, again, a delayed paralysis. That one was considered a serious adverse event because the investigator gave the patient steroids for a two-week taper and, because it was a grade six paralysis, thought that it was appropriate to treat. The others were partial pareses, delayed manner, much better prognosis, and resolved spontaneously. The patient with the

persistent weakness is a grade two result with a lower eyelid weakness at this time.

In terms of revisions, revisions in this trial are considered failures. And as otologists, we know that failures really are unsuccessful outcomes that cannot be corrected. But we understand that, again, for the purpose of reporting, they have to be considered failures here. The three revision patients in this study have been surgically repaired, and we'll go over those results in a moment. One patient reached their four-month endpoint with a successful outcome. Two were at two months at the time of reporting, and they had positive numbers in both SRT, word rec, and bone conduction metrics.

If you look here, this is what has been reported, and these are the three revision patients. However, the bottom two that are at two months are actually now at four months, and the four-month data shows that the central patient had no change between the two-month and four-month data, but this last patient here has increased the SRT to a +10 and the word rec score to a +30 at four months. So these are now -- actually as of now at the four-month point.

In terms of the revisions, all of the patients who underwent revision had a delayed

progressive reduction in function. It wasn't an immediate change from one testing point to the next. So this suggested to us that this was something that was more like a fibrotic process that was slowly strangulating the vibration of the PCT. Imaging was difficult to assess because of the electronics and, obviously, the CAT scans scatter.

So the patients were re-explored, and what was found in one case that was not mine was that there was a osteoneogenesis bridge that went from the scutum to the incus and that froze the sensor joint. There was also a fibrosis around the facial nerve -- I mean around the facial recess. And so both the driver and the sensor were replaced in that patient. In the other two, there was fibrosis around the facial recess, basically preventing the driver from functioning properly. When dissection was taking place, you obviously have to remove that soft tissue, and the entire driver and stapes complex was covered in scar tissue. So in digging that particular driver out, you have to disarticulate it from the stapes. Otherwise, obviously, you would disrupt your stapes. And so the EnvoyCem has to be taken off of the tip of the driver in order to extract it so that all of the other soft tissue in the middle ear could be cleaned

with an unobstructed view. And so that's how that took place. And you can see that in all three cases, the patients have had very good reconstructive outcomes thus far.

So in terms of the risk/benefit profile, they seem to be similar to what we see in other middle ear surgery, cochlear implants, and implantable devices for the ear. You've already heard about the battery replacement. It's an infrequent procedure. Seems to have minor risk with obviously good benefits for the patient. Disarticulation of the distal incus doesn't seem to be a significant problem since we now have innovated a new reconstructive option, which we didn't have before for these patients.

I'd also like to point out that no patient in the study had any kind of sensorineural deafness, which is critical. So we have not destroyed anybody's hearing. And all told, I feel comfortable saying that the benefits of the Totally Implantable Esteem Device have a clear advantage for the risk involvement.

Thank you for your attention.

MR. SPEARMAN: Thank you. We're going to go over the clinical trial results now. And maybe

1 just a preface of this, anybody who has been involved
2 in medical devices knows nothing happens overnight,
3 and certainly, that was the case for the Esteem.
4 The original development of this started
5 back in '85. In '95, we started full development at
6 Envoy Medical. Of course, coming after that were
7 animal studies, the first acute human trial. In
8 2000, we did our first feasibility trials in Germany
9 and the U.S. We learned a lot from those things,
10 came back, and in 2004 started a clinical study for
11 three years. That's called the 0203 study if you've
12 seen that in the Panel packs. And then in 2008
13 started our pivotal study that we're here to talk
14 about today.
15 A little background on that 0203 study,
16 that was what we call a previous generation Esteem.
17 We had 72 subjects in that study. Some things that
18 are nice about this since it started in 2004, we now
19 have patients from that study that are three to five
20 years of run time, so we have long-term reliability
21 data on safety and efficacy that these patients
22 haven't changed over time. There were no device
23 failures of the Esteem, and the objective, the non-
24 inferiority objectives, effective measures were met
25 in the study.

What we did find during that time, as one would expect in many studies like this where we don't have an animal model to work with, is we started finding some high rates of revisions when we first started doing the surgeries. And there were actually -- primarily, it was a result of this driver to stapes connection coming loose on patients. And that was the cement coming loose from the stapes. And that happened nine times in the first 22 patients. So we kind of called a time out, got all the medical advisory board and clinical investigators together, and went through and looked at this in a serious way. And what we developed from that, or as what we called our best practices technique on how to do this surgery in a step-by-step matter and the critical elements of the surgery that we could teach to others. And when we did that and went back and did 50 more surgeries, we found that the rate dropped to only five driver-stapes disconnections. And as Dr. Catalano -- it's a very simple procedure to go back in and reconnect it. But, nevertheless, it had to be a second procedure.

The good thing about this also is that we could identify this driver-stapes disconnect immediately when we were turning on the patients at

activation because we could tell that it had come loose. And one positive note about that, though, is all these patients who did have revisions had successful outcomes.

So that brings us to the pivotal study. And we decided in working with the FDA that we would do a new study for a couple of reasons. One was to go back and look at these best practices all on their own without all the data from the other study. And, in addition, we had addressed even further this issue of driver-stapes connection, and we had developed an optimized technique for applying the cement. And rather than -- in the past, we would put the driver in, and the surgeon would have to go through the facial recess with limited access and try to put the cement around the -- over the driver and onto the stapes. And there was limited access sometimes.

We developed another technique, as Dr. Shohet showed us, and that was to first pre-coat the stapes entirely around it so we had a very, very positive bond onto that stapes, then place the driver over it, and then put another layer of EnvoyCem over the top. And that's called the pre-coat technique, which you may have read about. And what that did is that resulted in very positive connections and no

driver-stapes failures in this study.

We had also had some technological advances within the processors. Dr. Kraus mentioned updated technologies that patients could get in a processor. Well, during that time of the 0203 to 0204 study, we had developed some improved gain within the processing and in a dual channel architecture, which allowed us to do a better fitting arranged for patients, especially those with more significant sloping losses.

And, in addition, we had improved the battery life from two and a half to five years on the previous generation, to four and a half to five years. And we also developed a smaller personal programmer about the size of an iPod that a patient uses to adjust their device.

The clinical study was the same -- virtually the same trial design as the 0203 study. Our primary efficacy endpoint in the 0203 study was SRT, and we expanded it to word recognition score as well in this study. And we followed the -- obviously followed the FDA guidelines to ensure we had proper power for efficacy.

As was mentioned earlier, the inclusion criteria, adults 18 years of age and older, mild to

severe sensorineural loss, a speech discrimination score of greater than or equal to 40%. When we first started this study and in the 0203 study, it was only 60%. But what we realized is we had enough power, enough gain, and enough benefit for patients that we could reduce that to 40%, and I believe we had eight or ten patients in that category, and they all have done -- that's been a very good indication for patients because it really gives them a lot more benefit. Normal of Eustachian tube, normal middle ear anatomy, and enough adequate space in the facial recess and the mastoid cavity in order to implant the transducers were required.

So this was a nice kind of a study to be able to do because, like the previous middle ear implant studies, what we did was we compared the patient's hearing -- the patient's Esteem to their hearing aid to their unaided condition. So we had the patients acting as their own control because it was the same ear in all cases.

The study was approved for 50 to 60 patients and up to ten sites. We had 60 patients enrolled in this study very, very quickly, and three sites did all of those enrollment within the few short months. Of those 60 that were enrolled, 57

1 actually were implanted. Fifty-four patients at the
2 time that we closed the clinical database had reached
3 the four-month efficacy -- reached the four-month
4 data points. As was mentioned, there were three
5 patients that were revised, so we treated them as a
6 separate cohort. And we had 52 patients who had ten-
7 month data. Two hadn't quite reached their ten-month
8 data point at the time we closed the clinical
9 database. Average age was 53 years of age, ranging
10 all the way from 18 years of age to 77. And in this
11 case, we have 2/3 men and 1/3 female.
12 When you hear the term endpoint, four-month
13 endpoint, that's actually four months post
14 activation. So what happens is a person has the
15 surgery. Two months later they're -- time for
16 healing of the process of the surgery -- they're
17 turned on and then activated two months later. So a
18 four-month endpoint is actually six months post-
19 activation -- excuse me -- four months post-
20 activation, six months post-surgery, and ten months
21 would be one year post-surgery for the people who
22 look at it from that standpoint.
23 Our primary objectives for effectiveness
24 and safety were SRT and word rec scores for
25 effectiveness, and for safety, we looked at severe

adverse device effects and preservation of the cochlear function through the use of bone conduction tests, as well as monitored failures in the test. Our primary effectiveness objective of SRT, we're comparing the patient's Esteem to their hearing aid at a four-month post-activation endpoint.

And we had two criteria here for effectiveness. One was for non-inferiority, and that was that the lower confidence bounds of the 95% confidence interval would be greater than -5 dB of the patient's hearing aid. So, essentially, as we looked at the statistical range, that it would be better than that. On the other hand, we had criteria for superiority, and in order to make a criteria for superiority, we had to have that same lower confidence bound that was greater than 5 dB better than a hearing aid.

And as we looked at the clinical results, we found a normal distribution that one would pretty much expect in any trial with an average at a 10.6 gain of the SRT over the hearing aids. And in looking at the confidence intervals, and it remains constant for ten months -- matter of fact, we always found a little bit of a gain on ten-month patients, and then they tend to level off from there is what we

saw in the 0203 study. The lower confidence interval now is 7.1. So if we look at the 7.1 and compare it our non-inferiority criteria, we find that that indeed was met, and the 7 dB was greater than 5 dB set, so it meets the pre-specified superiority criteria as well.

Word recognition score, again, comparing the patient's Esteem to their hearing aid for word recognition, we use a form of post-activation, and we used a 50 dB presentation level. This is just slightly before -- below conversational level. It's a fairly discriminating threshold, or presentation level, to see differences between devices. We utilized the Thornton-Raffin model for determining if a patient was doing equivalent to, worse than, or better than their hearing aid. And it's a fairly difficult model to do better than, I suppose, because there has to be a fairly large improvement in order for a patient to do -- to be scored as a better than subject. For instance, if a patient has a 50% speech word recognition score with their hearing aid, they would have to get, essentially, a 70% with the Esteem in order to be considered better than. So they have to have literally a 20-point increase, virtually, at almost all levels.

And what we found was that the majority, 56% of the patients, did score better than their hearing aid. Roughly a little over a third were equivalent to the hearing aid. And four out of -- excuse me -- let me go back here -- and four were below. At ten months, the numbers were fairly similar, a little bit more on the better and a couple of more in the below.

And, again, we had a fairly normal distribution here with an average of about overall of all patients a 21-point gain with a lower confidence interval of 13.3, which is considered statistically significant improvement. And to put that into perspective, unaided the patients were averaging about 10% word rec scores at this presentation level, about 47% with their hearing aid, and 69% with the Esteem. That's roughly a 45% improvement over the aided condition.

For severe adverse device effects and failures, we were monitoring those, and here, for safety issues, we went to a ten-month endpoint, or one-year post-surgery, to see any more long-term effects that might not be realized or seen in the first six months.

And in looking at that -- I think

1 Dr. Catalano talked to most of these -- there were
2 three failures, which resulted in revisions. Those
3 were all due to fibrotic tissue formation around the
4 driver sensor, and they were not device failures of
5 the device itself. All three were revised as we show
6 up here. At the time of this, all were doing well.
7 And as he just mentioned, all three have now been
8 revised with successful outcomes, have reached their
9 successful outcome point of four months on efficacy.
10 There was one facial pain and weakness that
11 was treated with medication, he mentioned. We had
12 two surgical implant/incision issues. One was an
13 infection, which was successfully treated with
14 medication, and another had to do with tissue
15 breakdown and exposure of the processor, and that
16 resulted in the patient being explanted and
17 successfully reconstructed with the Helix
18 incudoplasty technique. Overall, there were 6 out of
19 57 SADEs in six unique subjects, and they've all been
20 successfully resolved.
21 When we look at the bone conduction, we use
22 that in order to look at the cochlear stability of
23 the patients, and that we compared to their pre-aided
24 baseline -- pre-unaided baseline condition; that is,
25 before they -- when they just enrolled in the test,

in the study. And we looked at both four months and ten months post-activation. And one note on here, we ended up using a forehead placement because in the past study -- this was one of the lessons we learned from the previous study -- was using a mastoid placement to try to do bone conduction, the processor would be many times in the way of where the previous bone point was or it would be touching. So we went to a forehead placement so we could have the same consistent delivery of vibrations to the patient, both with the unaided, aided, and Esteem conditions.

In doing so, we looked at these and found that there were no changes in bone conduction, no significant changes at four months or ten months. On an individual basis, looking at the safety algorithm that was developed, no patients developed any loss of frequencies at four months. At ten months, we had one subject who had 4 kHz -- had their bone conduction go from 55 dB pre-implant to 75 dB.

You know, we were concerned about that. We looked at it. We found that that patient -- we looked up their air conduction scores and found that their air conduction scores were both 45 dB at four-month to ten-month. That hadn't changed. There had been no change in the programming settings of the

device. Their SRT scores hadn't changed, and their word rec scores haven't changed. So we don't know what to say about this, if it's a spurious reading or what, but all their other indications show that it's stable.

We also had some secondary objectives to look at, pure tone average, speech and noise, and two subjective questionnaires, the APHAB and the Envoy Questionnaire. For pure tone averages, we looked at the three frequency pure tone average versus unaided just to see what kind of a gain does the Esteem give to a patient in its raw form as well as the four months -- and that was done at four months post-activation. And what we saw was this is the gain. The pure tone average was 27 dB with a peak of gain at 36 dB across all patients at 2K.

For the speech in noise, we looked at the Esteem versus the patient's aided condition at four months. And what we found is that there was no significant difference from the Esteem to the patient's baseline hearing aid in this test either at four or ten months.

We utilized the APHAB Questionnaire, which is called the Abbreviated Profile of Hearing Aid Benefit. It's used routinely in looking at benefit

provided by hearing aids versus unaided conditions. It was also used in the previous Soundtec PMA to look at the device, the implant versus hearing aids. And a version of this called the PHAP, the Profile of Hearing Aid Performance, was used in the Soundbridge study.

So basically, they're related. And this was used in those studies, and we used this as well to try to determine what type of benefit people saw from the Esteem and then compare that to the benefit that they saw with their aided condition. And this was four months post-activation. And what we found was a significantly -- a significant improvement of roughly about ten points across all the different categories of the Esteem versus their aided condition.

And, lastly, we did the Envoy Questionnaire. Now, this was a questionnaire we developed. There was no large-scale validation. We had used it in the previous study to look at certain characteristics that we found that patients thought were important and utilized those and asked patients to comment on those on a scale of 1 to 5, 1 being significantly worse, 5 being much better, and 3 being the same.

And what we found on these in -- things like clarity of sound, listening to speech in noise in the real world, how natural the voices sound, how well did someone understand conversations, their lifestyle, how self-confident they are in being able to go out with this device, it was 70 to 85% of those patients rated this Esteem as somewhat to much better than a hearing aid. And those numbers stayed consistent six months later.

So, overall, if we look at the clinical trial results, we can look at this and say that the data supports that the Esteem is statistically superior to the hearing aid on the SRT, statistically met the pre-specified endpoints for that category. It was statistically superior to the hearing aid in word recognition score. We had stable cochlear function and a 5.3% revision rate, and in the secondary objectives, a 27 dB improvement equivalency. I guess it would be statistically -- I think the statisticians would say statistically non-different than the hearing aids, whereas APHAB was statistically superior. And in the Envoy Questionnaire, the majority are somewhat to much better than hearing aids.

Thank you.

DR. STACH: My name is Brad Stach, and I'm an audiologist at Henry Ford Hospital in Detroit, Michigan. I serve on the Medical Advisory Board of Envoy. I have no equity interests, but I am paid for my time and travel.

I want to talk today about audiologic perspective and try to just amplify some of what Mike Spearman talked about in terms of the outcomes that we've seen in these patients.

I'm going to talk first for a moment about the hearing aid experience itself, and those of you who see patients on a daily basis know that not a day goes by when we don't encounter patients who come in and say, "I know I have a hearing loss. I know it's a problem for me. And I want to do something about it." And by do something, they don't mean get hearing aids. They mean they want it fixed. They know that no one wants a hearing loss and no one wants there to be -- they don't want it to restrict their function in any way, and if they find that they do, they want it fixed. And sometimes they'll even be angry that we can't fix it with surgical or pharmaceutical solutions.

I mean, to be sure, modern hearing aids have helped many people and helped millions of people

each year. The technology is tremendous and just keeps getting better all the time. And patients do benefit greatly from conventional devices. But as Mike said earlier, people want to hear 24/7. They want to wake up in the morning hearing. They want to hear in the shower. They want to have the best hearing they can have, and they want to regain the obligatory sense that they had before.

And they also don't want to stick things in their ears. They don't want to have to remember to take them on and to put them on and take them off, to have squealing in their ears when they hug somebody, to change batteries, buy batteries, or remember to carry batteries, to clean their devices, and to have to adjust them as the environment changes. And they don't want to appear to be impaired.

The real advantages of the Esteem come from the way that sound is delivered. And just as another summary, the -- it really doesn't matter how you drive the middle ear, whether you put a magnet on the tympanic membrane or a magnet on the ossicular chain, driving it directly creates a more natural sound to subjects, again, regardless of how that driver is affixed. And that's part of the advantage, the naturalness of the sound, and that's something that

all the patients will say when they first experience it.

But probably the real beauty here is the location of the microphone. Preserving the location of the microphone at the tympanic membrane permits all of the natural filtering and resonant characteristics of the outer and middle ear that are so important for special hearing. Probably said another way, you think about the millions of dollars in R&D that have been spent on trying to make hearing aids adjust because you've removed the microphone from the tympanic membrane and placed it on the side of the head and destroyed all of those spatial hearing cues in the process of doing so.

If you've ever listened to a hearing aid through a stethoscope or even on your ear, the first thing you'll notice is the lack of dimension of sound, call it a wall of sound, where all sounds seem to sound equal, and it's difficult to know where they're coming from. And the sensor being at the tympanic membrane solves many of these problems in a very, very important way. And then, finally, in terms of its value of not showing impairment, it is totally implantable.

Well, let's talk about the Esteem and some

of these clinical outcomes. And I want to just kind of give you some perspective of what these outcomes mean. One of the -- you'll see that there is a lot of talk about gain of the device. If you are fitting modern hearing aids, you don't really think about gain these days. In fact, if you ask an audiologist "How much gain did you give that patient yesterday," they would look at you as if you're old because we just simply don't talk about it anymore. We measure the output of the device in the ear canal to different input levels of sound and then measure those against targets. Now, those targets are attached to gain, but we really don't think about the gain in that transparent way anymore.

In this device, we have no way to do that. We can't measure the output on the other side, and so we have to infer that gain from looking at the difference between a person's threshold without the device and threshold with the device, subtracting those and coming up with some assessment of how much gain is being delivered to that patient.

And that's what the speech reception threshold data do, simply show an estimate of functional gain of the device using speech. And the question is can the Esteem provide gain at a level

comparable to conventional hearing aids. As difficult sometimes as these gain measures are, as functional gain measures are to do, the answer is, yes, in fact, they can give you the kind of gain comparable to hearing aids and in some patients showed significantly more gain was able to be delivered through the implanted system.

But gain isn't really everything. It's just how much amplitude is being delivered. Another question is what is the ear doing with that amplified sound at suprathreshold levels. And so the second question is at suprathreshold levels, can speech be recognized as readily with the Esteem as with conventional hearing aids? And again, we asked a very direct question: At a comfortable listening situation, can a patient hear single syllable words presented in quiet? Can they recognize those with this device in a way that we would expect, given the amount of gain that they're getting from the device? And the answer is yes, yes, they can understand speech in a manner that we'd expect. Word recognition scores were at least comparable at suprathreshold levels with hearing aids and in some cases actually exceeded those levels even using the fairly strict criteria of Thornton and Raffin for

that analysis.

Okay. So we're getting sufficient gain with this device. The device seems to deliver speech in an effective way. Is there any way in which noise adversely influences the ability of the ear to hear through this device? That question was addressed by asking was hearing a noise in any way adversely affected by use of the Esteem, and the answer is no. QuickSIN data showed no difference between hearing and noise with the Esteem and with a conventional hearing aid.

And, finally, then we ask the patients, "What do you think about your hearing ability?" And one technique that was used is the APHAB, as Mike Spearman said. Now, the APHAB is a very popular instrument. It's used quite a lot clinically. It's also used in a number of research articles. Over 120 articles have been published that use APHAB for comparison purposes, everything from digital hearing aids to analog hearing aids, middle ear implants, cochlear implants, and BAHA devices.

It has some challenges to it. As in any kind of non-blinded trial, when you ask a patient what they think about the device that they're using, there is some potential for bias in that. It's also

a problem because people don't remember very well how they judged another device that they might have thought was inferior or superior in some place, and so sometimes the numbers don't translate very effectively. The other problem with it is it's not really all that sensitive a measure of small changes in perception.

In a very recent article that came out by the folks who developed the APHAB, they did a study comparing digital hearing aids to analog hearing aids over a ten-year block of time, and they showed that although the digital hearing aid users were twice as successful in use of the device, they showed very negligible differences in the outcome on the APHAB.

But we use it anyway because it's a standard measure of these things and ask patients, "What do you think about your listening in different environments?" And what the patients in this study said was that, yeah, we are receiving subjective benefit from these devices and showed significant benefit in some patients.

And then, finally, the Envoy Questionnaire, again, was trying to get at the point of the device itself and some of its benefits, and patients seemed to appreciate the outcomes of that.

Now, to be sure, we're still delivering sound to an impaired ear. And that impaired ear is still going to have trouble with frequency resolution, temporal resolution, and dynamic range issues. And there is nothing about the nature of this driver in delivering that signal to that impaired ear that is any different than any other delivery. So it's quite like -- that's why we're seeing the distribution of outcomes that we're seeing in this rather than something skewed more to the right. We're still delivering sound to a cochlea that is not functioning appropriately. It's likely that enhancements in the signal processing of the device over the years will help to overcome some of those challenges faced by some of the subjects.

In summary, then, Esteem provides gain and suprathreshold hearing to an extent comparable or better than conventional aids. It seems to provide real-life benefit beyond conventional hearing aids, and it gives us a unique tool to help in dealing with hearing loss in patients.

DR. BROWN: Good morning, everyone. My name is Scott Brown. I am a biostatistical consultant to Envoy Medical. I have no equity position or financial interest in the company, but I

have been compensated for my time and travel.

And I'm here this morning to talk a little bit about the statistics. Now, what I'm not going to do is to talk about the study's general statistical methods. Obviously, we'll be happy to answer those questions as they arise. What I'm going to do right now is just to talk about a couple of specific issues that are of particular interest.

And the first of those is that FDA has pointed out a potential issue with site poolability. So there were three sites in the trial, and one of the basic notions of multi-center clinical trial analysis is that you want to be able to combine the data across the sites that you have used. And we agree with FDA that there is potentially an issue. We disagree a little bit about the magnitude of the issue.

If you look here at this slide, it shows the top row, labeled unadjusted, is the simple site analysis of the SRT change at four months. And you can see there that there is a p-value less than 0.01, which suggests non-poolable data. So this is an issue.

So what do we do? Well, we went and inspected the probable causes of the differences

among the sites, and what we discovered was that if you account for patient baseline characteristics, if you look at the differences in the patients at baseline, prior to the Esteem implant, that their baseline SRT score as well as their baseline level of hearing loss, in fact, account for most of the difference you see among the sites. And so that's that second row, which is labeled adjusted, and you can see there the differences between the sites have become much smaller, not technically statistically significant, although still close, and, really, this is explanatory. This says to us the reason these sites differ is largely due to the sorts of patients they enrolled, which, in a sense is a good thing. This is why we do multi-center trials, in order to get a broad spectrum of patients with some heterogeneity among them.

Nevertheless, we still agree with FDA that it's important to look at what happens if you try to account for this potential site variability. And when you do that, you have a couple of choices on how to handle this. Now, we've already presented the protocol-defined pre-specified analysis of the SRT data. And in that pre-specified analysis, we show a claim of superiority over the hearing aid for SRT.

Anything else that is done is going to be a sensitivity analysis. It's going to be post hoc. It's going to be exploratory, and it's going to be for the purpose of trying to clarify the data. And that's exactly what we're doing here.

When you want to talk about site variability in statistics, you have at least two options. They are the so-called fixed effects and random effects models, and there is a legitimate debate in statistical practice about which one is the right one to use and when. But where there is very little debate is that when the number of sites is small, and in this case, three qualifies as a small number of sites, statistically, the fixed effects model is the appropriate one to use.

There are several references we could have sited for this purpose. This is one from an article by Senn in *Statistics in Medicine.* Simply put, the fixed effects model is to be preferred when the number of sites is limited. And let me show you what I mean by that.

This slide shows, first, the four-month means, which is to say, the SRT changes at four months, for each of the three sites in the trial, not adjusted. These are simply the site totals. And

1 what you see here is the confidence intervals and the
2 point estimates. The unadjusted model here is the
3 one that we have already presented. It is the
4 protocol-defined pre-specified analysis. And you
5 look at that confidence interval, and you can see
6 that the lower thing is 7.1, which is above the
7 threshold of 5 needed to declare superiority.
8 The bottom row there shows the results of
9 the random effects model, which is the one that FDA
10 is going to be discussing in their presentation.
11 That random effects model shows a lower confidence
12 bound of -9.4, and if one were to accept that
13 analysis, the implication is that not only is this
14 not superior to hearing aids and SRT, but, in fact,
15 it's not even non-inferior. The primary efficacy
16 endpoint would not have been met.
17 And, really, let me show you -- when I say
18 that the random effects model doesn't work well with
19 a small number of sites, here is what I mean. Very
20 intuitively, look at each of these three sites one by
21 one. Each of those sites by itself has met the
22 threshold for non-inferiority. Each one of those
23 lower confidence bounds, 5.4, 12.2, those actually
24 show superiority by themselves. The third site even
25 meets the criterion for non-inferiority by itself.

So each one of these sites individually has sufficient evidence to show non-inferiority of the primary endpoint. But when you use the random effects model, you put all three of them together, and they fail to meet non-inferiority.

The problem here is the one I mentioned. The random effects model relies very, very heavily on the number of sites, and it simply does not perform well in a situation like this, where the number of sites is limited.

And I would suggest that this actually violates our logical intuition as to how the data analysis should look. And, again, the point is that the fixed effects model is really the more appropriate one to this circumstance. And you can see that under the fixed effects model, in fact, we do have, again, a confidence interval that is above 5 and that, based upon both the unadjusted protocol-defined model and the fixed effects model, accounting for site variability, the claim of superiority is supported.

Changing gears for just a moment, there is a brief talk I'd like to have about the safety as well. This is the bone conduction data, which we talked about a little bit earlier. And what we are

presenting in our analysis of the data are these numbers here. And we mentioned the fact that at ten months, you have one patient with a bone conduction issue, not clear of the causes or of the effects, but there is one in there.

FDA has also conducted a worst case analysis, which are shown in the next two columns. Now, there absolutely is a place for worst case analysis in statistics. It's especially relevant when you have missing data that are not liable to be retrieved and that may have gone missing for suspicious reasons, by which I mean, for example, patients lost to follow-up during the course of a trial. If you have adverse clinical outcomes and a patient drops out of the trial before something can be measured, it's quite reasonable to say, well, you know, let's just imagine the possibility that this patient had a negative outcome.

This particular set of analyses, however, the patients that we're looking at here, there are eight patients shown here in the worst case analysis versus the zero that we show. There are nine here versus the one that we show. Those are the same eight patients, and they are as follows: Three of them were not implanted at all, two due to anatomical

1 difficulties and one due to the finding after
2 enrollment that they actually did not meet an
3 inclusion criterion. Three of them were revisions.
4 One was an explant for which the bone conduction was
5 measured post-explant and was found to be normal.
6 And the remaining patient is one for whom a four-
7 month visit has occurred, but not the ten-month
8 visit.
9 So the important point here is that for
10 three of these cases, the implant never took place
11 and the data were not meant to be collected. For the
12 fourth case, the explant, normal bone conduction was
13 verified after the explant, and for the four
14 additional cases, data are being collected on those
15 patients. They are not lost to follow-up. The data
16 are not missing. They simply aren't all in yet.
17 So my point being that, statistically, we
18 would argue that a worst case analysis is not as
19 enlightening as it might be in another circumstance
20 where these patients, for example, are lost to
21 follow-up.
22 Thank you.
23 DR. EYDELMAN: Before you proceed, let me
24 just interject. I wanted to point out that
25 Dr. Brown's presentation was not included in the

slides that were distributed to the Panel members.

MR. SPEARMAN: Okay. I thought they were. I'm sorry. I think most of it was there, but we added some things this morning that we had sent to you, but I don't know if we had copies made. I apologize, and we could do that in between here.

Just a few closing comments. There is a couple of other issues which may have -- look like they've come up, so we just thought we'd address one of them -- a couple of them. One is the issue of mild loss patients, and are they represented adequately in this study. If we consider how the standard audiological classifications are used and what we use in classifying these patients, we used the 3-point pure tone average which people use to define mild, moderate, severe, and profound loss. And when we look at the statistics and distribution of patients, we would expect 31% of the people, of all the hearing loss patients, have mild loss.

But as we all know, very few people who have a flat mild loss actually seek help for hearing treatment. The type of patients who seek help for hearing treatment for mild loss are those who have difficulty hearing. And the reason they have difficulty hearing is they have a mild loss with a

1 sloping loss to a moderate or severe category. And
2 that makes it very difficult for them to understand
3 speech. And these, you know, we would submit are
4 really -- these are the type of patients we indeed
5 had in the study, and they are indicative of the type
6 of patients who have mild loss.
7 And we might offer if this is a concern, as
8 far as how someone would go about determining this if
9 they're an audiologist/otolaryngologist and wanted to
10 describe this, we would think that mild with a
11 sloping loss may be more descriptive in helping
12 people look at that. But certainly, these are
13 considered mild loss patients by the definitions
14 used.
15 And the last issue was a post-approval
16 study. We've seen questions on that, heard about it.
17 Just to give you a little background on that, when we
18 were asked to submit the PMA -- when we were
19 submitting the PMA, we were asked to submit a post-
20 approval study, and the concern was the long-term
21 reliability of the Esteem device. Fortunately, we
22 have a lot of good long-term reliability from the
23 Esteem -- we call it the Esteem I -- but the Esteem
24 I, so the 0203 study which we talked about, three to
25 five years, and the patients have done exceptionally

well during that time and been stable. We have the lab data on the devices, which last for 20+ years, accelerated aging testing.

But one of the questions that came up, well, we had a little bit slightly different new processor and technique of bonding the stapes to the driver, so how do we know how long this will go? And our suggestion was that we would continue to run a post-approval study by taking the existing study patients and following them for five years into the future as well on all the metrics that were used in this test. So that would be 57 patient plus 5 continuation patients, and that would certainly show the safety and long-term reliability of the device.

One other issue has surfaced, and that's what about new implants or even new surgeons, how do we know about the safety of the device in the more expanded rollout. And one of the things that we look at is that any severe adverse device effects, failures, new implants or done by a new surgeon, actually, would be captured and reported by the normal post-market surveillance and reporting methodologies, annual reports, or MDRs. And, you know, one of the ways -- if someone thinks that -- if we're looking at the annual report being a little too

long -- much of a longer time period, we do six-month reports all the time, and that could be another option of shortening up the reporting over the first two years.

So having said that, we'd just like to conclude that the Esteem really represents an entirely new dimension, or a new category, in hearing treatment, that is, the totally implantable middle ear device, which really hasn't to this point been in existence. And as a result of that, it brings an awful lot of benefits to the table, as we discussed earlier, that really outweigh the risks, and that it's safe and effective for use. And most importantly, a significant portion of the intended hearing loss population will gain clinically significant results.

Thank you.

DR. LEOPOLD: I'd like to thank the Sponsor's representatives for their presentation. Does anyone on the Panel have a brief clarifying question for the Sponsor? Remember that the Panel may also ask questions of the Sponsor during the Panel deliberations later this afternoon. When speaking, please identify yourself at the beginning. Yes. Ms. Lonsbury?

DR. LONSBURY-MARTIN: Yes. Brenda Lonsbury-Martin. In replacing the battery in the revision surgery, does one have to use a little miniature Glasscock jackhammer to get that out? Is it not cemented into the temporal bone?

DR. KRAUS: Yes. Dr. Kraus. No. When we replace the battery, we incise the capsule that surrounds sound processor battery. We free it from the capsule, and it just rotates right out of the pocket. We do not disturb the transducers at all. They're left in place. We do test them with a capacitance meter to make sure that the PCT crystals are still intact and have good capacitance, but Glasscock stabilizers are not utilized during the battery replacement.

DR. LEOPOLD: Go ahead, Dr. Cheung.

DR. CHEUNG: Steven Cheung from UCSF. Along this battery issue, will the patients have some indication that the battery is running out or will -- how will patients know? Will they simply wake up one day and it doesn't work?

DR. KRAUS: Dr. Kraus. Actually, built into the sound processor are two tones as the battery starts to deplete. So as the voltage drops in the battery, when the patient turns on the device, they

get two soft tones, beep beep. That tells the patient that they have two months left on their battery and they'll need to seek battery replacement. So it doesn't just quit on them. They have a two-month grace period in order to get the battery replaced.

DR. LEOPOLD: Dr. Kileny?

DR. KILENY: Thank you. I have a question regarding stratification relative to hearing loss, and in particular, patients categorized in the severe hearing loss category. In looking at the data, it appears that these patients have shown very high gains in word recognition scores relative to their preoperative aided condition. In fact, some apparently went from near zero word recognition to up in the 80s, and the average for this group is much higher than for the mild and the moderate group, the mean being almost 30 dB. So what I'd like to know, to what extent did you ascertain that the preoperative hearing aid was optimally fitted, and how do you explain going from almost no word recognition to such high values, at least in a handful or maybe just two or three patients?

MR. SPEARMAN: As far as the hearing aids were concerned, the protocol called for the

audiologist to fit those hearing aids to the manufacturer's specified conditions and then to verify those with real ear measurement. From what we've seen, there are just some patients who were very low to start with. And what that 50 dB word rec score -- even with hearing aids, when they had very low thresholds unaided, with the gain that they're getting was very -- they had very poor word rec scores at 50 dB. And quite frankly, those patients had a lot of headroom for the power of the Esteem to actually deliver just more energy and bring those up to, you know, those substantial gains, is really one of the things that we saw.

A lot of those patients -- quite frankly, the moderate severe and severe loss patients tend to have a lot more room to deliver more gain, where you get up to the moderate loss patients, their hearing aid already puts enough gain into them to get them into the audibility index. They don't really want or accept a whole lot more than what we have. But in the lower ranges, we have more gain to give them to get them up into the audibility speech ménage.

DR. LEOPOLD: Dr. Hirsch?

DR. HIRSCH: Barry Hirsch. Another question for each of you is you mentioned about

replacing the battery. In the labeling, it is said that the device should be either tied down or titanium mesh is used to secure the device initially. Does that change the exposure that you need, and do you advocate tying it down again?

DR. KRAUS: Dr. Kraus. We do recommend stabilizing the sound processor in the initial procedure either with sutures or -- we don't use titanium mesh, but you can use Gore-Tex or Prolene mesh. That's in order to have the sound processor not migrate at all. We learned this from cochlear implant work.

When you do the battery replacement, we actually have a very firm capsule around the device. And it's not necessary to re-suture or re-stabilize it because when you close the pocket, it's locked back into the original capsule that formed around it. So there is no necessity to have to add extra stability.

DR. LEOPOLD: Dr. Cueva?

DR. CUEVA: Bob Cueva. If Dr. Catalano can answer, the timeframe for the delay, you mentioned a couple of them were around one week. The patient who had the paralysis, can you give me an idea about the time delay between that?

Another question in terms of surgical technique, certainly you need a large facial recess to be able to do all the work you have to do. Is it preferred that bone be left on the sheath of the facial nerve or are people taking it off to try and get maximal exposure?

And then this is more toward material sciences. The EnvoyCem, does it have an exothermic reaction during the setting, which many bone cements do, and that might be an issue in terms of if I have an exposed facial nerve sheath and an exothermic reaction might cause some facial nerve injury?

DR. CATALANO: Thank you. Peter Catalano. In terms of the time delay on the facial paralysis, I believe it was three days after surgery. It wasn't my patient, but that's what I'm told, and that patient was aggressively treated with medications, as we spoke about.

In terms of the extent to which the facial nerve is -- sheath is exposed, personally, when I do the surgery, I do not in any way expose the actual sheath of the nerve. As you are aware, there are patients who have -- in the tympanic segment of the nerve, and in my patient, it was a diabetic, and it was a week later, and, you know, we can anticipate

1 something like that in that population.
2 And in terms of the cement, the MedCem,
3 which is placed into the mastoid, does not have any
4 exothermic reaction to it. So there is no heat that
5 is coming off of that cement as it cures. In terms
6 of the ionomer cement, the EnvoyCem, that cement is
7 placed only on the transducer and the ossicle. The
8 contact with the ossicle is extremely minimal except
9 on the capitulum of the stapes. But on the incus,
10 it's quite minor. And there is minimal to no heat
11 that is generated from that cement as well. There is
12 no cement that is placed anywhere in contact with the
13 middle ear mucosa.
14 When the MedCem is placed, which is the
15 hydroxyapatite cement that secures the transducer
16 into the mastoid, gel foam is placed in the facial
17 recess to prevent any of that cement from migrating
18 anywhere out of the mastoid. And then once that is
19 cured, the gel foam is removed. So we take every
20 precaution to prevent any cement from getting
21 anywhere because we don't want to have any kind of
22 unexpected event from that.
23 DR. LEOPOLD: Dr. Kenna?
24 DR. KENNA: Marly Kenna, Boston. I have
25 two sets of questions. One is for the site

variation, the variation between sites, and I'd be curious to know what you looked at in terms of adjustment. Was it SRT, preoperative WRS, so forth?

And then perhaps on the adverse events side, there were several patients that had taste change, and it doesn't look like -- it looks like a fair number of them continued to have that at four and ten months, and I'm wondering what that might be.

And related, several of these patients appeared to have unsteadiness or vertigo, which might be a problem in the older patient population that's being targeted for this device.

Thank you.

DR. BROWN: On the issue of the site variability analysis, there were actually 26 baseline characteristics that were inspected for their relationship to the SRT outcomes. I don't have the list offhand. It is in our report, and we can hunt those up if you wanted to hear them.

What was found is that, specifically, the two most relevant predictors were baseline hearing loss and, of course, the baseline SRT value. And really nothing surprising about that. It's typical that when you're evaluating a change score, which is what we were doing here, that you would expect the

baseline value to be correlated with the outcome, and that's exactly what happened.

DR. CATALANO: Peter Catalano again. With respect to vertigo, that was very transient. There was nobody who had persistent vertigo from the procedure, and I agree with you. That would be an important consideration.

And in terms of the taste, the chorda tympani nerve is either manipulated or removed depending on access issues for the facial recess. And that's where the taste disturbance is likely coming from. As you know, in some patients, there is significant variability in terms of how much the chorda tympani contributes to taste with their other particular avenues for that. In some patients that's a critical nerve. I was surprised in talking to Mike Glasscock -- he says that in every stapes, he was told by Bill House to take the chorda tympani routinely. I never do that in a stapes, but that's, you know -- and those patients seem to do very well as we do stapes.

So that's where the taste comes from. It also takes time for taste recovery to be seen. And so I think that in the 03 study, we've seen a lot of those patients resolve their taste dysfunction. But

in this group, because of the follow-up, not everybody has hit that.

DR. LEOPOLD: Dr. Hall?

DR. HALL: Joe Hall, UNC Chapel Hill. This is really a follow-up to Dr. Kileny's question. And one important point is that near threshold, the performance intensity function for speech is quite steep so that even a 2 dB in the speech level could result in a 15-20% increase in speech recognition. And so the point really is that any comparison between conventional hearing aids and this device, I think, would have to be extremely careful to look at that and to perhaps go to a great extent to make sure that the hearing aids and the device were being compared on an even playing field in that regard because of the sensitivity of that performance-intensity function.

DR. LEOPOLD: Yeah, Dr. Sininger?

DR. SININGER: Yeah. I had a follow-up to that as well. I was a little concerned about the number of subjects who had very poor word recognition scores aided in the selection process. And I noticed that there was a provision in the procedures to try to optimize the hearing aid fitting before moving on, and I'm wondering if we can see some of that data.

How many of these subjects with very poor word recognition scores were, in fact, measured on real ear measurements and refit as the procedure pretty much says they might be, or were these simply taken at face value, the aided, you know, responses that they came in with, knowing that they may have not had adequate amplification fitting.

I had a couple other questions, too. One was the procedure for the bone conduction. There is no mention of contralateral masking in the opposite ear. I'm assuming that that was done appropriately, but it's not mentioned in the procedures. And also the procedure for the word recognition scores, there is no mention of what the materials were or whether or not those were recorded or live voice measurements. But I would like to see that data if it's available on the refitting and the real air measurements.

MR. SPEARMAN: That's a good question. The sites were instructed to do it. I think we might have that data, but we don't have it here with us. We didn't compile that to look that up.

We know that some patients were -- their hearing aids weren't functioning properly -- hearing aid was given to them, they had to go back and --

their specificity for one month, and that happened in a number of cases, but I don't know the exact number as we stand here.

Could you touch on those other two subjects?

DR. SININGER: I just wondered what the procedure was for the word recognition scores, live voice or materials --

MR. SPEARMAN: Recorded voices.

DR. SININGER: They were all recorded?

MR. SPEARMAN: Yes.

DR. SININGER: And do you know what the materials were?

MR. SCHILLER: Hi, good morning. Peter Schiller. I'm chief technical officer for Envoy Medical. NU-6 recorded 50-word lists were used for the word rec. Just to clarify, we talk a lot about word rec. Our primary endpoint was measured at 50 dB, fairly challenging, particularly with a lot of patients with moderate and severe hearing losses.

DR. SININGER: Fifty dB hearing level, am I right?

MR. SCHILLER: Correct. We also evaluated at their MCL. So both metrics were tracked. The primary endpoint or the co-primary endpoint was at 50

dB.

Just a follow-up on the real ear measurement, every patient's hearing aid fitting was verified with real ear measurement. That was integral to the protocol.

DR. SININGER: But we don't have access to that data?

MR. SCHILLER: I believe we do. It's in the case report forms.

DR. SININGER: Okay.

DR. LEOPOLD: Dr. Norton?

DR. NORTON: Susan Norton. I have follow-up questions to Yvonne's and Joe's. How was the SRT determined and what was the step size? Typically in audiology, that's a 5 dB step size, and a 5 dB variation is considered test/retest as is audiological data.

And then it looks like you probably had a fair number of patients where the bone conduction thresholds exceeded the maximum limits measurable with a lot of audiological equipment. And those would have contributed significantly to your 0 dB bone conduction shift and made it impossible to see an effect. So can you provide us with the data on how many of those patients there were where you could

not measure a shift?

And then it's pretty hard to get a 0 dB word rec score.

UNIDENTIFIED SPEAKER: Zero percent.

DR. NORTON: Pardon?

UNIDENTIFIED SPEAKER: Zero percent.

DR. NORTON: Zero percent, I'm sorry, zero percent. So I'm wondering if you could provide us with information about the levels at which the word rec scores were tested pre and post, if it deviated. I assume you used 50 dB for all the post scores, but the pre-score, I had a very hard time figuring out whether you were at 40 dB plus SRT or UCL or what from the description.

DR. LEOPOLD: Let me interject here. A lot of these sound like relatively technical things for which data could help. If you want to delay and provide this data after lunch, that would also be acceptable.

MR. SCHILLER: Certainly.

DR. LEOPOLD: But go ahead and give the comments.

MR. SCHILLER: Hello. Peter Schiller again. The SRT was tested in 5 dB increments using recorded words. Does that answer that question?

DR. NORTON: Yeah. So you can't consider a 5 dB effect significant?

MR. SCHILLER: Not on a single patient on a single day. Bone conduction, I believe there -- following up on a previous question, too -- was tested with masking at the pre-implant condition and also on the follow-up, so with forehead placement, the contralateral ear was masked.

DR. NORTON: But my question is even your mild hearing losses at 2 and 4 kHz here, their bone conduction thresholds would have exceeded the maximum measurable threshold, measurable with audiologic -- audiometric equipment.

MR. SCHILLER: Yup.

DR. NORTON: Therefore, you could not have measured a shift, and how much did that -- what percentage of your data was that the case, and was that counted as a 0 dB shift?

MR. SCHILLER: If they had a baseline non-response at a particular frequency -- and you're absolutely correct -- 70 to 75 dB is the test limit for most of these stimulators. If they had a baseline non-response, we couldn't evaluate a change. We did incorporate with help from the FDA a safety algorithm that also considered the EnvoyGram to

evaluate higher levels of cochlear function, and we can detail that later. It is included in the protocol.

And then I believe the last question was regarding word rec scores. Fifty dB was tested at baseline screening and also every follow-up, 50 dB presentation level also at the most comfortable listening level. So that was done both aided and unaided. So several test levels for word rec.

Does that answer your questions for the word rec? All right. Thank you.

DR. LEOPOLD: Thank you. Dr. Ishiyama, I believe, has a question?

DR. ISHIYAMA: Yes. I have several questions. According to the data provided, there appears to be a pretty significant incidence of a taste disturbance from one site. However, there was one site that didn't have any taste disturbance. Was there any way to describe why this occurred?

The second question that I have is the incidence of facial nerve injury. In stapes surgery, the incidence of delayed facial paralysis is less than 0.01%. In the cochlear implant surgery it's less than 0.1%. And if you include the data that you provided today, where you have three patients with

delayed facial paralysis out of 57, that translates to 5.26%. Is there any explanation as to why the incidence of delayed facial paralysis is high for this particular surgery?

DR. CATALANO: The site difference -- Peter Catalano -- sorry -- the site difference with respect to taste disturbance had to do with what I mentioned earlier, with preservation of the chorda tympani and the need to gain a larger access in the facial recess for successful implantation. So that was just a technique variation depending on the size of the facial recess that was open. And again, even if the chorda tympani was removed, as we talked earlier, not everybody is impacted by that. So that's two explanations for that.

DR. HIRSCH: Can I just follow up on the facial nerve issue --

DR. LEOPOLD: Yes. Dr. Hirsch? Yes?

DR. HIRSCH: I'm sorry. Would you clarify whether at your ten-month follow-up, is there one or two people who have facial paresis issues?

DR. CATALANO: There were four people reported. One was a spurious, which I have the adverse event -- two had a paresis. One had a paralysis that were reported. The two with pareses

have, at this point in time, December 10th, resolved to House-Brackmann Grade 1. The paralysis patient is a House-Brackmann Grade 2.

DR. LEOPOLD: Peter, while you're at the podium, can you please give us the type of taste disturbances of which they complained? Is it a loss? Is it a distortion?

DR. CATALANO: Oh, I'm sorry. Good point. It's a distortion in every one of the patients, distortion in taste.

DR. LEOPOLD: Specific salt, sweet?

DR. CATALANO: I mean, I don't know. For all the sites, I can't answer, and I, as you mentioned, didn't have many. I'll defer to my colleagues to answer that for you. And Dr. Kraus is going to answer your facial nerve question as well, so I'll let him answer both of those.

DR. KRAUS: Dr. Kraus. The taste disturbances were minor and just distortions in my series. The chorda tympani nerve often just runs right directly through the facial recess, and in many cases, at least in my series, had to be sacrificed.

I'd like to address the question about the facial paralysis incidents. Actually, in cochlear implants, if we look at it, Noel Cohen reported in

1988 in *Annals of ORL* a facial paralysis rate of 2%. It was reported by Tom Roland in 2000, in the book *Cochlear Implants* by Waltzman and Cohen, a facial paralysis rate of 1%. And Dr. Lalwani, who is part of the Panel, reported in 1998 in *American Journal* the otology of facial paralysis rate of 4%. So there is a range of about 1 to 4% in cochlear implant patients, and we were at 5%. So we were within the range.

DR. LEOPOLD: Dr. Portis, did you have a comment before?

DR. PORTIS: Yes. I didn't hear any reference to the need for any type of patient training or rehabilitative efforts that were made in order to help perhaps ensure the efficacy of this procedure.

MR. SPEARMAN: Maybe that's one of the very beauties of this. This is kind of like a hearing aid in a sense. It's not like a cochlear implant where there is a great deal of rehabilitation. The patient is hearing naturally. We do find that just using the device -- there is no special thing that patient has to do, but upon activation, they start to get acclimated to a whole new world of sound that they haven't heard before, a lot of sounds that they

1 didn't hear like keys and coffee sloshing and these
2 fine, high frequency pitches that they really weren't
3 getting before. So they get used to that the same we
4 all do when our brain gets retrained.
5 The other thing we found is that they
6 improved from the two-month endpoint, or two-month
7 visit, to the four-month and then to the ten. They
8 just kept improving on the ability of their --
9 usually their speech and their SRT scores went up --
10 if you saw that one slide, they went from 10.6 to
11 11.7 from six to ten months in SRT. And we always
12 saw somewhat of a little bit improvement. At about
13 ten months, one year post-surgery, in the first
14 study, we saw that level off now over the year. So
15 it takes -- over time, they get better and better and
16 then it kind of levels off. But they're able to hear
17 immediately, and there really isn't any specific
18 training that they have to do to gain the benefits.
19 DR. LEOPOLD: One more question.
20 Dr. Connor?
21 DR. CONNOR: Thank you. Jason Connor. So
22 I'm the statistician, so please pardon me if this is
23 a naïve clinical question, but I'm trying to
24 understand something about the three patients who
25 were enrolled who aren't included in your denominator

of 57. So did these patients receive sedation and some incision, and at that point it became clear that there wasn't room? I think that was the general issue, that there wasn't room for this implant.

DR. SHOHET: Thank you for your question. Jack Shohet. Those three patients were my patients. Two of the patients, and one of the two patients -- two of the patients were anatomic issues. One patient did not have an adequate mastoid cavity to be able to get the transducer to fit completely within it. And she had received intraoperative sedation. She was actually already under general anesthetic. I had done a mastoidectomy, and the transducer just could not fit in through that facial recess with the limited mastoidectomy. Her chain was not disarticulated. She was not disrupted -- and it was not disrupted in any way. And so we closed up the wound, and she had no ill effects from that.

Second patient had a retracted TM, and it did not look retracted significantly under binocular microscopy in the exam room. But it was retracted enough so there was not enough room between where the driver needed to be placed lateral to the stapes capitulum and the tympanic membrane so that if I put the driver in, it would have been in contact with the

tympanic membrane, which would have resulted in significant feedback. And so in this patient, the driver was not placed, the chain was never disarticulated, his ossicular chain was not manipulated in any way, and he was also closed up and had suffered no ill/adverse effects to his hearing.

The third patient changed his mind as to which ear he wanted to have implanted on the day of surgery. And so we had not tested -- he had not worn a hearing aid in the ear that we were -- that he wished to have implanted, and so we did not end up implanting him that day.

DR. CONNOR: So he didn't ever even receive sedation?

DR. SHOHET: He didn't receive sedation. I terminated the procedure at that point. Thanks.

DR. LEOPOLD: Thank you. We now are going to take our morning break. Let's take a ten-minute break and resume at 10:45 a.m.

Remember, Panel members, that there should be no discussion.

(Off record at 10:35 a.m.)

(On record at 10:45 a.m.)

DR. LEOPOLD: The FDA will now give their presentation on this issue, and Dr. Clupper, the FDA

lead investigator/reviewer, will begin.

DR. CLUPPER: Good morning, distinguished Panel members, members of Envoy Medical Corporation, and audience members. I am Daniel Clupper, the team leader for the Esteem PMA.

Envoy Medical Corporation has submitted a pre-market approval application to FDA for a first-of-a-kind device, the Esteem Totally Implantable Middle Ear Hearing System. This marketing application describes the safety and effectiveness of this device system, which is designed as a non-visible alternative to conventional air conduction hearing aids.

The applicant conducted a clinical trial, IDE G070162, to assess the safety and effectiveness of the device system after Sponsor-defined best practices in surgical techniques were developed during study IDE G00321 to address the observed failures in device performance.

FDA has reviewed the pre-market application for the Esteem Totally Implantable Hearing System. Because this is a first-of-a-kind, fully implantable hearing system to treat mild to severe sensorineural hearing loss, we are seeking Panel members' expertise and input in an open public meeting of the ENT Panel.

The Esteem device is also the first implantable system to require disarticulation of the ossicular chain and partial resection of the incus for device implantation.

Today, we are discussing only the clinical results associated with this PMA. The manufacturing information and pre-clinical study results have already been reviewed and approved by FDA in prior modular submissions.

The FDA staff members involved in the review of P090018 are shown here. Following this introduction, Dr. Peng will discuss the device system effectiveness. Then Dr. Khan will speak to the device safety. Dr. Johnson will outline the stats analyses, and Dr. Soldani will discuss post-approval plan considerations.

Dr. Shu-Chen Peng, an audiologist and hearing scientist will now discuss the device system effectiveness.

DR. PENG: Good morning. This morning, you have heard about the applicant's presentation on the objective of the G07162 clinical trial, the effectiveness and safety endpoints, analyses and results for each endpoint. Here, I will be presenting the FDA clinical audiology review on the

applicant's PMA submission.

To begin with this presentation, I'd like to give a study overview from the perspective of clinical audiology. The applicant's study was conducted as a non-blinded, single-arm study. In other words, the study utilized repeated measures within subject design. Each subject served as his or her own control. This study design has been historically adopted in investigational device exemption studies involving auditory prosthesis, including cochlear implants and implantable middle ear hearing devices. Also, it is known that patients with hearing loss constituted a heterogeneous population. This study design helps to reduce treatment effective variance and permit statistical inference to be made with relatively fewer subjects.

The co-primary effectiveness endpoints of this study, word recognition score and speech reception threshold, which will be described in detail in a minute, are considered as relatively objective measures in assessing hearing benefit.

A total of 60 subjects enrolled in this study. Among them, 57 subjects were implanted with the Esteem, 54 subjects had data available at the four months interval, and 52 subjects had data

available at a ten-month interval. The mean age of the 57 subjects was 53 years. Thirty-eight, or 67%, of these subjects were male. Nineteen, or 33%, were female. Once subject was Asian, and all the other subjects were Caucasian.

The subjects' hearing loss was diagnosed at an average age of 32.5 years. Of the 57 subjects, 54 subjects' onset of hearing loss was gradual, three subjects' onset of hearing loss was sudden. There were 10 subjects whose degree of hearing loss, based on pure tone average, fell in the range of severe, 44 fell in the range of moderate, and only 3 subjects' hearing loss fell in the range of mild.

There were two co-primary effectiveness endpoints. The first one was to compare the speech reception threshold between the Esteem and the pre-implanted aided condition. The second one was to compare the word recognition score at 50 dB HL between the Esteem and the pre-implant aided condition.

The first co-primary effectiveness endpoint, SRT, was to measure SRT using the Esteem at four months as compared to the pre-implant aided condition. The focus of the analysis for this endpoint was to compare the group mean SRT at four

and ten months relative to the pre-implant aided condition.

This slide shows the group results for SRT. The applicant has presented these results earlier this morning. Basically, the group SRT decreased from an average of 41.2 dB HL in the pre-implant baseline aided condition to 30.6 and 29.4 dB HL at four and ten months, respectively. The applicant concluded that these data suggest that with the Esteem, the SRT is not only non-inferiority, but also superior to the SRT in the pre-implant aided condition.

Note, however, statistically significant site effect was observed across the three study sites, which will be described by Dr. Terri Johnson in her presentation in more detail. This site variability was not taken into consideration in the applicant's data analysis.

The second co-primary endpoint, WRS, was to measure WRS using the Esteem at four months as compared to the pre-implant aided condition. The analyses were performed at both group and individual levels. At the group level, the mean WRS was compared at four and ten months to the WRS in the pre-implant aided condition. At the individual

level, WRS was compared using the 95% critical difference boundaries described in the Thornton and Raffin 1978 study for the 50-word list based on the percent correct scores.

This slide shows the group results for WRS. As was reported by the applicant, the group WRS changed by an average of 21.7 and 19.8% at four and ten months, respectively, when compared to the WRS in the pre-implant baseline aided condition. Note, however, similar to the SRT results, statistically significant site effect was observed across the three study sites. This site variability was not taken into consideration in the applicant's data analysis.

This table shows the individual data. Specifically, the distribution of the proportion of the individual subjects' WRS with the Esteem at the four and ten months, respectively, that is, better than, equal to, or poorer than the WRS with their own hearing aids in the pre-implant aided condition.

As we can see from the table, at four and ten months, 93% and 88% of the subjects' WRS was significantly better or equivalent to the WRS with their own hearing aids. However, at both four and ten months, there is a portion of subjects' WRS that was significantly lower than the WRS with their own

hearing aids. Specifically, 7% and 12% of the subjects' WRS was significantly lower than the WRS in the pre-implant aided condition.

Also, please note that, similar to the SRT results and the group results with WRS, statistically significant site effect was again observed for the individual WRS across the three study sites. This site variability was not taken into consideration in the applicant's data analysis. This issue will be addressed by Dr. Johnson in her presentation.

Per FDA's request, the applicant performed additional analysis on the stratified results for the two co-primary effectiveness endpoints, SRT and WRS. Specifically, change in SRT and WRS with the Esteem relative to the pre-implant aided condition was compared among subgroups based on the following subject characteristics: Age, baseline hearing, loss severity according to pure tone average, baseline unaided WRS presented at the maximum tolerable level, and lengths of hearing aid use experience.

The applicant's analysis indicated consistent results among all subgroups, stratified based on each of the subject characteristics listed on this slide. Based on these results, the applicant concluded no statistically significant difference

observed among subgroups. However, when evaluating these analyses, it is important to keep in mind that there were only three subjects in the subgroup of mild hearing loss. All other subjects' hearing loss was either moderate or severe. This limited sample size of this subgroup may raise a potential concern when attempting to generalize the present results to patients with a mild hearing loss.

This slide is not in the Panel pack, but it shows the effectiveness outcomes for the three subjects with mild hearing loss. As we can see here, all three subjects improved in their PTA and SRT. However, all subjects' WRS is 10 to 15% lower with the Esteem when compared to their own hearing aids. The results with QuickSIN and APHAB are mixed among the three subjects.

The Panel will be asked to comment on the data that were just presented. That is, the primary effectiveness endpoint data were available for only 3 subjects with a mild hearing loss, 41 with moderate loss, and 10 with severe loss. Please comment on the proposed Indications for Use for this device for each category of hearing loss, namely mild, moderate, and severe. Please discuss if these data are sufficient to support effectiveness for each of these

categories.

As for the secondary effectiveness endpoints, the first one was to compare the pure tone thresholds and average between the Esteem and the pre-implant unaided condition. The second one was to compare the QuickSIN, or speech-in-noise test, results between the Esteem and the pre-implant aided condition. There were two quality-of-life comparisons using the Abbreviated Profile of the Hearing Aid Benefit, or APHAB Questionnaire, and the Esteem Questionnaire.

This slide presents the group and individual results of the first secondary effectiveness endpoint, change in pure tone average, or PTA. The group results indicated that, at four months, the mean change in PTA was 27 dB. At the individual level, at four and ten months, 96 and 92% of the subjects, respectively, had a greater than 10 dB increase in PTA. There were no subjects at both intervals who had a greater than 10 dB decrease in PTA.

Another secondary endpoint was the QuickSIN or a speech-in-noise test. The endpoint was to compare the QuickSIN test results using the Esteem at four months as compared to the pre-implant aided

condition. The QuickSIN test is the test for loss in signal to noise ratio that helps to understand that realistic expectations for the patient's potential improvement in noise with amplification.

The results indicated that, compared to that in the baseline aided condition, the mean change at four and ten months was -1 and 0 dB, respectively, to achieve the SNR for the 50% correct score. Based on these data, the applicant concluded that the Esteem system is not different from the hearing aid in improving speech recognition in noise.

There were two quality of life secondary endpoints. The first one was the Abbreviated Profile of Hearing Aid Benefit, or APHAB Questionnaire. The APHAB Questionnaire is the self-reported measure that directly compares handicap or disability before and after amplification or rehabilitation. This questionnaire was validated in a group of hearing aid users in Cox and Alexander, 1995. It has never been validated in any of the patient populations with implantable middle ear hearing devices.

The applicant reported the APHAB results at four-months interval. At this interval, 53 subjects' data were available for analysis. Compared to the baseline-aided condition, there was an average

increase of 10.9% in the overall score.

On this slide, the overall APHAB scores are presented for individual subjects. The first three rows of the table here display the proportion of subjects whose overall APHAB scores was at least 5% better as compared to their own hearing aids; together, 60% of the subjects whose overall APHAB score was at least 5% better than that in the baseline aided condition.

The last three rows display the proportion of subjects whose overall APHAB score was at least 5% poorer as compared to their own hearing aids; note that together, 20% of the subjects whose overall APHAB score was at least 5% poorer than their APHAB score in the baseline aided condition.

The second quality-of-life endpoint was the Esteem Questionnaire. The Esteem Questionnaire was developed by the applicant for the purpose of gathering subject feedback and comments on the use of the Esteem relative to the re-implant aided condition. This questionnaire has never been validated in any patient population.

This table shows some of the results at four and ten months relative to the baseline aided condition. The numbers in blue represent the

proportion of subjects who judged the Esteem as somewhat or much better than the baseline aided condition while the numbers in red represent a proportion of subjects who judged the Esteem as somewhat or much worse than the baseline aided condition.

As we can see, although about 70 to 80% of the subjects judged the Esteem as somewhat or much better with their hearing aids -- than their hearing aids, there was a portion, about 10 to 20% of the subjects, who judged the Esteem as somewhat or much worse than their hearing aids.

Compared to the baseline aided condition, some subjects experienced decreased performance in the following effectiveness endpoints: WRS, APHAB, and Envoy Questionnaire. The Panel will be asked to consider these results in their deliberations for the effectiveness of the Esteem system.

As for the safety outcomes, there were two co-primary safety endpoints. First, cochlear stability, which was measured by comparing each subject's pre-implant bone conduction, or BC, safety algorithm, or SA, thresholds to the subject's thresholds at four and ten months post-activation; second, rates of occurrence for serious adverse

device effects and failures and revisions. This second safety endpoint will be addressed by Dr. Angie Khan in her presentation. And I will be focusing on the first one, cochlear stability.

For the endpoint analysis, bone conduction thresholds were measured using the forehead probe placement. If any bone conduction thresholds fail outside the stability range, that is, plus or minus 10 dB, then safety algorithm was used. With the bone conduction measure alone, there is a possibility that bone conduction test/retest variability may result in test results outside the plus or minus 10 dB limits due to the equipment limitations and probe placement.

For this reason, the applicant developed the safety algorithm back in G000321. In safety algorithm, the EnvoyGram function is used as an in situ audiogram to directly stimulate the cochlea. The safety algorithm was previously validated by the applicant and reviewed by the FDA.

This slide shows the group results for bone conduction thresholds. As a group, at four and ten months, the subjects' mean shift in average bone conduction thresholds across 500, 1,000 and 2,000 Hz was 0.1 dB and -0.8 dB, respectively, relative to the baseline condition.

To assess the individual results, the applicant adopted the following change criteria, that is, the subjects' change in BC or SA thresholds was considered to be indicative of decrease in cochlear function if two out of the four test frequencies had a greater than 10 dB change or one frequency had a change of 20 dB or greater.

Based on these change criteria, the applicant reported the individual results in four and ten months. Recall that there were 54 and 52 subjects who had data available at four and ten months, respectively. At four months, no subject had a BC/SA threshold shift greater than the change criteria. Note, however, there were two subjects whose BC/SA thresholds could not be determined. This is because these two subjects had a BC/SA threshold measurement missing at one or more frequencies.

At ten months, one subject had a 20 dB BC/SA threshold shift at 4,000 Hz. At this interval, there was one subject whose BC/SA thresholds could not be determined since this subject had a BC/SA threshold measurement missing at one or more frequencies.

The applicant concluded that these BC/SA data supports stable cochlear function through four

and ten months post-activation. Note, however, the BC/SA results could not be determined in some subjects. Specifically, among the 57 subjects implanted, BC/SA results were missing or undetermined in five subjects at four months and six subjects at ten months. This factor needs to be taken into consideration when assessing the outcomes for this co-primary safety endpoint.

Based on the cochlear stability data, the Panel will be asked to comment on the following: Of the 57 subjects implanted, cochlear stability data were available in 51 subjects at ten months. In other words, six subjects did not have cochlear stability data available for analysis. Of these, one subject exhibited significant threshold shift at 4,000 Hz. Do these data provide adequate support of long-term safety of the Esteem system?

This is the end of my presentation. In the next presentation, Dr. Angie Khan, who is an otolaryngologist, is going to address the safety endpoints and safety outcomes in her presentation.

DR. KHAN: Good morning. I'll be discussing the device safety issue of the Esteem Totally Implantable Middle Ear Hearing Device.

Although we have already heard this morning

about the procedure to implant Esteem, I would like to briefly recap the anatomy and surgical approach required for implantation, as both have an impact on device safety.

To successfully place implantable components of Esteem system, the temporal bone anatomy must be normal, normal tympanic membrane, and normal functioning Eustachian tube, together with a healthy mastoid. In addition, thin-cut axial and coronal CT scans performed on each potential subject before enrollment are used to assure that sufficient space is available for the implantable components of the Esteem system.

As shown in these two radiographic pictures, critical measurement include a 22 mm distance between the incudostapedial joint and the sigmoid sinus for the placement of the driver, and a 4.5 mm distance between the tegmen and scutum for the sensor transducer attachment to the incus in the -- space.

The tympanic membrane information is important. We heard earlier from Dr. Catalano -- I'm sorry -- Dr. Shohet that we had inquired -- the FDA had inquired about the two patients that were removed after enrollment because of low tympanic membrane

finding. We were unaware of the fact that they had undergone anesthesia for this procedure.

The surgical approach for placement of the Esteem device requires a standard mastoidectomy followed by an opening of facial recess to expose the middle ear. The top picture demonstrates the narrow facial recess opening to the middle ear, a space drilled between the facial nerve here and the chorda tympani nerve there. While exposure to middle ear can be excellent, as seen in the lower picture, facial recess approach, even in experienced hands, puts the facial nerve as well as the chorda tympani nerve at risk of injury during this procedure. Once the mastoid well is created for the sound processor and the middle ear is exposed, the area is ready for placement of implantable components of Esteem system.

After gaining entry into the middle ear, many critical surgical steps must occur during placement of the Esteem device. First, a disarticulation of the article, as you heard earlier, is necessary to position the device and separate sensor input function from the driver output function. Once disarticulation of incudostapedial joint is accomplished, a 1 to 3 mm portion of the long process of the incus is removed.

The last critical step is that of sensor and driver attachment to the appropriate ossicles with the use of EnvoyCem. This step of driver-stapes interface bonding had evolved over two clinical trials, a previous trial, G000321, and the current trial, 070162. I will discuss the driver-stapes bonding step in the next slide.

In an earlier version of Esteem device, under a separate IDE, G00321, of 72 subjects, a high failure rate of 14 events were believed to have occurred due to inadequate bonding at the driver-stapes interface. In order to address this high failure rate, the applicant developed best practices, which were used in the subjects enrolled in the latter part of this study. Best practices included careful cleaning of all mucosal and fibrous tissue on the capitulum and around the stapes neck followed by drying of the surface of capitulum using a low wattage laser to assure all moisture is removed and better bonding is promoted.

In addition to best practices I just mentioned, a new two-step procedure was implemented in the current pivotal study in an effort to further enhance adhesions of the driver-stapes interface. The first step of this new procedure is application

of a pre-coat of EnvoyCem completely around the capitulum and the neck of the stapes to make good cement bond to the stapes. The pre-coat application gives the surgeon better visibility and access to the stapes and allows for more complete application of the cement.

After the pre-coat has set, the driver is then attached to the pre-coated stapes and a second application of EnvoyCem is accomplished. The photograph seen on this slide provides a view of the middle ear and mastoid cavity with driver and stapes connection and sensor and incus connection. This is prior to the surgical wound closure.

This slide, compiled by FDA from the data provided by the applicant, notes improvement in revision surgeries from the previous G00321 to the current trial. Introduction of best practices, two-step bonding at driver-stapes interface, and other design changes have reduced the rate of revision surgery from 28% in the previous trial to 7% in the current trial.

Dr. Peng already discussed the first safety objective of the cochlear stability. I will now discuss the second co-primary safety objective of this study, which was to determine the incidence of

1 severe adverse device effects, or SADEs, and the
2 incidence rate of device failures and replacements.
3 All six SADEs of the current trial fell under
4 applicant's last definition on this slide, that is,
5 required intervention to prevent permanent impairment
6 and damage.
7 The applicant sponsored a clinical events
8 committee, which determined that there were six SADEs
9 reported in six subjects for an incidence of 10.5% in
10 the study population. Among the six SADEs, three
11 were due to limited benefit from the device, which
12 resulted in revision procedures. One subject had
13 incision infection, which resolved with medication.
14 One other subject, who had incision breakdown more
15 than once, required explantation of the device. Six
16 subjects experienced severe pain and facial weakness,
17 which resolved with steroid therapy. I will discuss
18 the SADEs of limited benefits in more detail on the
19 next few slides.
20 Three out of four subjects who experienced
21 limited benefit at or after activation of the device
22 required exploration and revision surgery. Fourth
23 subject resolved without intervention. While fibrous
24 adhesions were noted in the facial recesses of all
25 three subjects, other observations were reported

related to the cements used in these surgeries. For example, in one subject, MedCem was noted to be restricting the movement of the incus. In another subject, an unusually small amount of EnvoyCem was noted at the driver-stapes interface. In the third subject, driver tip was noted to be pulled away from the stapes in addition to small amount of EnvoyCem at driver-stapes interface, but with intact bond.

These findings led to interventions in each of these three subjects. During surgical intervention for Subject 103-22, removal of the sensor and the driver was required in order to remove the fibrous adhesions. In addition, surgeon removed the MedCem, restricting the incus. Subsequently, a new sensor and driver were placed.

Driver output was noted to be low for Subject 109-24. After removal of fibrous adhesions, a new driver was implanted together with application of a greater amount of EnvoyCem to boost the driver-stapes bonding.

The driver output was also noted to be low for Subject 109-22. After removal of the fibrous adhesions surrounding the stapes and driver, a new driver was implanted, and a greater amount of EnvoyCem was applied to secure better connection.

Of the three subjects, one subject has reached four-month endpoint. Remaining two subjects had reached a two-month postoperative period but not the four-month endpoint at the time of PMA submission.

Based on my discussion so far, Panel is requested to consider whether the rate of revision surgery in the current pivotal study, due to limited benefit, support reasonable assurance of safety. Also, what additional measures, if any, should be taken to address this issue?

This slide summarizes all adverse events of this study. The summary was compiled by FDA from study data provided by the applicant. A total of 133 adverse events occurred in the current study. Fifty-two of fifty-seven, or 91% implanted subjects experienced at least one adverse event. Multiple, 2 to 8, adverse events were experienced by 36 of 52 subjects. Seventy-eight percent of adverse events have resolved, and 21 remain unresolved in 26 subjects at the time of this PMA submission.

Grouping of all adverse events, or AEs, in nine broad categories on this slide was compiled by FDA from raw data provided by the applicant. This slide represents the number and percentage of

subjects with adverse events out of 57 implanted subjects. Taste disturbance was the most frequent adverse event reported in 24 of 57, or 42% of the subjects. This event has not resolved for 8, or 14% of the subjects, beyond a year and a half since implantation.

Of note, adverse events, facial paresis/paralysis, were noted in 4 of 57 subjects, for a prevalence of 7%. This adverse event has not resolved for two subjects at the time of this PMA submission. However, I must add that Dr. Catalano provided update on this subject: Adverse events, occurrence of middle ear effusion, and headaches have all resolved.

This slide summarizes the four facial nerve-related adverse events in this study. This summary was compiled by FDA from the study data and case report forms provided by the applicant. Facial nerve adverse event in Subject 103-24 was noted a week following the implantation procedure, was given prednisone as an intervention, and adverse event was reported resolved in two months following the onset. However, this was the only subject adjudicated by clinical events committee as SADE.

Facial nerve adverse event in Subject 105-

40 was noted on the day of implantation procedure, received no intervention, and was reported resolved in approximately a month and a half. Two other subjects with facial nerve adverse events, 103-25 and 109-26, were noted to have the adverse event within five and ten days, respectively, following implantation.

They both received prednisone and remained unresolved beyond a year and a half of the time of PMA submission. Neither of these two subjects were adjudicated as SADEs, although these events do appear to fall into one of applicant's definition of SADEs, which is required intervention to prevent permanent impairment and damage.

This slide shows the number of adverse events and SADEs across each of the three participating sites and was compiled by FDA from the study data provided by the applicant. While the occurrence of SADEs across three sites was not too different, as seen in the red bars, wide variability of the total number of adverse events occurrence was noted across three sites, as shown by the blue bars. Site 109 had least number of adverse events, noted to be 17 events in 17 patients, compared to Sites 103 and 105, with 50 and 66 events, respectively. All

three surgeons are experienced and had participated in the previous G00321 study.

Based on what I just discussed, Panel will be asked to comment on significance of type and rate of adverse events observed. Do the data support reasonable assurance of safety for the device? Please also comment on variability of adverse event occurrence across study sites.

If Esteem implant is explanted, ossicular chain must be reconstructed to restore continuity in hearing. The most common ossicular reconstruction technique, as we already heard, utilizes PORP, partial ossicular reconstruction prosthesis. However, applicant has introduced an incudoplasty technique of reconstruction, performed in both previous, G00321, in two subjects, and in current study on one subject.

As Dr. Kraus already explained, a titanium endoskeleton bridges across the ossicular chain defect. After EnvoyCem application proximally on incus and a micro -- on capitulum, a continuous structure is built with the EnvoyCem to complete the incudoplasty.

These four audiograms show air conduction thresholds on patients reconstructed either with

incudoplasty or PORP. This is the only patient reconstructed with PORP. The other three are incudoplasty. These audiograms were compiled by the FDA from the audiometric data provided by the applicant. The blue data points represent the pre-implant conduction thresholds, air conduction thresholds, and green dot data points represent the post-reconstruction air conduction thresholds.

On this audiometric analysis, 3 of 4 subjects had some decrease in air conduction, particularly at high frequencies. Two subjects, 102-05, which is this one, and this one, 103-17, also exhibited decrease in air conduction thresholds between 250 and 1,000 Hz. Consideration should be given to these results when discussing the effects of ossicular reconstruction.

The battery life of the sound processor is projected by the Sponsor to be about four and a half years if the Esteem device is left active at all times. On the other hand, if Esteem device is used for only eight hours each day, it may last up to nine years, to estimated replacement indicator.

When the sound processor battery needs to be replaced, it may be done under local anesthetic. The previous incision is reopened, as previously

described by Dr. Kraus. The sensor and driver leads are removed from the connector ports, which are right here. Then the sensor and driver leads are inserted into the new connector ports of the new sound processor. The new sound processor is placed in the already existing surgically created bed in the temporal bone, and the incision is closed.

In closing, final question in addressing the safety of the device need following considerations: Do data in this study support reasonable assurance of safety and effectiveness for the Esteem system? In your discussion, please consider: The device requires disruption of a normal intact ossicular chain and partial resection of incus. In cases when the device may need to be explanted, ossicular chain reconstruction is required to restore hearing. Device battery must be replaced in approximately 4.5 years of 24/7 device activity.

This brings an end to my talk. The next segment will be presented by Dr. Terri Johnson, statistical reviewer for this PMA.

DR. JOHNSON: Good morning. I'm Terri Johnson. I will present the FDA statistical review on the study device.

I will briefly recap the study design, show

how the sample size was calculated, and present the results of primary effectiveness and safety endpoints and their statistical issues. Then I will address the statistical question to the Panel.

It is a non-blinded, single-arm study. Up to ten investigational sites were planned, but only three sites participated, Site 103, 105, and 109.

Please note that the co-primary effectiveness endpoints, speech reception threshold, is assessed as decrease in SRT at four months from the baseline aided condition for each subject. Hypothesis testing was pre-specified only for the co-primary effectiveness endpoint, SRT. Therefore, the sample size calculation was driven by SRT.

It was based on one sample, one sided t-test for a mean. Hypothesis was that the mean decrease in SRT at four months from the baseline is greater than -5 dB with Type I error rates that are 0.025 and power of 80%. And it was assumed that the true decrease was zero with standard deviation of 10.5 dBs. Sample size calculated was 40 subjects. However, minimum of 50 and up to 60 subjects was agreed upon to increase the confidence in the safety of the study device.

The applicant used their analysis

population as all those patients who were successfully implanted with the study device and have the baseline and follow-up data. There were 54 patients at four months and 52 patients at ten months.

FDA has two more analysis populations in addition to the applicant's analysis population. The first population includes all subjects who were enrolled and signed consent form for the study, which consisted of 60 patients. Second analysis population includes, among those "all" population, subjects who are successfully implanted with the study device, which consisted of 57 patients.

Recall that the hypothesis for the co-primary effectiveness endpoint, SRT, was to test that the mean decrease of the SRT at four-month relative to the baseline pre-implanted aided condition is greater than -5 dBs. The applicant has presented that the mean decrease was 10.6 dBs with 95% confidence interval ranging from 7.1 to 14.2, rejecting an "all" hypothesis and concluding that there is evidence that the mean decrease in SRT at four-month from the baseline aided condition is greater than -5 dBs. However, these estimates assume no site variability.

This is a scatter plot of SRT at four-month, plotted against the baseline, the four-month SRT on the y-axis and the baseline SRT on the x-axis. This scatter plot was then stratified by three investigational sites.

This is a scatter plot of SRT at four-month against the baseline for Site 103 only, SRT for Site 105, and Site 109. These plots clearly show site variability in SRT. Site 105, in particular, looks quite different than the other two sites.

So site effect was statistically significant. And in presence of a significant site effect or site variability -- overall estimate of the mean that pools the data directly across the site is incorrect.

Then what can we do? There are two ways to present results in such a case. We can report site-specific result or report overall result. The site-specific results are reported with point estimate of mean and confidence interval of the mean. However, this approach cannot provide general overall conclusion for the study device. And conclusion can be applied only to these three specific sites and not generalizable to all centers in the U.S.

Please remember we are here for approval of

indication for use at all centers in the U.S. Therefore, site-specific results are not of interest here.

Therefore, an overall result should be presented with confidence interval that takes site variability into consideration. There are two types of variability to consider here, variability between sites and variability within site. The applicant's method only considers the variability within site and disregards the variability between sites.

Please note that this slide was not included in the Panel handout because I would like to comment a little bit on the reference that the applicant has presented. First of all, the paper only discussed randomized multi-arm trial, and we have single-arm trial. Second, I believe that the applicant presented a biased interpretation of the reference because the applicant presented only one point from the paper, when to consider using fixed effects. The author also listed four points, when to consider using random effects, and here are the four points. And I would like your focus on the fourth point here. It says if we're interested to say something about patients in a given center, the fixed effect approach leaves little alternative but to use

the result from that center only. The random effects approach will allow us to combine information with a given center with the information from all centers in a way which may be more appealing and useful.

So when we take both variabilities within and between sites into consideration, the 95 percent confidence interval for the mean decrease in SRT of four months from the baseline range from -9.4 to 29.7, including -5, and fails to reject a -- hypothesis and cannot conclude that there is a mean decrease greater than -5 dB in SRT at four months from the baseline.

This table presents the result of the second co-primary effectiveness endpoint, word recognition score. Recall that with the applicant's analysis population, there were 7% and 12% below hearing aided condition at four and ten months, respectively, using Thornton and Raffin critical difference criteria. However, with the implanted population, we have 12% below hearing aided condition at four months and 19% below aided condition at ten months.

Furthermore, the FDA computed the worst case analysis under the "all" population. It was computed by imputing six missing endpoints at four

months and eight missing at ten months as failures. In the worst case scenario, we have 17% below aided condition at four months and 23% below aided condition at ten months.

Similar with the SRT, there was significant site effect for WRS with below aided condition ranging from 0% to 20%. Furthermore, when adjusted for site variability, the 95% confidence interval for WRS at four-month ranged from -20.2 to 62, including 0, of no change.

This is a scatter plot of WRS at four-month against baseline. A concern arose on those subjects who had 0% score at the baseline. Please note that, due to the floor effect, these subjects would always do equal or better at any follow-up relative to the baseline.

This is a scatter plot of WRS for Site 103 only, for Site 105, and for Site 109. As you can see, when stratified by the site, the plots show a more clearer distinction between those who had 0% at the baseline and who didn't, particularly in Site 103 and Site 105. So the mean change in WRS was assessed by the categories of baseline WRS provided by the applicant. And it seems that those who had 0% WRS at the baseline improved the most. And the improvement

in WRS at four and ten months decreased as the baseline WRS increased. And those subjects who had greater than 80% WRS at the baseline show a mean decrease in WRS at four and ten months.

The two co-primary safety endpoints were serious adverse device effects and cochlear stability. There was no formal hypothesis testing pre-specified for these endpoints. Recall that the applicant reported earlier that there was no subject with bone conduction threshold shift at four-month assessed by bone conduction safety algorithm and one subject with a shift at ten-month.

However, in the worst case scenario with all population, again, assuming all missing or undetermined BC/SA as failures, there would be 13% of the subjects with a bone conduction threshold shift at four months and 15% with a shift at ten months.

The secondary effectiveness endpoints were pure tone average, QuickSIN, APHAB, and Esteem Quality-of-Life. There was no hypothesis testing pre-specified for any of the secondary endpoints. Therefore, please keep in mind that any p-values and confidence intervals presented in the PMA are uninterpretable.

In summary, FDA statistical analysis showed

significant site effect for both primary effectiveness endpoints, speech reception threshold, and word recognition score. After taking site variability into consideration, the lower bound of 95% confidence interval for the mean decrease in SRT was no longer greater than -5 dBs. FDA analysis also showed similar results for WRS. And here is the question to the Panel: Is the observed site variability a concern in interpreting device effectiveness?

Next, Dr. Federico Soldani will present post-approval study review.

DR. SOLDANI: Thanks, Dr. Johnson. Good morning, distinguished members of the Panel and members of the audience. My name is Federico Soldani, and I'm one of the epidemiologists in the Division of Epidemiology in the Office of Surveillance and Biometrics, at the Center for Devices and Radiological Health at the FDA, and the epidemiologist on the pre-market application review team.

I will now present the post-approval study considerations for Esteem Totally Implantable System. Here is the outline of my presentation today. First, I will discuss the general principles for post-

1 approval studies. Then I will comment on the
2 rationale for the post-market questions that the pre-
3 market study was not designed to answer but that may
4 be addressed in the post-approval study. Then I will
5 present the assessment of the applicant's post-
6 approval study outline. And, finally, I will
7 describe the post-approval study issues that we would
8 like the Panel to discuss on the design of the post-
9 approval studies if the PMA is approved.
10 Before we talk about post-approval studies,
11 we need to clarify a few things. The discussion of a
12 post-approval study prior to a formal recommendation
13 on the approvability of this PMA should not be
14 interpreted to mean FDA is suggesting the Panel find
15 the device approvable. The plan to conduct a post-
16 approval study does not decrease the threshold of
17 evidence required to find the device approvable. The
18 pre-market data submitted to the Agency and discussed
19 today must stand on its own in demonstrating a
20 reasonable assurance of safety and effectiveness in
21 order for the device to be found approvable.
22 There are two general principles for post-
23 approval studies. The main objective of conducting
24 post-approval studies is to evaluate device
25 performance and potential device-related problems in

1 a broader population and over an extended period of
2 time after pre-market establishment of reasonable
3 evidence of device safety and effectiveness. Post-
4 approval studies should not be used to evaluate
5 unresolved issues from the pre-market phase that are
6 important to the initial establishment of device
7 safety and effectiveness.
8 The reasons for conducting post-approval
9 studies are to gather post-market information,
10 including longer-term performance of the device; data
11 on how the device performs in the real world, in a
12 broader patient population that is treated by
13 community-based physicians and specialists as opposed
14 to highly selected patients treated by investigators
15 in the clinical trials; evaluation of the
16 effectiveness of training programs for use of
17 devices; evaluation of device performance in
18 subgroups of patients, since clinical trials tend to
19 have limited numbers of patients or no patients at
20 all in certain vulnerable subgroups of the general
21 patient population. In addition, post-approval
22 studies are needed to monitor adverse events,
23 especially rare adverse events that were not observed
24 in the clinical trials.
25 Before we proceed to the overview of the

applicant's post-approval study outline, let me remind that besides the investigational device exemption pre-market study, the IDE study, the Sponsor is conducting a continued access study, enrolling new patients until FDA decisions about PMA approval are completed.

This table presents an overview of the applicant's proposed post-approval study. To evaluate device longer term safety and the durability of treatment effectiveness, the applicant proposes to continue follow-up of the pre-market cohort. The study will be a prospective, multi-center, single-arm, open-label study. The study population would consist of at least 50% of treated patients in the IDE and continued access studies and would be followed for five years post-activation.

The primary effectiveness endpoint is speech reception threshold compared to the aided condition, and the study hypothesis is based on the same primary endpoint as the IDE study. The lower 95% confidence bound for the mean difference between baseline aided condition and five-year condition is expected to be greater than or equal to -5 dB.

Other effectiveness endpoints are word recognition score, WRS, compared to the aided

condition, co-primary endpoint, pure tone average, QuickSIN, speech-in-noise, compared to the aided condition, the APHAB Questionnaire, the Envoy Questionnaire, the most comfortable listening level, and the uncomfortable listening level.

The safety endpoints include bone conduction thresholds, using the bone conduction safety algorithm, adverse events, and serious adverse events, which could be device-related or surgery-related or else.

The applicant described its post-approval study plans earlier. We would like to bring to your attention to a few issues regarding the extended follow-up study. First, post-approval study questions were not formulated explicitly. Second, no sample size or power calculations and no detailed statistical analyses were provided in the post-approval study protocol. Third, there was no detailed enrollment plan of possible new patients and no detailed projected study timeline. Fourth, there is a lack of diversity in the patient population. In particular, patients are almost all of Caucasian ethnicity. Finally, there is no masking or blinding of patients, of clinicians, of raters, the audiologists taking study measurements, and of the

1 members of the clinical adverse events adjudicating
2 committee as well.
3 Based on the applicant's proposed post-
4 approval protocol and our initial assessment, we
5 would be asking the Panel during your afternoon
6 deliberations to discuss whether the proposed post-
7 approval study plans are appropriate to address
8 treatment effectiveness durability and longer term
9 performance in the U.S. population and to make
10 recommendations accordingly.
11 In particular, we will be asking the Panel
12 to address the following questions:
13 Given the currently available safety and
14 effectiveness data and if this device is approved, is
15 a post-approval recommended?
16 If a post-approval study is recommended, is
17 the applicant's proposal of a five-year continuation
18 of the current pivotal study appropriate?
19 Is a post-approval study of newly enrolled
20 patients to evaluate the performance of the device
21 under conditions of general use warranted?
22 If a post-approval study is recommended,
23 what do you recommend for the following post-approval
24 study elements:
25 Clinical endpoints that address the long-

1 term effectiveness of this device to aid
2 sensorineural hearing loss; the safety issues related
3 to devices implanted once used in a larger and more
4 diverse patient population; the different safety
5 issues potentially associated with patients' clinical
6 and sociodemographic characteristics, such as age,
7 gender, level of education, socioeconomic status, et
8 cetera; the safety issues related to devices
9 implanted by a group of newly trained surgeons, which
10 is surgeons with no previous experience implanting
11 the Esteem device. Given the observed site
12 variability in the pre-market pivotal study, would
13 you recommend masking or blinding the audiologists
14 conducting the study evaluations?
15 Then another post-approval study element to
16 consider would be duration of follow-up of study
17 subjects that address the potential long-term effects
18 of continuous vibration of the ossicles, for
19 instance, necrosis, with the Esteem system; the
20 durability of the connection of the sensor to
21 incus/malleus and driver to stapes with the EnvoyCem
22 cement.
23 In addition, we would like the Panel to
24 discuss if any additional issues or questions should
25 be addressed in a post-approval study and to make

recommendations if the device gets approved.

This concludes my presentation as well as FDA's presentation this morning, and we would welcome any questions that you may have.

DR. LEOPOLD: I'd like to thank the FDA speakers for their presentations. At this point, let's have some discussion. Does anyone on the Panel have a brief clarifying question for the FDA? Please remember that the Panel may also ask the FDA questions during the Panel deliberations this afternoon.

Dr. Kileny?

DR. KILENY: Thank you. Could we see the slide of the pre versus post SRT from Site 105? It kind of went by pretty fast and --

DR. JOHNSON: The scatter plot you mean?

DR. KILENY: Yeah, the scatter plot. Yes. Thank you.

DR. JOHNSON: This one, yes?

DR. KILENY: Correct. So what this shows -- and correct me if I'm wrong -- is that the baseline -- there is quite a range of preop, pre-implant thresholds, as expected, and at the four-month, there's quite a number of patients who have much better unaided SRT than preop. Am I

misunderstanding this? I mean, there is a bunch of them who are, like, about 30 dB, but some of them had preop at 60.

DR. JOHNSON: That's correct. If you draw a 45-degree angle on the lower right, it means improvement, because the lower the SRT, the better it is. So it's correct, yeah.

DR. KILENY: So, for instance, if I pick one point here, preop was about, let's say, 45 and postop it's 30?

DR. JOHNSON: Yeah.

DR. KILENY: And then another one may be close to 60 and postop --

DR. JOHNSON: Right.

DR. KILENY: -- again around 30?

DR. JOHNSON: Right.

DR. KILENY: Can somebody comment on that? Could this be some kind of an audiological testing artifact or --

UNIDENTIFIED SPEAKER: Yeah. As you all can see that at the baseline, quite some subjects, like four or five -- points are the same, falling at about 45 dB, but then at four months, there were also a bunch of subjects who had 25 dB. I mean, we can only suspect, but we don't know if it's artifact

or --

DR. KILENY: So if you pooled the data, obviously, given that these have improved --

UNIDENTIFIED SPEAKER: Right.

DR. KILENY: -- then the mean results will be affected by this in the -- to the effect that it will show less or no change pre versus postop, if you look at the means and standard deviations; am I correct?

DR. JOHNSON: Can you repeat the question, please?

DR. KILENY: Well, if some of these patients have improved actually, and there's other patients that maybe the threshold has changed, has increased a little bit, this improvement, this apparent improvement in threshold sort of biases the data toward essentially no change because these balance out the ones where there may have been a 5 or 10 dB change?

DR. JOHNSON: I mean, that would also apply to the other way, right? I mean, improvement -- if we have more patients with improvement, then, overall, we will see that the device is effective. If we have more patients who did not improve, then overall, we will see that the device was not

effective.

DR. KILENY: Um-hum. Okay.

DR. LEOPOLD: Any other questions from the Panel for the FDA? Yes? Dr. Sie?

DR. SIE: Kathy Sie from Seattle. I just have a quick question for Dr. Khan. You talked about the patients requiring revision surgery. I noted that there were 20 in the first phase or the earlier trial, but in the documents we had, there were 25 described requiring revision surgery.

DR. KHAN: These are revision surgeries whether they were done for limited benefit or, you know, other device issues like battery failure or whatever. These are total number of all revisions.

DR. SIE: Okay. Thank you.

DR. KHAN: And in this current study, there were three for limited, and one revision was for explantation.

DR. LEOPOLD: Dr. Connor has a question?

DR. CONNOR: Yes. I think this is probably for Dr. Johnson. So one of the things I was hoping to see that I thought I was going to and didn't, on Slide 59 -- and I think our numbering is off one -- it talked about looking at the analysis also with 60 patients and 57 patients. I was hoping to see

1 something like, you know, an ITT analysis, where we
2 looked at all 60 patients who entered, understanding
3 that three, essentially, didn't get the implant even
4 though it sounds like two of those three were
5 anesthetized and had an incision made. And three
6 more weren't counted because, essentially, things
7 didn't immediately go well. But I would like to know
8 if you had those numbers, what the point estimate and
9 confidence interval for the SRT at four months is,
10 essentially, for everyone six months after the
11 surgery was supposed to have happened, because I
12 think what we're being shown is definitely optimistic
13 because we're not counting six or, essentially, 10%
14 of patients who presumably received no benefit or
15 little benefit at six months if, you know, some of
16 those three revisions actually had their revision by
17 then, but, you know, were maybe only two months in or
18 hadn't even had their device turned on yet.
19 DR. JOHNSON: Thank you for your question,
20 Dr. Connor. No, we have not looked at or computed
21 confidence interval for all 60 subjects. We did this
22 analysis for all implanted population and separately
23 for all population, and we believe that for 57
24 implanted population actually is not a worst case
25 analysis or really imputed analysis because three

subjects at four months who did not have endpoint received revision surgery. And we're actually looking at -- the outcome -- are looking at failures due to the first implantation. So requiring revision surgery, we consider that a failure actually.

For those three additional subjects who did not receive implantation, we did feel that that is kind of ITT population because these three subjects were -- did meet inclusion/exclusion criteria and did sign consent form. For whatever reason, we found that there is little discrepancies later, but these three patients did not receive implantation, therefore, did not have endpoint outcome, and we did only impute worst case analysis for this one. Therefore, there is no confidence interval.

DR. LEOPOLD: Yes, Doctor?

DR. CUEVA: I'm struggling with the need for a little guidance, and that relates to -- although the wordage, the verbiage, rather, of safety and efficacy are focused on the device, and many of the things that we're looking at in terms of site variability have to do either with patient selection or possibly execution of the surgery, and then that's really a surgical issue of safety and efficacy. How do we separate, or how do we adjudicate what's

relative to the device, which may perfectly function and be safe and efficacious, but then, you know, has to be implanted by a human surgeon and therefore is going to be variable in the ability to execute a surgery perfectly. You know, is the device approved, but how do we pick the surgeons? I mean, that's part of the struggle I'm having in terms of, you know, safety and efficacy for the device versus the surgeon.

DR. JOHNSON: That's an important issue that we need to consider. However, from the data, the way the data is presented, we could only detect site variability with statistics. I'm not quite sure how we'd be able to address that type of specific question.

DR. EYDELMAN: This is Dr. Eydelman. Let me just add to my colleague's comment here. Any time we look at the safety of the device, we look at the safety of the device at the end stage of its implantation for that particular patient; i.e., you have to assume that the patient would not have had any side effect had he or she not undergone the surgical procedure. Therefore, we look at it as an in totality, as in what happened to that patient as a result of having that device implanted.

DR. LEOPOLD: Yes, Dr. Cheung?

DR. CHEUNG: Steven Cheung from UCSF. Question for Dr. Johnson, Slide 73. A point of clarity: It seems to me that you're showing data for subjects where a word recognition score baseline is less than 40. Is that correct -- which, to my understanding is outside the inclusion criteria for the study. No?

DR. JOHNSON: Is this the slide, Dr. Cheung?

DR. CHEUNG: 73.

DR. JOHNSON: Mean change?

DR. CHEUNG: It's a scatter plot --

DR. JOHNSON: Scatter plot? Okay. This WRS scatter plot?

DR. PENG: May I clarify? The inclusion criteria is based on the -- a different presentation under unaided condition. That is the maximum tolerable level. So it doesn't conflict with the results here.

DR. CHEUNG: Okay. Thank you.

DR. PENG: Sure.

DR. LEOPOLD: Further questions? Yes, Dr. Lalwani?

DR. LALWANI: We learned earlier that the

1 two of the three not included in the analysis of the
2 60, the three that were not, two actually underwent
3 surgery. So even though they didn't have a device
4 placed, they had an adverse outcome, and the
5 assumption is that this will also occur in patients
6 who are selected, undergo surgery, that will not have
7 the device placed. How do you deal with that because
8 it wasn't really in the severe adverse effect? It's
9 not really in the adverse effect at all. And how
10 does that affect the statistics or analysis from the
11 FDA?
12 DR. JOHNSON: Terri Johnson. Yes, that's a
13 good point. That's one reason why we presented
14 analysis just using the all implanted population and
15 also all enrolled population. And I felt that saying
16 that it's a worst case scenario is kind of self-
17 explanatory. And we believe that it's, just as
18 Dr. Connor has commented, it's very close to what we
19 call intent-to-treat analysis population, where we do
20 intend to treat these population. They were
21 eligible, and they were about to receive the
22 implantation. So for whatever reason, these
23 population were eligible, and they would receive the
24 device. However, it just didn't show effectiveness
25 basically.

DR. EYDELMAN: Perhaps Dr. Khan can add to that statement.

DR. KHAN: FDA inquired about these patients and was told that this was a visual exam that they had low tympanic membrane and were not included and were not implanted. This is new information that they actually underwent surgical procedure. And so I would agree with you that this would be adverse event.

DR. LEOPOLD: Additional questions? Yes, Dr. Hirsch?

DR. HIRSCH: Barry Hirsch from Pittsburgh. In the proposal from the manufacturer, one of the criteria was for having a normal tympanic membrane. And as I recall reading the FDA summary, that inclusion criteria is not present. Can you comment on that?

DR. KHAN: One place it is reported is in the long list of inclusion criteria. In the other place in the executive summary, it's not reported, but that was part of it, and I presented that, that it should be a normal tympanic membrane.

DR. HIRSCH: But not listed on your inclusion criteria?

DR. KHAN: It is listed in one part, as I

said, in the long list of inclusion criteria. There was a short list in the beginning of the executive summary where it's not listed, but in the long list, the detailed list, it is listed.

DR. LEOPOLD: Dr. Kenna?

DR. KENNA: Marly Kenna, Boston. I just have a clarification. For post-approval studies, if such a study or series of studies is recommended, there were some things listed by the FDA that were not listed by the company. Would those things be required to be included in any kind of post-approval study, or would you work with the company to come up with those criteria, hypotheses, and so forth?

DR. SOLDANI: Well, I mean, first of all, we would like to have some feedback, I mean, of course from the Panel on the issues that I raised, and then I think, and afterwards, the next step would be to work interactively with the Sponsor to figure out, I mean, what is needed on the part of the FDA for the post-approval study and what the Sponsor can actually agree with. So this would be -- I mean, this is normally how we work to figure out what the post-approval study -- what the design is going to be and how the measurements are going to be taken, et cetera. Does that answer your question?

DR. KENNA: Yes. Thank you.

DR. LEOPOLD: Dr. Norton?

DR. NORTON: Susan Norton from Seattle. It was indicated that the sample size was calculated by the Sponsor and the FDA together. And you chose a 5 dB change, or 5 dB or greater change in the SRT, and I still have questions about why you selected that since that's the step size, and why it isn't 10 dB or greater, which, with your revised confidence intervals would mean a lot more people have no benefit?

DR. JOHNSON: Terri Johnson. Yes, the sample size was calculated by the applicant, and FDA analysis confirmed the sample size calculation, whereas how the acceptance criteria was formulated, I did not review the IDE, so that question may be addressed by Dr. Peng?

DR. PENG: Shu-Chen Peng. Okay. So the applicant had two IDEs, long history, okay. So it was based on the previous study. And, okay, so let's put it this way. So the 5 dB, if I didn't take it wrong, I think they viewed that as the measurement error, you know, the boundary for the measurement error. So they lower it to -5. If it's non-inferiority, that's the boundary, the lower boundary.

1 And does that make sense? You have something to --
2 DR. NORTON: No. I'm not sure we're going
3 to clarify my question. I'm not expressing myself
4 very well, I guess. Thank you.
5 DR. LEOPOLD: Additional questions, anyone?
6 Dr. Connor? And this will be the last question
7 before lunch.
8 DR. CONNOR: So I think this, in part, is a
9 follow-up to Dr. Cueva's question and regards sample
10 size. So, you know, it's impossible for a surgical
11 procedure to separate the device's safety and
12 efficacy from surgical skill basically. And along
13 that line, you know, in a way, I think about this not
14 as a sample size of 60 or 57 or 54. I think about
15 this with sample size three with repeated
16 measurements, that we know how three surgeons implant
17 this device, and one of which didn't really do very
18 well at all. And that may have nothing to do with
19 the surgeon, but the surgeon's patients. So it
20 sounds like the trial was approved for up to ten
21 sites, and the Sponsor only ran three sites. So in
22 that sense, the sample size is only 1/3 as big as we
23 expected. So do you have any comments about that or
24 whether you were surprised that it was three sites
25 instead of ten or the generalizability of this device

to be used by all surgeons, given we only know how it's used in three surgeons?

DR. EYDELMAN: Dr. Eydelman. Just want to point out that the Sponsor proposes a trial. We review it, and we bring it here for your recommendation. So during your deliberation, you can recommend modification. You can recommend, should you choose not to find it approvable at this point, you can make further recommendation about how to modify the trial. So we'll look forward to your recommendations.

DR. LEOPOLD: It's now time to break for lunch. We will reconvene, again, in this room one hour from now, at 1:15. We want to make sure we're back here at 1:15 because we need to give adequate time for our public forum speakers.

Please take any belongings you may want with you at this time. The ballroom will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

Panel members, please remember that there should be no discussion of the PMA during lunch amongst yourselves or with any member of the audience.

Thank you.

(Whereupon, at 12:15 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

DR. LEOPOLD: This is Dr. Leopold. I'd like to begin our afternoon session. Our first session is our open public forum, and I'd like to thank the FDA speakers for their presentations. We will have seven people interested in speaking at our public forum. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate record for this meeting. Additionally, please state your name and the nature of any financial interest you may have in this or any other medical device company. We'd also like to limit your comments to about five minutes. And we have a comment now from Dr. Kane.

DR. KANE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes it is important to understand the context of any individual's presentation.

For this reason, FDA encourages you, the open public hearing or industry speaker, if there are any, at the beginning of your written or open

statement, to advise the committee of any financial relationship you may have with the Sponsor, its product and, if known, its direct competitors. For example, this financial information may include the Sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking, however.

DR. LEOPOLD: Our first speaker is Ms. Amanda Amy Pajula. I'm sorry for pronunciation.

MS. PAJULA: Turn it on. There we go. Hi. My name is Pajula, and I am here, sponsored by Envoy Medical Group. They're paying my travel and accommodation expenses today, and I'm delighted to be here.

I am from St. Paul, Minnesota, where we have a lot of snow right now. I'm 35 years old, and I have two children, both boys, ages five and eight, so it's another reason I'm excited to get away for a little bit. I wanted to tell you a little bit about my history of my hearing loss and then share with you

some of the struggles I've had in the years leading up to this day, I guess.

At the age of eight, I was diagnosed with sensorineural hearing loss in both ears, relatively the same level, so both of my ears -- I don't really have a good ear, per se. As a child, I didn't remember struggling so much when I was eight, nine, ten years old. It was kind of looking to the classmate next to me to see what they were doing as opposed to looking at the teacher. But as I got older, I experienced great difficulty trying to live with and manage living with a severe -- moderate to severe is what, you know, I'm labeled -- hearing loss.

And the ages where it really started to affect me were in my pre-teen years, in my high school years, in college, and then as I began to see what kind of an impact this loss was going to have on my career and ultimately my whole life. It was a constant struggle. I always was on the edge of my seat while I was in classes, leaning forward, trying desperately to try and, you know, get the right information. I went so far as to change my major in college because the professor that was leading the class that I was taking, which was advertising -- it

1 was a small school -- and that professor spoke all
2 about his experiences. He was not one of those
3 professors that just read from the textbook and that
4 I could study really hard and do well. And I changed
5 my major because it was so difficult.
6 And I started to see kind of a pattern of
7 that happening in my life, you know, accommodating my
8 life to my hearing loss. I had my first hearing aids
9 when I was in college. I was very vain and probably
10 didn't get an adequate hearing aid. I had a
11 completely in the canal one, which I used at times.
12 It squealed sometimes when I was close to someone,
13 and I eventually quit wearing it altogether.
14 About nine years ago, when I realized I was
15 pregnant with my first child is when I decided, okay,
16 I've really got to take care of this, give hearing
17 aids a good try, and $6,000 later, I was a hearing
18 aid wearer. They helped me, you know, a great deal,
19 especially at first. In a situation where I was in a
20 very quiet room in a controlled setting, they were
21 wonderful.
22 As far as a day-to-day basis, you know,
23 when you have a career and you're trying to answer
24 the phone and you're trying to hear all these dates
25 and listen at a meeting, it was not a good situation

for me. Every time I was on the phone, I would have to pull my hearing aid out and try and struggle to hear what was said. Voicemail was also hard to understand.

You know, so the struggle began. And what started to happen is I started to, you know, react to the anxiety of every situation. My life became very, very small. And I realized I was in a career that wasn't me at all, but, you know, it was what I had to do to accommodate to this hearing loss.

As far as my own productivity, when I was at home, I was an educated woman with two young children at home, and there were times when I was not even able to make my own doctor's appointment because I couldn't hear the person on the other end of the phone. So I would have to call my husband at work or text -- we did a lot online -- and have him make that appointment for me. So it became kind of a depressing situation.

My children, it was more of a safety and a danger situation. We spend a lot of time in the pool, at the beach, you know, sledding right now, skiing, and it was always a situation where I was absolutely honed in on them because I couldn't, you know, I couldn't hear. I couldn't understand if my

1 child was in the water -- I couldn't look at him and
2 say, "Are you okay?" I wouldn't hear him. So I
3 couldn't pay attention to anything going on around
4 me.
5 I was lucky enough to find out about this
6 study by accident. I was online and found a website
7 for people with hearing loss, and everyone was
8 talking about their different hearing aids they've
9 tried, and I thought, well, maybe a better hearing
10 aid is going to make my situation better. And I was
11 on that website when I heard about this study.
12 Excuse me. My mouth is drying.
13 You know, when I first found out about the
14 study, I was very, very excited about the
15 possibility. It was something I dreamed about. I'd
16 always talked to my surgeons, my doctors, saying why
17 isn't there something that they can just put in my
18 head? Why isn't there something out there? So when
19 this came along, I was very excited.
20 I had my surgery in January of 2006, so
21 I've been an Esteem patient for four years now. I've
22 also gone through a battery replacement. My surgery
23 was uneventful, you know? It was successful,
24 although I was a little bit sore at the end -- oh,
25 thank you. Thank you very much. I was a little bit

sore at the end. I did come out of the surgery okay.

About four days after the surgery, I was standing in front of the mirror, and I noticed kind of -- that my lip wasn't moving in the left side. And, you know, I thought it was kind of funny at first. And throughout the day and kind of into the next day, it became kind of the whole left side of my face. So I am one of the patients that experienced some paresis, and that was very challenging after that happened. You know, I called the surgeon, and they had -- you know, were very interested in what was going on, and went to see him. He put me on steroids, so I was on kind of a medication regiment for about, I think it was, like, 13 days. My paresis lasted about two and a half to three months, so it was challenging. Even when I was turned on, I still had a little bit of it. What they determined was it was, you know, that a couple days after surgery, my facial nerve had been just kind of irritated and that it was just part of the healing process.

And the way that I recovered was that it, you know, it was a slow recovery. It got a little better over time, such that, you know, a month and a half I was turned on, it was gone. And you can look at me very closely now and see that it isn't

1 something that I've dealt with at all.
2 I want to talk a little bit -- I don't want
3 to take up too much time -- but I do want to talk
4 about the significance of being turned on and how
5 that affected my life. I had been a hearing aid
6 user, and when I went into the room the day it was
7 time to, you know, turn me on, the very first thing
8 that I noticed was -- when they, you know, clicked it
9 on -- was the ventilation system in the room. And
10 the reason that was kind of significant to me was
11 because it sounded like a ventilation system. It was
12 a clarity that I had never heard before. It was
13 amazing.
14 That day, my family was with me. They were
15 out in the car. And I got back in the car after
16 being turned on. The turn-on appointment lasted
17 about an hour. And I got back in the car. And my
18 three-year-old, you know, said, "Mommy, is your ear
19 fixed?" And that was such a big deal to me because
20 in the car I always had to turn around and say, "Look
21 at Mommy when you talk." And I was sitting in the
22 passenger's seat, and I could hear. I could hear.
23 My husband was talking to me and, you know,
24 putting his hand in front of his face and, "Can you
25 hear me now? Can you hear me now?" And I mean, it

was just absolutely the most amazing thing I've ever experienced. We turned on the radio and there were songs, I mean, songs that I never liked before that I was loving because I was hearing layers of bass and all these other different, you know, parts of it.

My biggest thing as we rode along was I could hear my two-year-old -- this makes me cry -- singing to himself. He was in the, you know, seat kind of directly behind me, and he was singing to himself a little song that he learned at school or something. And I never knew that that was something that he did. And my husband said, "Oh, haven't you heard? He does that all the time."

So it's these moments in life that, despite wearing a hearing aid, I was never able to be a part of. If I go back into other parts of my life that I talked about before, the struggle I had with my career, shortly after the implant, I went back to work, and I was able to, you know, participate in things fully now. I attend meetings, and I make comments at them. And I am more of a leader at work. In my family, I am much more of a role model to my children, and I'm able to lead a much more productive life than I ever imagined.

I am so behind this device. I've been

through a battery replacement, something that I did have some concern about just because of my surgery, you know, experience, and it was -- I was in the room for 30 minutes, and within 15 minutes of that, I was out, dressed, sitting, having a Coke and some crackers, and, you know, about 45 minutes after that, left, you know, to return in the afternoon to be turned on.

When I look at the maintenance that I've had with hearing aids, the times where you bring them in and it ends up being some awful expense or you have to get new ones or wait for two months, in four years, the only maintenance I've had on this device is a battery replacement. And that speaks volumes to someone who really had to worry about a hearing aid.

I have had a fabulous experience with this, and I hope that there -- you know, I want to remind you that there's millions of other people my age going through the same struggles that I went through. And we need an option out there. Hearing aids aren't doing it. We need an option. So I thank you for letting me have the time to share my experience with you.

DR. LEOPOLD: Thank you very much. Our next speaker is Dr. Michael Glasscock.

DR. GLASSCOCK: My name is Mike Glasscock. I'm an otologist, and I'm an adjunct professor at Vanderbilt University in Nashville. I am the chairman of the Medical Advisory Board for Envoy Medical. They pay for my time and expenses for travel, and I have a very minor equity position in the company. I also am a consultant to a company called Ototronic, and I have a small equity position in that. And I am paid for my time and for my activity. I apologize. I am having a little allergic reaction, and I can't keep from sniffling. I'm probably going to need to call on a rhinologist.

(Laughter.)

DR. GLASSCOCK: I'm sure there is one in the room. Let's see here. I told you -- this is different from mine. I apologize.

UNIDENTIFIED SPEAKER: That's okay. You're fine. There you go.

DR. GLASSCOCK: I didn't know Mike was a rhinologist. I need to go backwards here. How do I go back to the --

UNIDENTIFIED SPEAKER: There you go.

DR. GLASSCOCK: I need to go back.

UNIDENTIFIED SPEAKER: All the way?

DR. GLASSCOCK: Can you get me back to the

beginning, here?

UNIDENTIFIED SPEAKER: Yeah. I sure can.

DR. GLASSCOCK: And we need to -- thank you. Okay. I have actually been involved with this device since about 1986. I've been waiting about 23 years for this moment. And I'd like to talk a little bit about my personal experience with sensorineural hearing loss. You know, I was an otologist. I took care of numerous patients with sensorineural hearing loss and, as a physician and human being, always had empathy for them. But until I developed a hearing loss myself, I had no real concept of what these people went through. And it's just something that until it happens to you, you really can't know what it's like.

Now, I've worn hearing aids for several years in both ears, and I've been an otologist. I've been able to get them wholesale. And I will say that hearing aids help a lot of people. And in a quiet situation, they help me. But if I was to go into a noisy restaurant, I'd either take them out or I'd turn them off, and I'd smile and nod my head a lot, and God only knows what I agreed to. And talking on the telephone, I'd say, "I'm sorry, but would you repeat that, please? I'm sorry. I have a hearing

loss. Could you say that again and could you talk a little bit slower?"

And I've got a couple of really young grandchildren with those high, squeaky voices. And, you know, I just have to sit and look at them and try to decide what in the world is it they're trying to talk to me about. Talking on one-on-one, unless I could look directly at the individual, even in a quiet setting, I really had trouble.

And I could never tell I had the hearing aid in my left ear, but the right ear, I could always tell it was there. It drove me crazy. And the battery would go out. You know, I'd be doing something where I really couldn't stop. The battery would go beep, beep, beep, and then it'd go dead, and I had to replace the battery.

And I like to swim. I like to kayak. I obviously couldn't swim with my hearing aids, but I would have liked to have been able to kayak. My problem is I fall over a lot. And so I end up in the water. So I couldn't wear the hearing aids in the water. And I got to the point where it was so difficult for me that I really kind of cut back on my schedule. And I'm one of these high-energy people who really like to be going and doing things and

1 going to the meetings. And so that was a problem.
2 So I had to make a decision. And as an
3 otologist, I was obviously keenly aware of the risk
4 of any kind of mastoid surgery. You know, I could
5 get a facial injury. I knew I'd have to be
6 disarticulated. And I knew that, you know, worst
7 case scenario, I could get a dead ear. And I figured
8 that I might actually have a taste disturbance.
9 Now, my chorda was taken, and, luckily,
10 I've had no taste disturbance. But when I thought
11 back -- and I did several thousand middle ear and
12 mastoid procedures -- and some of those patients had
13 taste disturbance. And I studied my cases very
14 carefully every year. And most of those patients,
15 the taste disturbance went away within three to six
16 months. I only had one patient out of all of those
17 thousands that it lasted over a year.
18 And I realized that this was an
19 investigational device. I mean, I've been
20 investigating it since 1986, and I believed in it so
21 strongly, and I thought that using the eardrum as a
22 microphone was so elegant that I was willing to take
23 whatever risk there was. And I can assure you that
24 it's been well worth the risk.
25 Now, I'd like to share with you my

audiogram, and I happen to be one of those patients that is listed as a mild. And in the low frequencies, I am pretty good. But you can see the blue -- I drop off pretty badly. And this is the kind of hearing loss -- I got it in both ears -- if you go into a noisy restaurant, it drives you crazy.

Now, unfortunately, when I go in a noisy restaurant now, I can go to my B setting, which cuts out the low frequencies, pushes them down, click like that, and it's like a noise canceling headset. All of that background noise goes away. And I can sit and talk to somebody clear across the table. It's an incredible experience. And I don't know if you can see that on that slide, but unaided, my word discrimination at 50 dBs was 36%. At 70, it was 66. At ten months, with the Esteem, at 50, I was at 94% discrim, and at 55, I was 98. So it came up absolutely tremendously.

So with the Esteem, I can communicate in noisy restaurants. I can hear on the telephone without any problem. I can hear my grandchildren. I hear better on one-on-one. I don't have any maintenance, battery problems to deal with. I have no lifestyle restrictions. I swim with this device, take a shower in the morning, and I lead a much more

active life.

Now, the thing that when I've talked to patients, the one overriding thing they all tell me is, "I feel normal again." I personally feel normal again. And I can assure you once this device is approved, I'm having my left ear implanted with an Esteem.

Thank you very much.

DR. LEOPOLD: Thank you, Dr. Glasscock.

Our next speaker is Andrea Stine.

MS. STINE: Hello. I am Andrea Stine, and I have no financial interests in Envoy. They did pay for my accommodations to be here today.

I am 29 years old, and I'm from Omaha, Nebraska, and I received the Esteem implant in September of 2005 by Dr. Shohet, and my brother, my older brother, also received the implant in October of 2005. I have had a battery change, which took place in January of 2009, and like Amy said earlier, that was a breeze. The next day I was feeling fine, and so that was really no big deal.

After hearing loss, the Esteem is the closest I have experienced to having a normal ear. And I have worn hearing aids, top-of-the-line. Based on my audiogram, the Esteem is significantly superior

to the gain I received from a hearing aid. And you're welcome to pass my audiogram around if you would like to see it.

The Esteem is much more natural sounding than a hearing aid. And if you think about it, this really makes sense because it just takes advantage of the natural anatomy of the ear, and it uses the eardrum as the microphone.

A big thing, a big advantage about the Esteem is that I get to enjoy activities like exercising, swimming, showering, water skiing, all while being able to hear. I have two small children. And one experience I love to describe is when I take them to the beach now, I can hear and feel safe and secure with them. I can hear the crispness of the waves. I can hear them walking in the sand, the birds chirping, and the breeze.

I feel like I'm a better mother now with the Esteem. As Amy mentioned earlier, a big thing was my little ones in the back seat, I couldn't hear them before, and I'm a safer driver because I had to turn around and try to hear what they were saying, and now I can hear from behind me. And that's something my mom mentioned as well. She said, "I can't believe it. In the car, I can be having a

conversation with you and you can hear me," whereas before, even with hearing aids, I really struggled with that.

I feel safe and secure at night. I can hear through the night. And my three-year-old or my five-year-old wake up, I'm going to hear them. And that's a big deal to me.

One point I'd like to make is since I received my implant, I got pregnant and had my second child. So it's really neat to see that life can just go on. I had a cesarean section, had my implant on the whole time, and it just really didn't affect that experience at all.

Since I received my implant, I decided to run for Mrs. Nebraska. And my final question was, "How do you think we can help people with hearing loss?" And I talked about my family. We have a genetic form of hearing loss in my family. I talked about how it goes back six generations, and my ancestors met at a deaf school, and up until now, nobody really asked why or what we can do to treat it instead of a hearing aid. And so I decided to take a big risk and become a part of this clinical trial for other people who have hearing loss as well.

And I'm very, very happy that I did it. It

was wonderful to be able to hear my friends and family cheering for me that night. And I went on and won fourth runner up at Mrs. America. And I think it's safe to say if you knew me before I received this implant and after, that there is no way I would have had the confidence or self-esteem to do that. So I completely support this device, and I hope that we can share this with the millions of other Americans who have hearing loss.

Thank you.

DR. LEOPOLD: Thank you very much.

Our next speaker is Dr. Suzanne Bishop.

DR. BISHOP: Hello. My name is Suzanne Bishop, and I'm from Saint Simons Island, Georgia, and I have no interest in Envoy. They are paying all my expenses and accommodations for this visit here.

First, I want to tell you that I have had a hearing aid for eight years, and then I found out about the implant. And I read about it, knew all the risks about what I would be doing to my ear if, you know, it didn't work or did work, and I decided it was worth it to me because of the different roles that I have in my life.

One, I'm a mother also, and it's nice to be able to go to sleep hearing and to wake up hearing.

It's nice to be able to know that if the alarm goes off, that I'm going to hear it and be able to get my children out safely. I had lights put in my bedroom so in case the alarm went off, I would be able to see the lights hopefully, and I never really slept very well because of that. But now with my implant, I can go to sleep, and I have a nice sleep, and everything is great, and I can hear what's going on because you can't wear a hearing aid when you're sleeping. There is just no way you can do that and have a good night's sleep.

And also, I am very athletic. I do triathlons that included swimming, running, biking. You cannot wear a hearing aid with a helmet on. You cannot swim with a hearing aid on. You know, you can't hear when a bike is passing you or coming on your left. You can't hear that because you have a helmet on and your hearing aid does not fit under that.

With my implant, I can swim, I can ride, I can run, play tennis, everything. You don't have to worry about your hearing aid. But most importantly, I can hear better. When I did have the hearing aid on, when I put it in my helmet, I couldn't hear anything. It wasn't clear. And with my implant, I

can hear anything that's going on.

But most importantly is I am a dentist, and my profession is very important to me. And now with an implant, I can hear my patients talking to me. Before, I would have to depend on my staff, my assistants, to tell me what the patients were saying to me because my hearing aid could not hear the drilling, me talking, the patients talking. Everything was muffled with the hearing aid. I'd have to pull the hearing aid out of my ear when I was drilling because I couldn't hear anything but the noise. It was just static, and it was not comfortable for me. I did not feel comfortable working on the patient when I couldn't hear. I'd end up pulling my hearing aid out. Then I'd have to put it back in my ear so that I could communicate with my patients. My assistants were writing notes behind me, letting me know what the patients were saying to me because I could not concentrate. The hearing aid would just be muffled.

And then when I got the implant, I would have -- you have different profiles. I have one for my home, one for my office, and one when I go out. And I just change it to the different profile. And I could drill, talk to my patients, talk to my staff,

and do everything that you're supposed to be doing with a normal hearing aid, you know, with your normal ear without a hearing aid.

And also, I would have troubles with when I had -- I wear glasses, and that helps me see. So I like my glasses. A hearing aid would help me hear, but not the quality that I wanted to hear and that I needed to hear, just as a person, not even as a dentist or as a mother or anything, just as a human being. You want to be able to enjoy and hear things clearly as everyone else does around you. But I would take my mask off. My hearing aid would go flying across the room. I'd have to run and pick it up. And, I mean, I have expensive hearing aids, the best you can buy. I went through a hundred of them trying to figure out which one would work for me before I found out about the implant.

And once I found out about this implant, it has changed my life just dramatically. I mean, I feel so blessed to be part of this. And, you know, I just want to say that I'm hoping that you will approve this because it is the best thing out there, and I'm hoping it'll be approved because I'm ready to have my left ear done because I'm having to still sometimes -- I mean, I wear -- I usually go -- the

implant has done such a great job for me that I don't really have to wear my left one except when I go to a dental conference, or things like that, and I want to make sure I hear. But the quality that I get from my implant is incredible.

I can go to a movie and talk to someone beside me and hear the movie and enjoy it. I quit watching television because I could not enjoy television. I could not hear what was going on. But now I can sit back and relax and watch television. And it's just a different -- and you don't know it until you've worn a hearing aid, until you've experienced the difference.

You know, yes, like I said before, glasses do help you see and they help you see just like you did before pretty much. A hearing aid does not do that. And I see even my patients are frustrated, the ones that have hearing aids. They can't hear what I'm saying to them. And it's just frustrating to wear one and not be able to hear. And with this implant, I can hear everything just so nice and clearly, and the quality is incredible.

So I do hope that you approve this, and thank you for your time.

DR. LEOPOLD: Thank you very much.

Our next speaker is Ms. Mandy Taylor.

MS. TAYLOR: Good afternoon. My name is Mandy Taylor. I am 31 years old, and I'm from Ann Arbor, North Carolina. I have a severe hearing loss, and at 50 dB, I scored almost 0% with my hearing aids. I was implanted by Dr. Kraus of Greensboro, and it has been an absolute wonderful experience, a very positive experience in my life.

I discovered the Envoy Esteem trials while researching alternatives to the conventional hearing aid because I never did like hearing aids very much. I hated the feeling of occlusion, the sweatiness and tenderness that I felt when I took my hearing aids out. I had really bad acne in the ear canal, and my doctor -- often had to prescribe medication to clear this up. It's very painful with the hearing aids in the ear.

My constant need to turn the volume up on my hearing aid has caused a lot of feedback issues. I've always tried to push the volume to the very max. My hearing aids were always being sent out for repair. It was normal wear and tear, and as a pre-teen, using a lot of hairspray obviously clogged up the hearing aids.

So I was extremely self-conscious about my

hearing aids as a teenager. From about the ages of 13 to 25, I refused to wear my hearing aids. My mother tried to make sure I wore them. I would go to school, and just as soon as I was out of her sight, it went in my pocket. So it began to have a very negative impact on my social life and my school work. I ended up dropping out, and I became very withdrawn, very quiet. I didn't have a whole lot of friends.

And this past year, it has been a very -- just a very wonderful experience after I got the implant. So I've gained so much more confidence in myself. I am so much more active. I've joined the fire department full-time and the ladies auxiliary. I went back to school. I started subbing and being a peer tutor for kindergartners, and you know how difficult it is to understand four and five and six-year-olds. I had a lot of trouble with that before, but I have no issues with it now.

I really prefer my Esteem over my hearing aids because I just hear so much more clearly, and I don't have that feeling of a blocked ear canal. I no longer have maintenance issues, no routine cleaning of the ear wax. I love being able to do water-related activities and not having to worry about getting my hearing aids wet because there was a

1 couple of times when I was a child I would jump into
2 a pool, get my hearing aids wet, and of course, my
3 parents had to take care of that problem.
4 I just prefer the quality of sound from my
5 implant over the hearing aids, and that's very
6 difficult to explain, but the Esteem just seems more
7 natural. It sounds more natural than a hearing aid.
8 My hearing aids have always sounded really artificial
9 and tinny.
10 Another big plus for me is my daughter has
11 a medical condition. She has chronic migraines, and
12 they make her vomit all through the night, every 10,
13 15, 20 minutes. My implant, being able to keep it on
14 at night and being able to hear when I'm sleeping
15 enables me to be there to help her because she
16 obviously needs help through the night. If I were
17 wearing my hearing aids, I wouldn't have them at
18 night. I wouldn't be able to hear her and help her.
19 So I'm very glad that I'm able to hear her and help
20 her during the night.
21 By the way, she has a severe hearing loss
22 as well. I have three daughters. I have one that
23 doesn't have any hearing loss, I have one that has a
24 mild hearing loss, and one that has a mild to
25 profound hearing loss. She just got hearing aids.

And she's actually the reason why I had started wearing my hearing aids again. It was about the age of 25 that I finally started wearing my hearing aids because she was born, and I knew that if she had a hearing loss, I had to set the right example for her.

My family, friends, and peers have often remarked that they've noticed a huge improvement in my hearing since I've had the implant. They've noticed that I no longer rely heavily on speech reading. They don't have to repeat themselves as often now. And they've noticed a big difference in my speech.

And it's very difficult to explain the impact that the Esteem has had on my life in such a short period of time. I'm truly grateful to have been given the opportunity to have the implant. I wouldn't hesitate to do it all over again, and I'm really, really anxious about getting the second one done. I have a hearing aid in the unimplanted ear. I still don't like it, and I would love to be able to have that second implant done. And I'm also very, very hopeful that one day, my daughter, who is also hard-of-hearing, will benefit from these advances in hearing technology.

And by the way, I forgot to mention that I

have no financial interests in Envoy, of course, and Envoy -- I'm sorry -- what do you say -- they sponsored my trip expenses. So that's really all I want to say because I'm very, very pleased with my implant, and I really hope this is approved because it's going to help an awful lot of people.

Thank you.

DR. LEOPOLD: Thank you very much.

Our next speaker is Mr. Craig Arnold.

MR. ARNOLD: Good afternoon. My name is Craig Arnold. I'm a revision patient. I have no financial interests in Envoy. They have paid for my travel expenses.

I'm 65 years old, and I've been wearing hearing aids for over 25 years. I think some of it is hereditary. If I go to a family reunion, I see relatives on my mother's side, many of them have hearing aids, and many of them have lack of hair. So I guess that's where --

(Laughter.)

MR. CRAIG: I was a CEO of a thousand employee company in Minneapolis. I retired early because I really was struggling in meetings to hearing correctly. And when you're meeting with a customer, and you're trying to get a price increase,

and an intel says 4% is the most that will do, and I say, "Well, 3 would be great," you know, I've screwed up pretty bad. So I retired early. It was just too much of a struggle. Retirement is great, though.

I saw a notice in the Minneapolis paper that Envoy was looking for trial participants. So I contacted them. I had my audiogram sent in. But at that time, my hearing loss didn't match their product. So I was rejected. In 2008 they called me and asked if I was still interested. I was. So I had an implant done in May of 2008. And I was really excited, and my family was excited. Everybody that I tried to communicate with was excited. I had it done. I had it turned on, and it didn't work very well.

That is -- it's depressing and it's scary because you're doing something that you know hasn't been approved totally. So you don't know what's going to happen.

But I was approved for the revision. That happened in June of this year. And it was just amazing. After 30 days, they turned it on, and I could hear. Now, it wasn't perfect for me because I hadn't heard well for quite a while, so trying to block out other noises is something I'm still working

on. And the other thing is that I don't listen well anymore. My wife has always said that, but what I found is I was saying -- still, even after the revision, I was saying, "What," almost all the time.

And, finally, I realized I was listening to some of those things, I was hearing them -- I wasn't listening, I guess. So I said, "Carol" -- sometimes I call her honey, but I said, "Carol, next time I say what, don't answer me again. Say, 'Craig, what do you think I said?" And that's working. I'm finding that I am hearing a lot more than I realized just by listening better.

So I think I went from being discouraged, disappointed, to now I'm very pleased. I still think it's time. As I have used the remote to adjust to different sounds, it gets better all the time. And I'm happy with the implant. If you have any questions, I'd be happy to answer them.

DR. LEOPOLD: We'll perhaps work for questions later, but thank you very much for your comments. Please, speakers, stick around because I think the Panel may have some questions of you. Thank you very much.

MR. ARNOLD: Okay.

DR. LEOPOLD: Our next speaker is

Ms. Marsha Weiss.

MS. WEISS: Hello, Panel. Good afternoon. My name is Marsha Weiss, and I have been compensated for my time and travel by Envoy, and I have no interest in the company. I was implanted in 2006 by Dr. Jack Shohet in beautiful Newport Beach. I live about 30 miles from him, and it's a pleasant drive, and I enjoy going there.

When Envoy called me and invited me to this group to speak to you, I had to think about it for a while. What was I going to say? Where do I begin? (Singing) Where do I begin to tell the story of how great the Envoy miracle is, the real story of how Esteem gave back my life. Where do I start?

Being diagnosed with progressive nerve damage in my 30s was devastating. I was a mother of five children, a preschool teacher, classroom volunteer, and a wedding and funeral singer. Professionally coached from age ten, I sang in many choirs and competed in local talent shows. I met my husband auditioning for a professional vocal jazz group, and we've been performing together for various paid gigs and charity events ever since.

Eventually, my hearing loss progressed to the point that double hearing aids didn't work well.

So I isolated myself from public situations. Unable to hear conversations correctly, I became withdrawn, developed very low self-esteem and depression. Phone conversations were frustrating, and I felt embarrassed asking people to repeat themselves and thought they viewed me as special needs.

In 2002, filling in at my husband's business as secretary, I lasted a total of one day because I couldn't interact correctly with the clients or on the phone. My husband and I had to stop performing because I couldn't hear the pitch, key changes, or harmonies. I stayed home and found I could communicate better on computer, and I learned computer techniques. It afforded me a chance to learn a skill, but I was interacting silently with others.

Then we saw this ad for the Envoy clinical trial, and my life changed. My husband cut out the ad, placed it in front of me, and said, "Call now." Well, I did. I was implanted in February of 2006, and the first time I heard from the implant, it just astounded me. I could hear sounds I hadn't heard in a very long time, birds chirping, rain on the roof, traffic, babies cooing, all sounds taken for granted by normal hearing people. The sound quality and

clarity is as close to normal as one can get. Hearing aids don't come close.

Now I could start living a normal life. I started singing again, rehearsing with my husband to see if we could go back to performing. After an adjustment setting or two, we did. And it was so wonderful to be singing together again.

Then I decided it was time for me to help others. I went to my local community senior center to volunteer my services in any capacity to do with computers. Now I am teaching various levels of computer classes in their computer lab.

One day a student asked me if I could come to her home and help her on her home computer. Well, that was the start of my new business. It was born. I started Puter Tutor Lady, going to seniors' homes, tutoring one-on-one with their own computers. I love the interaction and so enjoy hearing their life stories that they generously share with me, sometimes for hours on end.

I joined some business networking groups and interact with other professionals trying to generate more business in this current economic climate. I even hear well enough to be a secretary of one group. I have once again connected with

family and friends and share many social events through business and singing. Many have noticed the change in me. I am more outgoing, eager to join in, and confident that I can hear and interact with all life has to offer.

As of last month, I had the sound processor and battery change. And it affords even better hearing quality. I thank God I was chosen to receive the implant. I only hope you will approve the Envoy device and allow all qualifying Americans the chance to experience what I have, a life-changing miracle.

And now it's time to pay forward. I would love to be an ambassador of hope and share this miracle life-changing story with others in the hope that they, too, will come to experience the joys and blessings of hearing the incredible sounds of life taken for granted by the hearing world.

Thank you so much.

DR. LEOPOLD: Thank you very much. And, please, thank you for all the speakers who have so bravely come up and given us their stories. Do any of the Panel members have questions for any of the speakers? Anything?

I have one question. Do any of you -- I know Dr. Glasscock mentioned that your chorda tympani

was cut during your operation. Do any of the Panel [sic] members remember taste disturbances? Can they describe what they were? This was the most common side effect listed, and I'm wondering what your stories of the taste disturbance were.

UNIDENTIFIED SPEAKER: I didn't have any.

UNIDENTIFIED SPEAKER: I didn't have any.

MS. WEISS: None at all.

DR. LEOPOLD: Mike?

DR. BISHOP: I had it in the beginning --

DR. LEOPOLD: Can you come to the microphone, please? And as a dentist, I really respect your comments here.

DR. BISHOP: And as a dentist, that was hard because I felt when I had the taste, I felt like it was giving me bad breath at first. So as a dentist, it was very difficult.

DR. LEOPOLD: So you said you had it on one -- on the right side?

DR. BISHOP: Um-hum. I had it on the right, where my implant was placed. I had a little bit of metallic taste for several months, but then it gradually went away.

DR. LEOPOLD: Okay.

DR. BISHOP: It's almost like when you have

sinus problems when you have the drainage. It's similar to that, very much so. But then I had it for a few months, and gradually, it just disappeared.

DR. LEOPOLD: Thank you.

DR. BISHOP: You're welcome.

DR. LEOPOLD: Anyone else have any problems? No? Dr. Connor?

DR. CONNOR: So my question -- I'm sorry I don't remember the name, but it's the lady in red with the beautiful voice. Did I hear correctly that your implant was 2008 and that you'd had a battery replacement?

MS. WEISS: No. 2006.

DR. CONNOR: Okay. All right. Thank you.

DR. LEOPOLD: Any other Panel questions for the speakers?

(No response.)

DR. LEOPOLD: Thank you very much. We'll move now to our formal Panel discussion. Although this portion is open to public observers, public attendees may not participate except at the special request of the Panel. Additionally, we request that all persons who do speak identify themselves each and every time. This helps the transcriber identify who is speaking.

Does any Panel member have a question of either the Sponsor or the FDA? Go ahead, Dr. Hood.

DR. HOOD: Linda Hood. I had a question about the stapedius muscle and stapedius reflex, if that is affected in any way in the surgery, if there is a change in middle ear muscle reflexes or if there is a contraindication to measurement?

DR. LEOPOLD: Can you identify yourself, please?

DR. SHOHET: Sure. Jack Shohet. I don't know if we measured the emittance postoperatively, but I can tell you that intraoperatively, we do not section the stapedial tendon. So, hopefully, it should not be affected, but I don't know with emittance testing if that is actually borne out.

DR. HOOD: Thank you.

DR. LEOPOLD: Dr. Wie?

DR. SIE: Kathy Sie --

DR. LEOPOLD: Sie. Sorry.

DR. SIE: -- from Seattle. Do any of the surgeons, either patients or otherwise, have concerns about the prospect of multiple revisions required? Say people need a battery change every four years, and you're 30 years old when you get it, you know. You may require many changes over a lifetime, and

knowing that the risk goes up with revision surgery, do you feel like that's potentially problematic?

DR. SHOHET: Jack Shohet again. First of all, the battery lengths are actually getting a little bit longer. The first generation, I think, was the shortest capacity. And I think as they're developing newer battery technology, this current generation, we're hoping to get even further out. So yes, revision surgery is always a concern, but with the battery replacements, we are not affecting the transducers. We do not actually go into the mastoid. It's all done through the postauricular incision with a much more superficial dissection. We're not all the way down to the transducers, so there is really no risk of dislodging those. But there are other risks, obviously, to revision surgery. And so having to undergo revision surgery to do a battery replacement is unfortunate, but it's certainly necessary with this battery technology. Eventually, it's got to be changed. And as we develop better technology, that interval will hopefully increase.

DR. KRAUS: Eric Kraus. I actually don't have any hesitations or reservations. In fact, I just replaced a battery in a patient who was the 0203 study, and she just got an Esteem 2, one of the new

devices, and there is a little bit of scar tissue, but, again, it's a very limited dissection. The processor comes right out of the pocket, and you just put it back in. So we hope in the future we may have a longer lifetime battery as our technology gets better and maybe even a rechargeable option in the future.

DR. LEOPOLD: Dr. Rosowski?

DR. ROSOWSKI: John Rosowski, Boston. We've heard from both the Esteem people and from several of the users of it about how natural this sounds. And one suggestion is that part of that is coming from the natural ear canal resonances. Now, as a scientist and somebody who has looked at these things, those natural ear canal resonances depend a good bit on their being a natural middle ear load and that if you do things like interrupt the incudostapedial joint or rigidify the ossicles, I might expect there to be some significant differences in those natural ear canal resonances.

So when the Envoy people showed those graphs in the beginning, were those based on former research or were those actually based on measurements in the people who were in a preparation that has the Esteem in place?

MR. SPEARMAN: Let me just ask one clarifying question. Was that the residence curves?

DR. ROSOWSKI: Yeah. You showed -- it looked like maybe Shaw's data that showed the ear canal resonance data.

MR. SPEARMAN: That's what that was based on. That was just the basic concept of what the natural anatomy does and then what we do from there.

DR. ROSOWSKI: It's possible that the ear canal resonance is going to be much sharper in a different frequency than what naturally might occur is my concern.

MR. SPEARMAN: Yeah. You might want to answer this, Peter, but I know we leave most of the anatomy in place with the tendons and everything, but there could be some changes, although we've done a lot of work in the past on laser vibrometers.

DR. SCHILLER: Peter Schiller. Just a quick clarification. The transducers that go in approximate the acoustic -- that's seen from the canal. It's not a perfect match. And of course there is patient-to-patient variation. So through our development and through temporal bone considerable work, approximating it, and come pretty close, but of course it's not exact in every patient.

1 DR. ROSOWSKI: Thank you.
2 DR. LEOPOLD: Dr. Lonsbury-Martin?
3 DR. LONSBURY-MARTIN: Yes. Lonsbury-Martin
4 from Loma Linda. The Esteem folks, you mentioned in
5 your user manual that you do require a training
6 procedure for indications and instructions for use
7 and surgical application. Can you elaborate on that
8 a little bit, what that involves and how you apply
9 that?
10 MR. SPEARMAN: Yes, I can. Unfortunately,
11 I don't have the slide for everybody. I'll have to
12 explain it. Part of the best practices was realizing
13 that for new surgeons, they would have to come up to
14 speed and get to the level of -- now, one of the
15 things we did is we first established surgeon
16 criteria, and that were fellowship-trained otologists
17 and neurotologists, aural otologists, that had
18 extensive experience in facial recess surgery, such
19 as cochlear implants, chronic otitis media, chronic
20 mastoids with or without cholesteatomas, et cetera.
21 So people that were very experienced. We don't want
22 other surgeons in that because it takes more time to
23 train, and we want the very best results for patients
24 anyway.
25 In addition, the surgical procedure

training we set up -- maybe a number of us are pilots, including Dr. Glasscock and Dr. Kraus. And we really set this up to be more like flight training, and that is very, very rigorous. It starts off with a Module 1, which is four days of temporal bone and didactic training, in which case they are learning all of the best practices, and they're probably doing six to ten temporal bones to really learn. Now, they already know how to do the facial recess. They have to learn, as Dr. Shohet said, how do a little bit larger facial recess, but that's very easy for them to do.

And then it's really this positioning of the driver and sensor, the cleaning of the stapes, and then it's also things such as what happens when things don't go right. Let's say after the intraoperative testing they're not -- it's not working the way we thought. So then they have to learn to take it out and put it back in successfully and pass the intraoperative testing data because we have that equipment in the laboratory.

After four days of that, then if they pass all of those and demonstrate best practices, then they can go on to Module 2, which is really the practical testing in which they have to do at least

two temporal bones perfectly to ISA conditions as well as take in and out and remove the transducers.

Following that, there is Module 3, which is to go and observe surgeries with an experienced implanter so they can gain the knowledge and watch actual surgeries.

Module 4 is prior to their first surgeries, they will go through one or two more temporal bones to demonstrate that they can do it again, because sometimes there might be some disconnect between the training time and their first patients.

And then Module 5 is that they're proctored by an Esteem surgeon, a very experienced Esteem surgeon who will then sign them off that they're able to do the surgery effectively.

DR. LEOPOLD: Dr. Lalwani?

DR. LALWANI: I have a question for the company. A comment was made earlier about how 5 dBs in a speech reception threshold is test/retest variability, and therefore, is this really an adequate demonstration of superiority? And there was some allusion that it was the company that decided the 5 dB test. Could you comment about the rationale? Is this an accepted difference in performance, or why was five dBs chosen, given that

it is so close to test/retest variability?

DR. BROWN: Scott Brown. A little odd to have the statistician answer this question, maybe, but the 5 dBs was chosen partly for statistical reasons. So the purpose here is 5 dBs is sort of the acknowledged step-up test/retest variability. And when you think about a statistical analysis of these data, what we wanted to show for superiority was that in a standard superiority analysis, there is no 5. Standard superiority in statistical analysis is just prove that you have some effect greater than 0. The reason 5 was chosen here was precisely for that measurement error test/retest concept, that the actual observed improvement over the baseline-added condition in the SRT, for example, was 10.6. The lower confidence bound on that is 7.1 in the original analysis. The fact that that number is greater than 5 tells us that not only is the device superior to the hearing, but that it's superior by a margin that rules out any sense of test/retest variability or measurement error in that process. So that was the purpose of the 5.

DR. LEOPOLD: Yeah, please?

DR. EYDELMAN: Just to come back to the previous comment, I just wanted to clarify that the

1 proposed training hasn't been submitted or reviewed
2 by FDA yet. However, if the Panel during their
3 deliberations wants to comment on the recommendations
4 for the training, we would be more than happy to
5 receive it.
6 DR. LEOPOLD: Dr. Sie?
7 DR. SIE: Kathy Sie from Seattle. Again,
8 about the surgical training, given the extensive
9 surgical training you described, do you have comments
10 about the differences between the sites, the
11 different speech outcomes between the different
12 sites?
13 MR. MULLIN: Good afternoon. My name is
14 Chris Mullin. I'm a biostatistician, consultant to
15 Envoy. I'm paid for my time and travel today but
16 have no financial interest in the company. Among the
17 factors that we looked at that predicted outcome, the
18 key one was really patient characteristics. So it
19 was that baseline hearing loss and baseline SRT. We
20 did not find characteristics that we could tie to the
21 surgery that were related to the efficacy outcomes.
22 DR. SIE: On a related note, then, it seems
23 that the patients were recruited from across the
24 country. Then how did you assign certain patients to
25 certain sites, and why was that not factored into the

assignments?

MR. SPEARMAN: I'm not sure about the factored in part, but as far as when we -- a lot of patients contacted us from around the country and where should they go. I think it depended perhaps on proximity to one of the sites is just really where it came down to because they had to go back over and over. So somebody in the northeast would typically go to the Boston site or they had contacted them before. We didn't look at factoring in any kind of demographics across the country in that sense. They just happened to be at that site.

DR. SIE: So it was patient's choice or convenience that made them go to one site versus another?

MR. SPEARMAN: Typically, that was it, yes. I wasn't involved in that, but, yeah, typically, it was just a matter of someone called and a site was recruiting.

DR. SIE: Thank you.

DR. LEOPOLD: Dr. Hirsch?

DR. HIRSCH: Barry Hirsch. A few questions for you. To take it one step on the training of surgeons, in your summary, it says that you intend to develop regional surgical centers in the United

1 States. Are you affording this to all well-trained
2 otologists? Are you going to have geographic areas
3 that you're intending to use for marketing?
4 MR. SPEARMAN: No. Our intention is not to
5 make it available, to not just general otologists,
6 but just -- not just general -- is to actually have
7 surgical centers and qualified surgical centers where
8 we have very focused activity and surgeons doing many
9 surgeries so that they're doing them over and over
10 again and repeating them and not just having people
11 doing a few a year. To do that, we would look at
12 surgical centers, for instance, at the three sites
13 that are already here, and then looking at opening
14 them in different regions of the country, I think as
15 you're suggesting, such as Texas or Florida, the
16 Northeast, and then having patients go to those
17 centers until they become so large that it becomes a
18 smart move to say, "Let's put one in Phoenix." And
19 then we would do the same thing there.
20 DR. HIRSCH: To extend that question, then,
21 if you have two surgeons in Seattle, Washington who
22 want to be participating or providing this, will you
23 limit it to one center?
24 MR. SPEARMAN: I think we would look at the
25 degree of commitment of the -- of how much time

somebody wants to put into it, into the training and continuously doing enough patients because we would like them to do many, many patients. We look at this like any other surgery, Dr. Glasscock doing acoustic tumors, or Bill House, is that the more surgeries people do, the better and more consistent and more reproducible the results will always be. And so we'd like to keep it to that. If we see that there is a market demand for that, to have two, we would actually look at having two sites.

DR. HIRSCH: And how will you decide which site gets the first bid?

MR. SPEARMAN: I think that's a matter of just talking to individual sites and talking to them and seeing who has the motivation of wanting to do this and focus on doing it, not just doing it from, you know, an interesting surgery and a very unique surgery, and then saying, okay, I'm just going to do it because I want to put it as one of the many, many things that I did. We'd like to really see specialists in this.

DR. HIRSCH: Can I continue? I have other questions. In the labeling, it said that the device should not be subject to MR scanning. Can the processor battery be removed if an MR has to be done,

and can the stimulator drivers/receivers still undergo MR studies?

DR. SCHILLER: Thank you for your question. This is Peter Schiller. Currently, we contraindicate for use of MRI. We are currently testing safety and efficacy aspects of MR. Our initial testing is very positive. As you probably know, it takes quite a bit of data, quite a bit of analysis and extensive testing to actually make that claim. We intend to continue it. If the results warrant a possible change to labeling, we would of course submit a supplement.

DR. LEOPOLD: Can you answer the question about the specific driver and sensor?

DR. SCHILLER: Yes. Yeah. The driver and the sensor are actually the ones that I'm referring to. Of course, the sound processor is also being evaluated independently. One of your questions was could the sound processor be removed, leaving the transducers in, and that's one of the scenarios we're looking at. But we don't know if it all has to come out, if just the processor has to come out, or if they can all stay in.

DR. HIRSCH: One final question. Thank you very much. That's clear. In labeling, also, it

1 indicates that only a bipolar electrocautery system
2 should be used, and it should never be used over or
3 near the Esteem implant. If you can't use this thing
4 near the implant, what's your suggestion for
5 hemostasis?
6 DR. KRAUS: Eric Kraus. We mean that you
7 don't want to actually bipolar the leads or bipolar
8 right on the sound processor. We actually used
9 bipolar cautery routinely in the battery
10 replacements. There really isn't that much bleeding
11 during them, but there is some, and we successfully
12 use the bipolar without any problems.
13 DR. HIRSCH: Then maybe it's just a
14 recommendation for labeling because it says it
15 shouldn't be used near the device?
16 DR. KRAUS: Yes. We'll clarify that in the
17 labeling.
18 DR. LEOPOLD: Dr. Rosowski?
19 DR. ROSOWSKI: John Rosowski of Boston.
20 I'd like to bounce an idea. I think there is another
21 possibility that could help explain some of the
22 differences across the three sites. And it gets back
23 to an issue that's been bothering me about the fact
24 that in this study, each subject acts as its own
25 control, and the control measurements are based on

some best fit hearing aid procedure prior to implantation. Now, we've talked a lot about the training at the three different sites to the surgeon. What about the training of the audiologist and/or the protocols for best fit of the hearing aid? If there were some difference in how or the efficacy of those procedures in the three centers, that might explain this difference that's based on starting speech reception thresholds, for example. Is that a possibility? Or how well or how common was the protocol that you used for doing the initial hearing aid testing and normalization?

DR. SCHILLER: Hello. Peter Schiller again. We kind of anticipated some questions. There seemed to be a little bit of confusion this morning regarding the baseline word recognition and some other testing with the hearing aid. We put a couple clarification slides together. I don't know if it's appropriate to bring those up or if I need to just go through this verbally.

DR. LEOPOLD: You may put your slides up.

DR. SCHILLER: Okay.

DR. LEOPOLD: And actually I was going to ask for response to the morning's questions, so now would be a perfect time to do that.

DR. SCHILLER: I will note this is all data that is just instead of considering word recognition score or SRT versus the aided, which is our primary endpoint --

DR. LEOPOLD: Can you speak closer to the microphone?

DR. SCHILLER: Yeah, sure. I'm sorry. This is the same data we've looked at. The difference is we've been speaking or focusing this morning on our primary endpoints, which are comparison of the Esteem device to the baseline hearing aid. I think most of this has been fairly clear. Things look a little bit more sensible or the way you would expect them when you look at the Esteem device versus the unaided condition. You see a little bit more normal distribution.

All right. So if I could get back to your basic question, which was the word recognition --

DR. ROSOWSKI: Well, it really has to do with just --

DR. SCHILLER: Oh, the fitting of the hearing aid, yes, thank you --

DR. ROSOWSKI: The fitting of the hearing aid.

DR. SCHILLER: So the fitting of the

hearing aid, the protocol is very clear. We actually worked with FDA. They were very helpful in helping us figure out an appropriate protocol. What we understood and of course the group there helped us with is that all the hearing aids have a different protocol. Today, a modern audiologist doesn't go -- and as Dr. Stach alluded to earlier -- go in and say, well, they need this much gain at this and they program that in. They plug it into a system, plug in their hearing loss, and it spits out a recommended fitting for them. So the protocol for fitting the hearing aids was very standard. It said use the manufacturer's best fit and then verify that fit with a real ear measurement.

DR. ROSOWSKI: So was there any question about whether the aid that the people walked in with was appropriate for their hearing loss or was there some attempt to match the aid to -- you know, because somebody who has got a severe hearing loss -- and I'm sorry. I'm not an audiologist, but my wife is one -- my understanding is somebody who has a severe hearing loss isn't going to be well fit by a little tiny in the ear canal, and there are some cases where behind the ear is better. So was there any attempt to fit an aid which was appropriate for their style of loss?

DR. SCHILLER: I believe there is language in the protocol that says audiologists at the investigational site needs to ensure that it's a properly fit hearing aid. Bear with me one moment. The one thing we did look at, too, is was the benefit provided by the aids consistent with what's in the literature, consistent with what's been reported in previous trials. The hearing aid -- and I'll yield to Dr. Stach here in a moment -- but the hearing aids in this trial, on average, improved SRT over the patient's unaided condition by 18 dB. It's very similar to what you'll see in the literature of 18 to 20. It's very similar to what was seen in the Soundbridge at 17 dB, and I believe the Soundtec was 19 dB. So we believe we're in the ballpark. It's not like they had low performing aids.

DR. STACH: The question is a very good one, and it was a question that Dr. Kileny actually asked earlier this morning and Dr. Sininger followed up on after that, and that is what was the -- you're comparing it to hearing aids. How are those hearing aids fit? Could those have been optimized differently?

The decision was made when the design of the -- this is my understanding because I wasn't

there, but the decision was made at the point of design of this study that, in fact, the best strategy would be to use best fit and verify best fit. And by that we mean that a digital, programmable hearing aid that is appropriate for the range of hearing loss that the patient has is, with all of its compression and everything else, subjected to an algorithm that turns out targets that is the best fit for that device. Then those targets are verified with real ear measurements.

And then it's not tweaked, okay? Then it's not tweaked from there because tweaking it, then, would begin to add bias in one direction or another to that basic, fundamental notion, okay? Now, it could be that that notion is wrong. And we know that in new, modern dynamic hearing aids, the idea of threshold is a very different one than in old linear hearing aids. And so it may well be that one manufacturer's algorithm provides more gain at near threshold level at lower levels than another. And if, in fact, one site were to have predominantly one algorithm and another, another algorithm, it could, in fact, change the contributing factor to what gives you the SRT for the aided device.

And so in all of these data, and I kind of

tried to allude to this earlier, but the decision had to be made to fit the hearing aid somehow. So that decision was made. Now, if that was a wrong one, at least it was consistent in the way it was attempted to be done. That may create some variability in the baseline SRT data for the aided data. And it may be that in some centers, there was more gain given, and in some centers there was less gain given, but the gain was given in the same way, or at least with the same strategy in mind. I hope that helps.

DR. LEOPOLD: Okay. Dr. Kileny?

DR. KILENY: Yeah. Let me just follow-up quickly on this. So can you give us kind of a scenario based on this explanation as to how would a reasonably, you know, textbook-fit hearing aid to a patient in the severe hearing loss category result in basically 0 word recognition, but then with the implant, in a few cases, it was way up to 80 or 90 or 90-some percent? I mean, that's great. I'm not complaining about it, but I'm just trying to understand how you make that sort of a quantum leap.

DR. STACH: Yeah. It's not fair. And it gives the -- it asks some question, and it's the fact that in certain cases, a best fit hearing aid is not providing sufficient gain to give decent word

recognition scores at 50 dB HL whereas the Esteem, which is a very linear hearing aid, and it's fit very linear, and the gain is adjusted to reach lower because it doesn't have all the compression circuits in it that keep it from -- that keep the dynamic range tucked in, you're just going to get more gain from there.

And so in one case, then, the best fit hearing aid would not be providing the kind of gain that -- remember, all it is, is gain that gives you the SRT. So it wouldn't be giving you the kind of gain that would get equivalent SRTs. And so you're not getting as much intelligibility off of one device as you are off of the other because the algorithms are very different because the devices are very different. That's how that happens, and it skews the data.

It'd probably be better to look at the absolute data, then look at the -- and look at the absolute data of the hearing aids, so you could see some of that, and then look at them together. And after this morning, I'm sorry we didn't try to make that a little more clear. But, no, you're thinking exactly correctly, and you caught it -- your thinking is right on target.

DR. LEOPOLD: Dr. Norton, you've been waiting a long time.

DR. NORTON: So this opens up -- so, you know, there is currently a hearing aid on the market that's the latest and greatest that uses sound recovery in a form of frequency transposition that when used as indicated by the manufacture actually makes, for many people, speech understanding worse. Now, taking your logic, you would suggest that it's okay for an audiologist to leave that patient with that hearing aid even though you have speech discrimination data that shows that it makes it worse, which is what, in fact, we seem to be seeing in your data because your unaided data are better than your aided data. Now, there is a major flaw here someplace.

DR. SCHILLER: Peter Schiller again. Thank you for the question because it brings us right back to what had me bringing up this set of clarification slides. Most of the morning, we focused on data for the implant at follow-ups versus their baseline hearing aid condition. We didn't talk a lot about their unaided condition and where everything lined up there.

So I tried to put in some clarification

slides here. This was the first one. I believe the FDA presented an interesting comparison of these three sites. They had this same data except on the -- they were plotting four-month SRT versus the baseline aided condition. So what it added into the data was effectively the hearing aid.

If we plot essentially the same data but versus the unaided condition, again, as the FDA group pointed out, data to the lower right corner is preferable, but you see much more similar distributions and much more expected distributions between the three sites. So that would be the first kind of clarification.

The second one is SRT improvement versus the baseline unaided condition. So histograms that we put up this morning showed SRT improvement versus the hearing aid. You did see a number of patients, lower performers, where they seemed to have gotten worse. If you look at their baseline unaided condition versus their post-implant benefit, patients were all getting benefit from the device. And it follows a nice normal distribution.

And then we had some questions this morning about the why did we have patients with 0% word recognition at 50 dB with the hearing aid. And

1 particularly, when we're looking at severe,
2 moderately severe patients, 50 dB is a very high bar
3 even with a good hearing aid for them to understand
4 words. One other point, too, that was in the
5 protocol, if they missed the first seven words in the
6 50-word list, we stopped. So if they got to seven
7 words, and they had all seven of them wrong, that was
8 it because these patients, if they're not doing well,
9 they get very frustrated, and they just check out of
10 the rest of the test. So --
11 DR. NORTON: Yeah. I'd have to argue that
12 that's not standard.
13 DR. SCHILLER: Well, that was the protocol.
14 It was something we actually -- we learned from the
15 previous trial. There was some reason for doing
16 that, but --
17 DR. NORTON: No. I do understand the
18 reason for it, but --
19 DR. SCHILLER: Okay.
20 DR. NORTON: I think my concern, the thing
21 I raised this morning again, and I'll just say it
22 again, that when I looked at the numbers, that 10 of
23 your 50-some patients who were otherwise -- there
24 weren't profound loss patients in there and who all
25 had at least 40% on a unaided score, so these weren't

completely distorted cochleas -- that ten had absolutely no word recognition score with using their hearing aids and that 18 of them were under that 40% range.

And so it looks, in the beginning, as if they could have certainly been fit better with -- this isn't standard for what I would consider a well-fit hearing aid. And since that's the basis of comparison -- I mean, I like this comparison, too. It's perfectly adequate to say look how much improvement there is over unaided, but when we're talking about a surgery versus a non-surgery, then we have to weigh that against how they could have done with a non-implantable hearing aid.

DR. SCHILLER: Yeah. Particularly to that last point, which is a very good one, other data that we collected was actually the word recognition at MCL. So because it was our primary endpoint, we spoke a fair bit this morning, and we've been focused a lot on word recognition just at 50 dB, but also evaluated was the word rec at MCL. That's what this chart actually shows was their baseline -- and you'll see that they're all above 40%. Of course, unaided, they're also even better than that with their baseline hearing aid. And, of course, their MCL

drops approximately 20 dB.

DR. NORTON: But that would give us a whole different set of statistics to look at --

DR. SCHILLER: Oh, of course, of course.

DR. LEOPOLD: Dr. Lalwani?

DR. LALWANI: Actually, I have a question for the surgeons. If anybody else has a question for him, I'm happy to wait.

DR. LEOPOLD: Go for it.

DR. LALWANI: The three different surgeons, I would like your -- how often did you need to cut their chorda tympani nerve to place the implant at your different centers?

DR. LEOPOLD: If each of you could come forward and just give us a number?

DR. KRAUS: Eric Kraus. Probably eight out of ten.

DR. SHOHET: Jack Shohet. I don't have absolute numbers. I would guess, yeah, close to that, seven/eight out of ten.

DR. CATALANO: Pete Catalano. Rare.

DR. LEOPOLD: Margaret?

DR. KENNA: Marly Kenna, Boston. So if two out of the three -- there is wide variation between the centers in taste. Yet it sounds like two of the

three centers -- I realize it's just off the top of your head -- probably cut the same percentage of chordas. So the question is why is there a big variation, I think, from a surgical standpoint, where one center had a much higher incidence of longer-lasting taste change than the other ones. I think that's sort of what we're trying to get at. Is there something else that we're not seeing?

DR. LEOPOLD: And maybe something that would help this is was taste testing done on any of these patients?

DR. KRAUS: Eric Kraus. No. Taste testing was not done pre or postop in my center. And the problem with the chorda tympani in this is that it generally runs right through the middle of the facial recess. And if you don't take it, first, you don't have good access, and secondly, you don't want the chorda tympani laying down on the driver, which would give you feedback because the chorda often is attached to the tympanic membrane, and that would be -- driving would be being picked up by the sensor then.

So in my experience, most of the time the chorda had to be removed. I think that, again, most of the taste patients was a distortion, and it

eventually faded, like we see in other middle ear procedures, particularly stapedectomy.

DR. LEOPOLD: Apparently, that's not as big a problem in Boston, and anterior tongue testing may help to sort some of this out.

DR. HIRSCH: Can I comment on that same thing?

DR. LEOPOLD: Please.

DR. HIRSCH: Probably in defense of the surgeons, I gather that you're forced to have the patients fill out a questionnaire at the four-month and ten-month post-activation, and you're forcing an answer from them, if I'm not mistaken. So you're saying: Do have metallic taste, do have altered taste sensation, and the third one was tongue numbness. So I gather if you have to force a patient to think about that, they're more than likely to think, yeah, I do have that.

Now, you take our cochlear implant plus/minus on that, but definitely stapes surgery, I mean, if you force that same issue on stapes patients, it's hard to know, but you may find that same incidence. And as Dr. Glasscock said, you know, you get this falloff after three or six months where it's sort of not in their face. So I think it's

something that we're forced to look at because there is hard data, and it says that this is close to 50% incidence. But at the same time, what meaning does it really have in the long term? And I think that's what's coming up from your responses.

DR. LEOPOLD: I can tell you there's IC patients who have long-term concerns regarding this from, like, stapes surgery. So it is an issue. And a lot of patients are afraid to tell their doctors.

DR. HIRSCH: And doctors are afraid to ask.

DR. LEOPOLD: Yes. Exactly. Dr. Norton, I believe you're next.

DR. NORTON: Okay. So, you know, I was concerned when you said mild hearing loss because I think of someone with a flat loss, and the examples that you showed are steeply sloping high frequency losses. And given that the gain one would expect from the ear canal is, you know, between 2 and 6 kHz, have you looked at your data in terms of high frequency average or degree of high frequency loss for the appropriateness of this device as opposed to averaging 500, 1,000, and 2.

MR. SPEARMAN: Yeah. You've hit on a very good point. Really, we look at the canal effects for the input coming in, basically the same way when we

look at a microphone for the input coming in. And then the digital processor has to start filtering stuff out. So we kind of look at -- but from the standpoint of what we're going to give in driving, definitely it's the higher frequencies, which are bounding the best cases for where this should be used. It's just that we have these -- you know, I think we've talked with a number of audiologists who go, "The problem is we have these conventional terms that go out there that are mild, moderate, and how do we define these from time to time?" And that's why we said it really is, from a mild standpoint, it's mild with that sloping or steeply sloping loss and high frequency averages.

You know, the other way of looking at -- and I'll throw this out there, and you guys can talk about it, but that was a 5 frequency average. Taking 3 and 4K into effect would drop that down, and those patients would be captured in that regard.

DR. NORTON: I have another question. You talk about verification that the device is functional intraoperatively. I didn't see any discussion really of how long that took, what you did, and how often a device had to be removed and a new one put in, in the operating room.

DR. SCHILLER: Peter Schiller again. The intraoperative testing typically adds maybe 5 to 15 minutes to the surgery, 20 maybe if there are difficulties with the anatomy or anything. Frequency with which a transducer would be pulled out and replaced is maybe one out of ten, and that process maybe adds, you know, another 15, 20 minutes to the surgery. Does that answer your question?

DR. NORTON: And what's your test procedure?

DR. SCHILLER: The test procedure, Dr. Shohet mentioned that we rely on laser Doppler vibrometry. We have a speaker and a microphone assembly that are placed in the outer ear canal to introduce sounds. Test procedure, effectively, as we measure the vibrational response of the middle ear ossicles to sound introduced externally, we complete the implantation of the transducers and then measure the net system response to sound once again reintroduced into the ear canal. So, effectively, we're looking just like if you looked at ASTMF-2504, we're basically following that procedure to evaluate it in that particular patient's ear. Does that make sense?

DR. NORTON: Um-hum.

DR. SCHILLER: Not really? We measure displacement before and after.

DR. LEOPOLD: Dr. Hall, I think you've been waiting?

DR. HALL: So for this testing, high gain is a pretty good thing because it could lead to lower SRTs and could lead to pretty good performance for a low-level speech input for a speech recognition. But of course, for real hearing aid use, you don't want to just crank up the gain. Can you tell us a bit more about how the gain was set for the Envoy for the testing?

DR. SCHILLER: Hello. Peter Schiller again. The testing at the time that the protocol was developed with the help of the FDA group was in late 2007, at that point, we did not have any patients implanted with this device. And so we agreed that the audiologist would do the fitting, that this device is effectively an analog hearing aid, and that the audiologist would fit it based on their judgment to the needs of the patient. So the device is turned on, the audiologist evaluates the patient's hearing loss, and through, you know, an iterative process of exposing them to different sounds, speech, at various presentation levels, the audiologist at the

investigative site would determine a fit.

DR. HALL: Thanks.

DR. LEOPOLD: Dr. Connor?

DR. CONNOR: Thank you. Jason Connor. I have two questions. One, this is to the Sponsor, but it relates to FDA Slide 71, which is the word recognition score at four months.

So it looks like at Site 103, essentially, 11 patients got better and 1 patient got worse. At Site 105, 15 patients got better and 0 patients got worse. But at Site 109, 4 patients got better and 3 patients got worse, and at every place, there were patients that stayed the same, too.

But to a statistician, first of all, 4 and 3 are about the same thing. And so this means that I have a 1 in 3 chance -- and first, I guess the second -- that I suppose that as a Sponsor, my best docs are the docs I include in a study. You know, you're going to train, you know, any further surgeons really well, but, you know, I've been on the Sponsor side, and I know you want to get, you know, the best you can to put in the study.

So the way I look at this is that there is essentially a 1 in 3 chance that I end up at a site where I have equal chances of getting better and

getting worse. And so I wondered if you had a comment about that and about site-to-site variability. And I understand that's a tricky question.

MR. SPEARMAN: And I'll let the statistician talk, but I think from a practical matter that there were significant -- I mean, a few people who did get worse were the very few minority at each site. So going to any site, the odds were one would do equal or better, right?

DR. CONNOR: Right. But at one site, there's a 20% chance you would do worse. And given what we've heard about, you know, maybe under the hearing aid conditions, that still is, you know, I don't want to say straw man, but a bit of that, but it's not the best possible hearing aid. Still, there's a 20% chance you would do worse than versus hearing aid at one of the sites.

MR. SPEARMAN: At one of the sites. Yes. But also it goes back to that normalization of the functional gain and the loss that the statisticians were talking about, that that site looks worse, but if you go back and normalize it with the other sites, it comes up. But we didn't do that for the individual patient analysis on word rec score.

DR. CONNOR: Right. And is there anything in common about the four patients who did worse than versus hearing aid, maybe physiologically or --

MR. SPEARMAN: I mean, their APHAB scores are all very high. That's the one thing that's very interesting about this device is even the patients who are doing lower still enjoy the device immensely because when they get in the real world, they're hearing from a different aspect. So we look at the audiometric test -- and this one thing we don't have yet is a very good fidelity test and some of these things which can really do some of these different speech-in-noise tests -- but in the real world, they love the device. And probably they're willing to accept a little bit lower performance from that standpoint because in the real world, they do better.

DR. CONNOR: Right.

DR. BROWN: Scott Brown. Actually, all I was going to do was agree that, you know, you're right. According to the data that we have, one of the three sites, you have a 20% chance of doing worse than the hearing aid, which balances out to 1 out of 15 overall: 1/3 times 1/5 is 1/15. That is what the data say. So there is no disagreement there.

The question I wanted to ask actually is it

was mentioned a bit ago about leftover questions from this morning. And, in particular, Dr. Connor had asked about the possibility of an intent-to-treat analysis for some of the data. And I don't know if it's appropriate for me to talk about that now or not.

DR. LEOPOLD: Go for it.

DR. BROWN: Okay. So the question, I believe, was that the analyses that you have seen in our slide presentation are based upon a protocol, a set of 54 patients. And those 54 patients exclude the three patients we've discussed who were enrolled but not implanted, and they also exclude the three revisions. And that decision was made in concert with FDA, that we collectively decided that that was the 54 patients to report. But it's a legitimate question statistically, and methodologically, what happens when you put those patients back in?

Well, first of all, we can actually put the revisions patients back in because even though they were held out of that analysis, we have their data, and it's actually on one of our slides, and I don't think we have those slides in this computer right now, but it was actually presented at one point this morning. The revision patients individually on the

SRT are a +5, a +5, and a +10, so each of those patients doing relatively well. Word recognition, they are scoring around 30, each of them, and none of them has a bone conduction issue. And like I said, it's on one of our slides, but I'm not sure which one. So we can add those scores back in very readily.

Then the remaining question is what do you do with people who didn't get the implant? For example, for SRT, how do you give those people a score? I would claim what you do is these people, they suffered the risk at least of anesthesia, so that has to be factored into the clinical decision, but statistically, what happened? They went back to their hearing aid. I think the proper thing, then, would be to impute them at an improvement of 0. They are just the same now as they were before because they didn't get the Esteem at all.

If you do all those things and then reconstruct an analysis of all 60 patients in a fully intent-to-treat sense, the SRT average becomes 9.9 instead of 10.6, which we showed, and the lower confidence bound becomes 6.6 rather than 7.1. So our analysis would still show superiority in SRT on that intent-to-treat population.

DR. CONNOR: All right. Good. Thank you for that thorough answer. I had one other question.

DR. LEOPOLD: If you could make it quickly, yes.

DR. CONNOR: Sure. So this is relating to Site 105, the four-month SRT plot versus baseline. I think it was surprising that essentially 13 of 18 patients had the exact same four-month SRT score. And 13 out of 18 getting the same score seems, you know, interesting in light of the variability at other sites. So I was wondering is there -- you know, and it looks like 25 from the plot. Is there something inherent that makes the tester put a 25 or was there any data integrity checks or audits, or did that raise a flag for anyone else that 13 out of 18 scores were the exact same thing?

DR. SCHILLER: Yeah. Peter Schiller again. The computer has locked me out here. I was going to reshow that versus the unaided condition. It actually follows the same trend as the other two sites. At Site 105, if anything, for patients with a moderately severe or severe hearing loss, giving that patient enough gain if they have a 10 dB SRT is not beneficial to them. And 25, if anything, I guess was kind of a lower bound of sensibility for the

audiologist there, that it did not make sense to improve an SRT beyond 25 for a patient.

DR. LEOPOLD: We've got two more questions, and then we really need to get on to the FDA questions. Dr. Portis, you had something to ask?

DR. PORTIS: Yeah, just two quick questions from the consumer perspective since that's my role here. Just a clarification about candidacy criteria. I guess I'm trying to see who would fit in that and how a person would go about getting referred for this device. So will they need to demonstrate in some way that the hearing aid is not providing them the benefit that they need would be the first part of my question.

MR. SPEARMAN: As far as a candidacy?

DR. PORTIS: Right.

MR. SPEARMAN: Probably, it comes down a lot to patients -- we don't anticipate patients who are enjoying their hearing aid's experience really flocking to this device. That's --

DR. PORTIS: So they would express to their physician that they are not doing well with their hearing aid --

MR. SPEARMAN: Well, they probably would -- people normally don't come in for something. They'd

be explained the entire -- all the labeling claims, which are being discussed today, and all of the risk of surgery and everything else, and they could make their own decision. But they would probably come -- people just would come in to express the fact that they're not happy. We can also imagine there'd be people who said, well, I don't mind my hearing aid, but I would really, like LASIK, I would like to not have it. And they've got to make a decision what are the risks of doing this, and even though I'm happy and would like to be untethered from a hearing aid, do I take that responsibility and risk and go ahead and do this. And that comes like any surgery whether it's, like I said, a LASIK or a knee surgery, or anything like that.

DR. LEOPOLD: While you're at the microphone, can you answer a quick question of whether you're going for a unilateral or bilateral indication on this?

MR. SPEARMAN: We've only done unilateral testing. You've heard -- I just heard an anecdotal from the surgeons of how many patients would have loved to have bilaterals, but it's just a unilateral indication.

DR. LEOPOLD: Do you see, then, coming back

for bilateral at some point in the future or --

MR. SPEARMAN: They would love to do that, and we would love to do that in the future for them. And, you know, like anything else, like LASIK, or something, we'd want to put some distance and time in there and counsel them on that.

DR. LEOPOLD: Okay. Dr. Hood has one question.

DR. HOOD: My microphone seems to be out. I just had a quick question about configuration of hearing loss. What we've seen in mild hearing loss appears to be, as Dr. Norton pointed out, more severe hearing loss or moderate in the higher frequencies. And yet the labeling indication suggests 35 as a minimum, I think, all the way across all frequencies. So would that include a more minimal type of hearing loss and also a rising type of audiogram? Since this specifically takes advantage of high frequency resonance characteristics, would the expectation be similar, or do you have data on individual patients that had a rising configuration?

MR. SPEARMAN: Evidently, we did have one rising patient, and that's really why we left that level on the inclusion criteria very high in case there was a rising where someone had low frequency

loss and had high frequencies that were within a mild range. We wouldn't consider that a mild patient by the pure tone case. We would consider them a moderate or severe by pure tones with a high frequency mild. That's why I suggested earlier -- and we couldn't put this in there -- but we look at this as for patients with mild sloping high frequency loss, that's where this would be intended. It's certainly not for someone flatlining all the way across 20 to 40 dB.

DR. LEOPOLD: We have a series of questions that the FDA has prepared that we need to get to. We will likely have time later on to do some additional discussion, but I would like to move on to discuss these FDA questions.

Again, if you are asked a question, please identify yourself for the transcriptionist. The copies of the questions are included in the meeting handout. Dr. Clupper, would you be willing to summarize for the sake of time each of these questions so that we can consider them?

DR. CLUPPER: And these are in the same order that you have on your sheet.

Number 1: Of the 57 Esteem Implantable Hearing --

DR. LEOPOLD: Instead of reading it, can you just sort of give us a summary?

DR. CLUPPER: Sure. So for the first one can you comment on the type --

DR. LEOPOLD: No? We have to read it? I'm sorry. Read away.

DR. CLUPPER: Okay. I'll start. Of the 57 Esteem Implantable Hearing System pivotal study subjects, 26 (or 46%) continue to experience device/procedure related adverse events (AEs) at the time of PMA submission. These include ongoing taste disturbance (in 8 subjects, 14%) and facial paresis/palsy (in 2, 4%).

Please comment on the significance of type and rate of adverse events observed in the pivotal study (see also Table XXVI in FDA Executive Summary). Please also comment on the variability of adverse event occurrence across study sites (also see Figure 11 in FDA Executive Summary). Do the data support a reasonable assurance of safety for the device?

DR. LEOPOLD: Thank you. And we'll be getting to the other seven in a minute. I'd like to go around the room just sequentially and get everyone's opinions on these.

Dr. Sie, would you be willing to start

1 this? I guess it's basically a question of safety
2 with this device.
3 DR. SIE: Kathy Sie from Seattle. It seems
4 that the main adverse effect of taste disturbance
5 is -- or the most common adverse effect of taste
6 disturbance is something we see frequently with this
7 type of surgery. The variability between the sites
8 is somewhat concerning. If there are best practices,
9 it seems that the practice should be more narrowly
10 defined, understanding that there are, you know,
11 patient characteristics that might force your hand
12 one way or another. I think the facial palsy issue
13 is a significant one because the implications of
14 permanent facial palsy, if that should happen, are
15 pretty significant for a patient. So I think these
16 are -- I'm not sure what you want as far as comments.
17 I think to me, those are -- the facial palsy is very
18 concerning.
19 DR. LEOPOLD: I don't need absolutely
20 everyone's comments on these, but I'd be interested
21 in other people's concerns/questions on this question
22 of safety and adverse events. Yes?
23 DR. ISHIYAMA: When you look at the data
24 presented --
25 DR. LEOPOLD: Dr. Ishiyama?

1 DR. ISHIYAMA: Yeah, Ishiyama from UCLA.
2 On Figure 11 from the FDA data, one site, 105, out of
3 18 patients, 17 patients, which means a great
4 majority of the patients developed taste disturbance.
5 However, Site 109 has none. This becomes a very
6 important point, in my opinion, because a lot of
7 these patients may potentially require bilateral
8 implantations because then we could have a pretty
9 high chance of developing bilateral taste
10 disturbance.
11 And the second question that I have --
12 concern that I have is high incidence of facial nerve
13 palsy. All of these are delayed. However, it's not
14 too clear to me at this point what exactly the
15 underlying mechanism is. The company's brochure
16 states that the incidence of facial palsy is 0.5%.
17 But in actuality, 5% of facial problem developed.
18 DR. LEOPOLD: Dr. Kileny?
19 DR. KILENY: Regarding the safety issues,
20 two comments. Number one, I believe we don't have
21 cochlear stability data on six patients, and I'm not
22 sure when that information will come in. I guess it
23 just wasn't sufficient --
24 DR. LEOPOLD: We get to that in a later
25 question.

DR. KILENY: Well, that's part of safety. And then regarding the facial palsy, I think that perhaps the labeling should reflect the fact that there's a higher risk than normal maybe because of the wider facial recess approach that this necessitates compared to cochlear implants, for instance.

DR. LEOPOLD: I think it's fairly obvious that the taste dysfunction is because the surgeon cuts the nerve, and --

DR. KILENY: Right.

DR. LEOPOLD: -- so that if that is going to be the protocol taught to all of these trainees, then you've got to tell people about that. When that happens, the taste is distorted for a while or lost. The way people compensate is that the normal side grows over to the other side. When you cut the second side, it all goes, and then you've got an ageusic person. So it is something to certainly consider, and patients need to realize that they have a risk of taste loss if indeed this is going to be the practice.

Dr. Lalwani?

DR. LALWANI: That was the purpose behind my question of surgeons is, is it routine to cut the

chorda tympani nerve, and is it required to place the device, and at least my impression from the two sites were that it was absolutely required, and the facial paresis, or delayed facial paresis or paralysis, is a reflection of yet getting the additional room to place this device as well. That is, maybe it required more thinning of the facial nerve during the surgical exposure.

DR. LEOPOLD: Let's talk about -- oh, Margaret?

DR. KENNA: I'm sorry. Marly Kenna of Boston. Also, just in looking at Figure 11, Site 105, which had the higher incidence of taste disturbance, also had a higher incidence of pain -- imbalance and numbness. So I just wonder if in review of the different site surgeons if, just in looking at best practice, it's interesting that one site -- I don't know if they have a bigger facial recess -- maybe they get a better view of the stapes, but it would be worth reviewing so that all of the numbers came down even if you have to cut the chorda.

DR. LEOPOLD: And I think the second highest problem was facial nerve, and we've already touched on that. Anyone else want to say anything about facial nerve? I suspect there is no surgeon,

at least, objectively surgeon-caused reason for this and that some people's nerves are a little more fragile than others. However, it's still unclear as to why these people, especially the delayed losses occurred, and perhaps further investigation will help to understand this.

Dr. Lonsbury-Martin?

DR. LONSBURY-MARTIN: Yeah. Lonsbury-Martin, Loma Linda. There is a mention that facial nerve monitoring is indicated or at least recommended. Is that something that was -- would help in this matter?

DR. LEOPOLD: I guess that's a question for the surgeons.

DR. CATALANO: Peter Catalano. That is routinely used in all the surgeries, the facial nerve monitoring. That would help with, obviously, dissection. The delayed palsies that occur late are usually due to delayed inflammatory changes that can occur. Thank you.

DR. LEOPOLD: Dr. Catalano, as a follow-up to that, do you -- do any of the surgeons recall for those patients who had the delayed palsies, which is basically the only kind you had, was anything unusual occurring during the operation? Was the monitor

1 going off more frequently? Can you remember anything
2 that would make you suspect that you are nearer the
3 nerve, the bone was thin or something?
4 DR. CATALANO: In the one patient that I
5 had that had the delayed paresis, she was diabetic,
6 and I mentioned that earlier. And that's a
7 predisposing factor. It wouldn't preclude her from
8 having an implant, but it's a risk factor, so we
9 would normally discuss that. I'll have the other
10 guys comment if you'd like. I don't know --
11 DR. LEOPOLD: Yes. Please have them come
12 up. Perhaps the literature should recommend that
13 diabetic patients be warned more about this.
14 DR. KRAUS: Eric Kraus. Actually, I agree
15 with Peter. The delayed paresis is usually
16 inflammatory. In one patient I had, I think that it
17 was actually due to us using the laser to resect the
18 incus, and we have now changed the laser settings,
19 and that pretty much has now disappeared.
20 DR. LEOPOLD: It was a heat effect you
21 suspect?
22 DR. KRAUS: I think it's a delayed heat
23 effect from the laser.
24 DR. LEOPOLD: Okay.
25 DR. KRAUS: And we've taken great pains

both in the lab now and in patients to protect that area with moistened gel foam to protect the tympanic membrane, the facial nerve, and the stapes, the footplate area, and that moistened gel foam serves as a heat sink, and we've done actually testing in the lab to confirm that.

DR. LEOPOLD: Thank you. Dr. Shohet?

DR. SHOHET: Thank you. Jack Shohet. There were actually three patients with facial paresis even though what you have says four. One of them was attributable to me.

DR. LEOPOLD: We got that.

DR. SHOHET: Okay. So you got that, three versus four?

DR. LEOPOLD: Right.

DR. SHOHET: Okay. Thanks.

DR. LEOPOLD: Yes?

MR. TIMLIN: I wasn't clear. Were all the sites using nerve monitoring?

UNIDENTIFIED SPEAKER: Yes.

DR. LEOPOLD: Any other comments regarding facial nerve? I think we can perhaps move on to -- Dr. Eydelman, is this adequate for Number 1?

DR. EYDELMAN: Yes.

DR. LEOPOLD: Can you read Number 2 for us,

please?

DR. CLUPPER: Number 2: In the current PMA pivotal study, 5.3% of the subjects (3 of 57) required revision surgery due to "limited benefit" from the device. At revision, the investigators identified fibrous adhesions which were thought to have caused the limitations in Driver and Sensor function.

a. Does the rate of revision surgery in the current pivotal study due to "limited benefit" support reasonable assurance of safety?

b. What additional measures, if any, should be taken to address this issue? Please include but not limit your discussion to the following: (i) additional pre-market clinical studies, (ii) labeling, (iii) surgeon training, and (iv) post-approval studies.

DR. LEOPOLD: Thank you. Yes. Dr. Hirsch?

DR. HIRSCH: Barry Hirsch. Can I ask a question regarding this, and that is when you went back in for the three cases, it was deemed that there was --

DR. LEOPOLD: This is a question for the surgeons?

DR. HIRSCH: The surgeons. I'm sorry. It

was deemed that there was reactive fibrosis occurring at the scutum or at the facial recess area and having to revise the procedure in order to remove that fibrosis or adhesive tissue. Can you anticipate anything you could do differently that would prevent that from happening in a patient?

DR. KRAUS: Eric Kraus. One of the patients was mine. It was the first patient in the study, who had a very small mastoid, just enough for the transducers. This patient developed fibrosis, but also neo-osteogenesis from the scutum to the sensor Envoy. He did well for a few months, and then it slowly deteriorated as that neo-osteogenesis occurred. This patient also had fibrosis in the facial recess just like you would see in a revision cochlear implant.

I think that the one way -- and we've struggled with this -- the best way is careful surgical technique, very good hemostasis, elimination of as much bone dust during the procedure as possible to help mitigate this effect. I do think there probably will be a few patients that will develop fibrosis, a fibrotic reaction no matter what we do. We have not explored using postoperative steroids, which might be another possibility.

DR. LEOPOLD: Comments regarding this surgical fibrosis scarring?

(No response.)

DR. LEOPOLD: I guess a second question that I would have for the surgeons is, is this a surgeon-dependent problem? I mean, was this a condition where you removed too much mucosa? I know in the sinal nasal area, that can be an issue. If you roughen up the tissue too much, you're more likely to get fibrosis, scarring, osteogenesis, and so on. At some point, it's a patient problem. Can each of you address, or one of you surgeons represent what may be the reason here, and can we be comfortable that this is not going to occur in a large number of people because we trained the surgeons correctly or because you trained the surgeons correctly?

DR. CATALANO: Pete Catalano. I jumped up to answer because I had two of the three patients, so I better answer that one for you. And you know better than anyone that I'm big on mucosal sparing for everything else I teach about. So you're right. We thought about, you know, whether it's mucosal irritation. We talked about glove powder. We talked about bone dust. All of these things we've tried to

mitigate against by changing our technique as we've gone through the surgeries.

But, you know, you're dealing with a small space. And when you put a prosthetic anywhere in the body, usually you have a reaction to it. When you put a foreign body in a soft tissue pocket, you obviously get a capsule around it. The beauty of these transducers is that they're in air, you know? They're not touching anything for the most part. They can't because otherwise you'd have feedback. But you do have some blood that occurs in there after surgery, and that may be the link. And I think that's how Eric's case, Dr. Kraus' case, got that osteoneogenesis.

So despite doing everything possible, you can have this happen. A colleague of mine just had to revise a stapes patient five times because the patient was reacting to the stapes prosthesis. We couldn't figure out why. We tested all kind of serologies, you name it. So I think what Dr. Kraus was saying is despite doing everything we could think of, short of using postoperative steroid regimen, which has its own issues -- we do use an intraoperative dose of steroids for many reasons, for postop nausea as well as to reduce some

inflammation -- you will always have, you know, on that bell curve, some patients who are going to have reactivity. And we'll continue to investigate this because it's important to us as it is to everybody else.

DR. LEOPOLD: You mentioned that this is -- Peter, stay up. Sorry. You mentioned that this is likely seen more frequently in a small cavity? Should we be revising the size numbers you gave us earlier as to how big a cavity you need to be a candidate for this operation?

DR. CATALANO: No. I didn't mean it that way. What I meant was, you know, even doing a TORP or a PORP, you know, you put something in that middle ear space, the space is limited, so you don't have, you know, three inches of space between the side walls. The transducers are small. They're the size of a PORP or a TORP.

DR. LEOPOLD: Are there patients with small mastoids who you've successfully done who didn't get fibrosis and scarring?

DR. CATALANO: Yes. I had two such patients.

DR. LEOPOLD: Dr. Kraus, you're nodding your head? I mean, do we have more than five

patients among the whole group?

DR. KRAUS: Eric Kraus. Yes. I've had some with small mastoids, and they did not develop fibrosis.

DR. SHOHET: Jack Shohet. I agree. I have had a lot of small mastoids without fibrosis.

DR. LEOPOLD: Tell me rough numbers.

DR. SHOHET: Oh --

DR. LEOPOLD: Three, six?

DR. SHOHET: Five to ten.

DR. LEOPOLD: Okay.

DR. SHOHET: Five to ten. I truly don't believe that a small mastoid predisposes to the fibrosis.

DR. LEOPOLD: Okay. Dr. Lalwani?

DR. LALWANI: So on the one hand, I'm reassured by the fact that the fibrosis caused their problem. On the other hand, given that fibrosis probably occurs in almost every single mastoid you do in mucosal tissue, certainly 5.3 in a short-term is concerning especially with respect to long-term outcome. So one of the things specifically about additional pre-market clinical studies or post-approval studies or something clearly is a need to make sure close follow-up of these patients to see

1 what develops over time.
2 DR. LEOPOLD: Thank you. Dr. Cueva? Yes.
3 I'd like to hear from most of the surgeons on this
4 because this seems to be a surgical issue.
5 DR. CUEVA: Thanks. Certainly a revision
6 rate of 5.3%, I think, compares favorably even to
7 conventional ossicular reconstruction. Probably have
8 a higher incidence of having to revise conventional
9 ossicular reconstruction than this. I'm not sure,
10 Dr. Lalwani, that over the long term you're going to
11 see any more fibrosis. I think the initial traumatic
12 event of the surgery, whatever happens in that early
13 perioperative period, is going to set you up, and if
14 it hasn't happened, then things actually tend to seem
15 to quiet down as months go by, at least in the
16 experience that I've had.
17 Just in terms of a question to the
18 surgeons, have you considered gel film in a way to
19 coat or kind of create pathways for aeration or a
20 lasting barrier in the early perioperative period to
21 try and reduce fibrosis around the devices?
22 DR. CATALANO: In terms of the long-term
23 data, if I can just comment on that, the 0203 data,
24 which is about four or five years old, does not show
25 any long-term continued or new fibrosis. So we feel

1 comfortable in realizing that. I think Dr. Cueva's
2 point is correct. It's the initial potential
3 intervention that would likely lead to any fibrosis
4 if you're going to see it, but after you get past
5 whatever that time period is, a couple of months, we
6 see patients doing well.
7 In terms of using any type of absorbable
8 material in the middle ear, thought about that.
9 There's some interesting work that's been recently
10 published in *RATS* looking at different types of
11 absorbables in the middle ear and mastoid. And, you
12 know, gel foam, for instance, had the worst rate of
13 fibrosis and, you know, granuloma formation and
14 foreign body reaction. So I'm not a big fan of
15 leaving something buried inside that is resorbable
16 because it has to go away somehow. And my thinking
17 is, well, the immune system is going to dissolve this
18 away just like a resorbable stitch. And what happens
19 with that? You can feel that stitch for quite some
20 time until it resorbs and the immune system has to be
21 activated. So we are thinking about these types of
22 things. Until we have the proper one, I'm concerned
23 about putting a resorbable that requires immune
24 activity to dissolve.
25 DR. CUEVA: If I might respond, the use of

gel foam in middle ear surgery as a way to try and reduce scarring has a decades long and probably dozens, if not hundreds of surgeons' experience, and it seems to work quite well.

DR. LEOPOLD: Thank you. Dr. Kenna?

DR. KENNA: Yeah. I just had a brief question. I know in the material we were provided, it did look like in the revisions the fibrosis was a concern. I'm just curious how you ruled out the cement as a possible source of reactive foreign body, and is there anything you -- if you thought so, is there anything you've done to ameliorate that?

DR. KRAUS: Eric Kraus. That was my patient that had the fibrosis and the MedCem close to the incus. Actually, that patient did very well initially, and we would have felt that if the MedCem was the cause of the incus partial fixation, that he would have not done well initially. And actually, the MedCem was up to the incus, but the incus was still mobile. I just noted it because it was right up close. So it did not appear to me at all that it was the MedCem. It was actually this neo-osteogenesis, almost a natural bridge between the scutum and the EnvoyCem.

DR. LEOPOLD: Thank you. Our continuing

discussion -- we need to get through these questions that the FDA has posed to us.

Dr. Sie, do you have a comment?

DR. SIE: I had a quick question about the revision. The revision rate for the initial study is quite different than for the current study, and it sounded like that most of the revisions for the first study were related to the bonding. But there still is significant difference even if you remove the 14 that had bonding problems. It seems like the revision rate was higher in the first study. Can you account for what changed? Did the materials actually change? And, finally, what was the period of time during which the first cohort required revision? So we have a ten-month follow-up with the current study. Is that long enough for us to assess a revision rate? I'm sorry.

MR. SPEARMAN: I'm not good at remembering multiple questions, but we'll try to get to them. Maybe to answer the last question, the revisions, once they happened, they all happened, I think, pretty much within the first year, and since that time, there's been no revisions after one year postop. We submitted that data before.

Certain things happened in the first study.

We had the battery and processor -- the processor had a boost process in it that could be turned on. Some of the audiologists had turned that on, and it was to try to give a lot of extra boost to the patients. And it caused battery depletion to be maybe 1.7 to less than 2 years. And that wasn't indicated in our informed consent. So that was considered to be a failure and a need for revision. That happened on several patients, and that was one of the other things that occurred

DR. SIE: Thank you.

DR. LEOPOLD: I'm going to ask some specific questions now. The FDA wants to know if in addressing this issue, do we need to make any further comments regarding the pre-market clinical studies? Do we need to know any more regarding this issue of scarring and so on?

DR. ISHIYAMA: Can I ask a quick question?

DR. LEOPOLD: Yes, please?

DR. ISHIYAMA: Akira Ishiyama from UCLA. I understand that you needed to introduce a cement to make the device adhere tighter to the incus and stapes bone. I'd like to hear from the surgeons how difficult it was to actually remove them at the time of revision surgery.

1 DR. KRAUS: Eric Kraus. The EnvoyCem bonds
2 very well. However, you can chip away at it just a
3 little bit. You have to do this very gently. You
4 can strike it with a laser, very low wattage, and it
5 will crack. You cannot vaporize the EnvoyCem because
6 it's a glass ionomer. I just would melt if you would
7 heat it up too much. But it actually can be removed
8 if it's done carefully. Generally, right at the
9 junction between where the new cement has been
10 applied to the pre-coated cement, it will break
11 there, and then you can gently remove the transducer
12 from the stapes. And we have done it successfully.
13 DR. LEOPOLD: Any Panel comments regarding
14 labeling that we should change for regarding this
15 issue or surgeon training? Dr. Kenna?
16 DR. KENNA: I think you've mentioned that
17 you have plans to consider surgeon training. It
18 seems that among the three of the surgeons, that even
19 though this sounds like, eventually, a relatively
20 straightforward procedure, it sounds like very
21 specific techniques would need to be utilized to get
22 an optimal result. So I assume that surgeon training
23 would be actually necessary.
24 DR. LEOPOLD: Right. If we did recommend
25 approval but with a post-marketing study, is this

1 something we'd want to study, fibrosis failure? I
2 guess I need yes or no sort of answers on this. Yes?
3 Got it. Okay. Dr. Eydelman, is that okay?
4 DR. EYDELMAN: Before you leave this
5 question, I'm not sure if I heard the consensus of
6 2a.
7 DR. LEOPOLD: Pre-market? Do we have
8 enough data now?
9 DR. EYDELMAN: No, no, no. It supports
10 reasonable assurance of safety?
11 DR. LEOPOLD: Panel, does this
12 discussion/presentation give us reasonable assurance
13 of safety that this device, even with this, what,
14 5.3% of fibrosis, that's okay? It seems to be
15 falling somewhere around the rate you see with the
16 stapes or ossicular plasty. And I'm seeing mostly
17 yes nods. Dr. Norton, you want to comment? This is
18 too high a number?
19 DR. NORTON: Well, I don't think the
20 benefit shown over a non-surgical procedure has been
21 demonstrated to the degree that it's risking --
22 DR. LEOPOLD: Then that maybe would be a
23 decision we would leave up to the patient and
24 indicate that there is a 1 in 20 chance of this kind
25 of thing happening, unless another number can be

1 better put there? But I guess the 1 in 20 number
2 would be the one we'd have to put there now.
3 Dr. Eydelman?
4 (No response.)
5 DR. LEOPOLD: Let's move on to Number 3,
6 then. Can you read Question No. 3 for us, please?
7 DR. CLUPPER: Of the 57 subjects implanted,
8 cochlear stability data were available in 51 subjects
9 at 10 months. Of these, one subject exhibited a
10 significant threshold shift at 4,000 Hz. Do these
11 data provide adequate support of the long-term safety
12 of the Esteem system?
13 DR. LEOPOLD: Panelists' comments? Yes?
14 Dr. Kenna -- Kileny?
15 DR. KILENY: Given that the six subjects on
16 whom we don't have cochlear stability data represent
17 10% of the total number, if there is a way, I would
18 like to see data on those. Again, there is only
19 one -- significant change, but we don't know what
20 happens to the other six. So I think that those data
21 are important to make this determination.
22 DR. LEOPOLD: So are you recommending they
23 get additional data or are you okay with the data
24 that's there?
25 DR. KILENY: Well, I can't remember anymore

what was the reason there is no data on those six? I thought it was just a matter of time.

MR. SPEARMAN: There was the three revision patients who have made it to four months with no bone conduction change at four months. And one thing to note about that is all the patients who have made it to -- even at two months or four months with no bone conduction change have all made it, you know, to ten months. We have one patient -- but that's historically been if there is no bone conduction change early, there hasn't been throughout the study.

The other patient was one was the explant patient of Dr. Shohet's. So once that patient was removed, they were checked for bone conduction, but they didn't come back for a ten-month check because they were not -- the study. There was one patient --

DR. KILENY: And he didn't change?

MR. SPEARMAN: He didn't change, no. There was one patient who had a four-month endpoint but had not made it to his ten or her ten, I'm not sure which, ten-month endpoint, but at four months, that bone conduction was stable. And that was it.

DR. LEOPOLD: Okay. Dr. Norton?

DR. NORTON: So those were patients in whom you just didn't make the measurements, but how many

patients could you not make the measurements because of equipment limitations? I asked that --

MR. SPEARMAN: You're saying the non-responders who were very low?

DR. NORTON: Yes.

DR. SCHILLER: I think your question is, at the baseline, how many's hearing was so bad, how many of the cochleas were so bad that their thresholds were above the equipment. There was one patient out of the 57 or the 54 at two-month that had all four frequencies beyond the test limits of the equipment. There were two patients that had three frequencies beyond the limits of the test equipment.

DR. NORTON: I'm not sure how --

DR. SCHILLER: I believe there were eight patients that had two frequencies, eight patients that had one frequency, and 33 patients had baseline measurements.

All of the patients that had a baseline measurement either through the follow-up bone conduction testing or through the EnvoyGram we were able to measure cochlear function at follow-up.

DR. LEOPOLD: Dr. Sininger, you want to add something?

DR. SININGER: Yeah. Yvonne Sininger. I

mean, given the limitations of bone conduction measurements in general and given that these are patients with, you know, tending towards high frequency hearing loss, I don't know how much emphasis we can place on demonstrating that there is no change in bone conduction over time and also given the fact that these are patients with sensorineural hearing loss who will have, regardless of which device they're using, will have shifts in their bone conduction over time.

And so I was not uncomfortable with the data as it stands. It, of course, would take monitoring over a longer period of time. But I would think that it would also need to be weighed against the expected amount of shift that you would see in any group of adults with sensorineural hearing loss over time. So extended monitoring might be advisable.

DR. LEOPOLD: So you'd recommend that if they did a post study, there would be some extended monitoring of cochlear function?

DR. SININGER: Yes. And perhaps not just bone conduction thresholds. Perhaps something like word recognition scores because you might expect if there was cochlear degeneration, that you might see a

shift there that doesn't ceiling -- you don't have a ceiling effect as you do with bone conduction.

DR. LEOPOLD: Other than that, any other concerns? Dr. Ishiyama?

DR. ISHIYAMA: Quick question. You may have already explained it. I just want the clarification. Three patients who had the revision surgeries, did you demonstrate the stability of the cochlea?

MR. SPEARMAN: The three patients with revision surgeries? Yes. Dr. Catalano had showed their results, and they had no change in their bone conduction at the four-month as well as the -- the two-month or the four-month.

DR. LEOPOLD: Dr. Eydelman, does that satisfy your concerns?

DR. EYDELMAN: Yes. Thank you.

DR. LEOPOLD: Can you please read Number 4?

DR. CLUPPER: FDA statistical analysis showed significant site effect for both SRT ($p<0.01$) and WRS ($p=0.01$). After taking site variability into consideration, the lower bound of the 95% confidence interval for mean decrease in SRT (a co-primary effectiveness endpoint) was no longer greater than -5 dB. FDA analysis showed similar result for WRS.

Is the observed site variability a concern in interpreting device effectiveness?

DR. LEOPOLD: Dr. Connor?

DR. CONNOR: So I certainly believe that there was site heterogeneity. And so I should say to Panel members, too, that the idea of the fixed effects versus random effects analysis is really answering two different questions. The fixed effects analysis is answering the question, essentially, what is the estimated effect in these three surgeons or the average of these three surgeons versus the random effects analysis is answering the question what is the expected effect with this 95% confidence interval in a random surgeon. And, of course, by a random surgeon, I mean a randomly chosen surgeon who is well trained and certified to perform this procedure.

So the latter question is really the more relevant question because we need to extrapolate this to all the surgeons who could be performing this procedure.

Along that line, you know, it's difficult to take three surgeons and extrapolate that to, you know, the clinical experience throughout the country, which is why I sort of asked FDA that maybe this is a more relevant question to the Sponsor of, if they

1 were approved, essentially, to do ten sites; it seems
2 the choice to do three clinical sites, you know, is
3 making it difficult for the Panel to identify how
4 relevant, you know, these three surgeons' experiences
5 are to all surgeons, and if you can comment maybe on
6 why you stopped at three sites -- I know a lot of
7 that is expense, and it's difficult to train more
8 people to get them online. But I think it comes down
9 to, you know, us having three site experience, it's
10 difficult, then, to understand how this might be more
11 broadly applicable to other surgeons.
12 MR. SPEARMAN: We can talk to the
13 statistician standpoint. I think what happened was
14 in the first study, we had maybe five sites and 72
15 patients. Here we had a limited number, 50 to 60.
16 And very shortly, the three sites, obviously, that
17 had been involved in the first study were always
18 active. They had their IRBs all there, and they
19 enrolled so many patients, we talked to the
20 statisticians, and said that three was powerful
21 enough. And that's really how that came about. They
22 just were able to fill this up. There was a lot of
23 patients who had a lot of interest after the first
24 study, and we just had enrollment fill so quickly
25 that we didn't have other sites.

DR. LEOPOLD: I think it's fair to say that in the general training of surgeons to do a procedure, let's take stapedectomy, there is a variability in how good each of those surgeons, or how effectively they do the operation. And some go on to be spectacular surgeons, even better than their teachers. Some are terrible, and you wouldn't let them operate on your dog and so on.

And it is, you know, they tend to separate out that way. And so I would be willing to put forward that, yes, there is site variability, yes, it's surgeon-dependent, and I'm not sure that these surgeons, all of whom are excellent, know what they did exactly that was good or bad, and we're still learning that. There are certainly some general surgical principles that can help in that regard, but we are humans. And I think that this is something that we're not going to be able to -- if this device goes forward, it's going to have to be performed by surgeons, and they're going to be able to do that.

Dr. Rosowski?

DR. ROSOWSKI: To answer a question at the end, my answer is yes, I am concerned about the site variability. And I guess one of my concerns is I don't know where it comes from. It's not clear to me

that it is surgeon-dependent. There's lots of other factors that are going on. And until that is better understood, you know, exactly what the contributions are, I'm going to continue to be bothered by it.

DR. LEOPOLD: Is anyone else in the Panel bothered by that? Dr. Cueva?

DR. CUEVA: I had the impression that some of the site variability, in particular related to SRT, was related to some of the patients' baseline preoperative data that tended to skew their results postoperatively. And if I'm incorrect, it may account for a great deal of that variability, if I could get clarification.

DR. BROWN: Yes. One of the slides that we showed earlier today -- it was actually my first slide -- was the unadjusted and what we're calling the adjusted site poolability analyses. And the point of that slide was essentially that most of the site variability is accounted for by differences in the patients at baseline. Very specifically, it was the baseline level of hearing loss and the baseline SRT, which were predictive of the ultimate changes in SRT.

And in some sense, that's not surprising. When you have the patients -- for example, if a

patient started off very, very well in SRT, there is a ceiling effect. They can't really get better. So this is almost what you would expect to see in an analysis of this sort.

Now, the question as to how these different patients arrived to these different centers, as was talked about before, the patient's choice of center was a matter of geographic convenience for them. So that's the why.

And the statistical wherefore is, yes, the difference in sites is largely a patient selection issue and not -- if it's surgical, we have found no evidence of that in the analysis.

DR. LEOPOLD: We need to keep our discussions among the Panel here more.

Dr. Sie, do you have concerns regarding this variability as a surgeon?

DR. SIE: I do have concerns from the public's perspective, from a patient's perspective how do you decide which surgeon to choose and are those results -- do those results become available. It seems that you could -- the only way to address the question of whether it's the surgeon or the patient is really to assign patients to the surgical sites controlling for their degree of disease.

DR. LEOPOLD: So do you have concerns, given what data we now have, about this?

DR. SIE: I do have concerns about it in that I think we need to have a better idea because there does seem to be a fair amount of variability.

DR. LEOPOLD: Specifically in terms of hearing level --

DR. SIE: Well, in terms of it's interesting that the speech outcome --

DR. LEOPOLD: What I'm hearing is hearing level, taste, and facial nerve?

DR. SIE: Right. And the --

DR. LEOPOLD: But we've taken care of those --

DR. SIE: And the center that has the more variable speech outcome seems to have less facial nerve, or less chorda, less taste effect.

DR. LEOPOLD: Yeah. But at least some of those are due to the hearing aid levels, and so on, that were done.

DR. SIE: Though the chorda issue is really a surgical technique issue, right?

DR. LEOPOLD: That's surgical technique. So we've dealt with that.

Dr. Lalwani?

DR. LALWANI: I am concerned about the -- if I look at this question, it says to me is the observed site variability a concern in interpreting the device effectiveness? So if the surgeon who puts it in is part of how this device gets put in and its outcome, and that is a variable, and that is a variable, such great variability, so it is a concern to me. That's about it.

DR. LEOPOLD: Okay. Yes, Dr. Sininger?

DR. SININGER: Yeah. I just have to say that over and above just the site variability, the variability in the preop scores, the data on the original hearing aid fitting are the ones that still are concerning me. And, I mean, with all respect to all our surgeon friends, it may not only be a surgical issue here that's, you know, leading to the differences in the outcomes. I think there could have been a lot better control. If I'm a patient, I want to know not only should I go through this surgery, and what are the options I'm going to have related to a non-surgical approach. And I think that the only way to compare those two is to have an optimized non-surgical approach, and I don't believe that that data was really optimized. I'd like to see patients with well-fit hearing aids compared to this

new device so that the true benefits could be --

DR. LEOPOLD: So perhaps that's something we could ask for in a post-market study or deny approval because we want it up front?

DR. SININGER: Yeah. I would have liked to have seen more of that data. Were they absolutely -- there's just so many who have very poor hearing aid performance.

DR. LEOPOLD: Any other comments?

DR. JOHNSON: Terri Johnson from FDA. I would like to just comment on the response that Dr. Brown, the applicant's statistician gave regarding statistical variability results adjusting for baseline. After adjusting for baseline SRT, there was still significant site variability. And we did also -- the FDA --

DR. LEOPOLD: Variability in their hearing results?

DR. JOHNSON: SRT.

DR. LEOPOLD: Yes.

DR. JOHNSON: At four months relative to the baseline. And FDA also conducted an analysis using the baseline as one of the adjusted factor and also looking at any possible demographic/audiologic history and other possible demographic factor,

whether those differ between sites, and after adjusting for those possible confounders, whether there is still site variability. And we found none. So it was just the baseline SRT value that was confounding factor. And then even after adjusting for the baseline factor, site variability was still there.

The result that the applicant has presented that shows p-value equal to 0.06, adjusting for baseline plus hearing loss, this hearing loss, well, in the protocol, this hearing loss was supposed to be measured with PTA. But in the data that was provided by the applicant, the data that they used for the hearing loss was measured by SRT, which was never pre-specified in the protocol. So I believe that this was one type of fishing expedition that they got one variable that made the 0.05 cutoff point.

DR. LEOPOLD: So if I'm understanding this correctly, the question if we're interpreting the device effectiveness, it is working correctly, but it's the site or the surgeon or the patient choices that are the -- or the geography of the site that's the problem. Can I say that?

DR. JOHNSON: With the data, with the statistical analysis, we cannot pinpoint what was

causing the site variability. The claim was that -- by the applicant was that after adjusting for the baseline SRT value and adjusting for the site variability of hearing loss of patients from site to site, the variability of SRT effectiveness at four-month went away. But the statistical analysis was incorrectly done.

DR. LEOPOLD: So can we still make the statement that the device, which is the question in front of us, that the device itself is functioning?

DR. JOHNSON: I'm not understanding the question clearly. I'm sorry.

DR. LEOPOLD: Dr. Lalwani?

DR. LALWANI: I think what she's saying is that the differences in performance of different sites cannot be explained by their baseline factors that they came in with, that there, in fact, is statistically significant differences of performance across sites that cannot be explained.

DR. JOHNSON: Thank you.

DR. LEOPOLD: Okay.

DR. JOHNSON: That's exactly what I'm saying, yes.

DR. LEOPOLD: Dr. Eydelman, is that sufficient?

DR. EYDELMAN: I believe so.

DR. LEOPOLD: Thank you. Let's move on. We are missing our break, but I would like to get through these questions, and I believe we can do it in the next few minutes. Can you do the next question, please?

DR. CLUPPER: Compared to their baseline aided conditions, some subjects experienced decreased performance in the following effectiveness endpoint: WRS (7% and 12% at 4 and 10 months, respectively); APHAB (20%); and Envoy Questionnaire (10-20% for the majority of questions). Do these results support reasonable assurance of effectiveness of the Esteem system?

DR. LEOPOLD: Panelists? Dr. Kenna? Okay. Yes, please, Dr. Cheung?

DR. CHEUNG: On a related question, do any of these measures that were mentioned relate at all or correlate at all with either exacerbation of underlying tinnitus, and how did you measure the -- how did you assess tinnitus?

MR. MULLIN: Chris Mullin. We did not perform an analysis to correlate outcome measures or efficacy measures with adverse events. We did, however, explore the site variability issue as

requested by the FDA. So that was an exploratory analysis the FDA asked us to do. Does somebody else want to report on the tinnitus? Can somebody else come up?

DR. SHOHET: Jack Shohet. Tinnitus was on case report forms -- questionnaire, and the surgeons also asked about tinnitus when they followed up postoperatively and preoperatively.

DR. LEOPOLD: Do you have a feeling as to whether that at all correlated with these performance results?

DR. SHOHET: I'm sorry --

DR. LEOPOLD: The presence or absence of tinnitus?

DR. CHEUNG: Steven Cheung. To get to the heart of the matter, is new onset tinnitus a proxy measure for hearing loss or some other adverse event?

DR. CATALANO: Pete Catalano. There were only two patients that had new onset tinnitus in the study --

DR. CHEUNG: Or some exacerbation --

DR. CATALANO: And they both resolved spontaneously. There were 16 patients that entered the study with tinnitus that were implanted with active tinnitus, and two of those patients had

persistent tinnitus afterwards, but they had it going in. But only two patients developed new tinnitus, and it resolved during the ten-month period. So there is no persistent tinnitus in those patients.

DR. CHEUNG: So is the measurement of tinnitus here present or absent, or did you have some sort of scaling, like a validated measure, something of that sort?

DR. CATALANO: No. There was no scaling of the tinnitus score. It was just present or absent; is that correct? That's correct.

DR. CHEUNG: Thank you.

DR. LEOPOLD: In order to try to find out what the Panelists think about this, let's go around the table, and each of you are going to respond -- just give me a yes or no -- as to whether you feel like these numbers on Question No. 5 are important or not. I want to start with Dr. Hirsch, to my right.

DR. HIRSCH: Thank you.

(Laughter.)

DR. HIRSCH: You'll go first?

UNIDENTIFIED SPEAKER: I'll go first.

DR. HIRSCH: Well, I'll take it.

DR. LEOPOLD: I'm looking for one word here.

DR. HIRSCH: Is that a yes or no word?

DR. LEOPOLD: Correct.

DR. HIRSCH: Yes, reasonable.

DR. LEOPOLD: Next?

DR. HOOD: No. I don't think so.

DR. LEOPOLD: You don't think they're reasonable?

DR. HOOD: Do you want a reason since I said --

DR. LEOPOLD: No.

DR. HOOD: Okay.

(Laughter.)

DR. LEOPOLD: Next?

DR. ISHIYAMA: Yes.

DR. LEOPOLD: Dr. Kenna?

DR. KENNA: No.

DR. KILENY: Yes.

DR. LALWANI: Yes.

DR. LEOPOLD: Dr. Lalwani? Okay. Dr. Rosowski?

DR. ROSOWSKI: No.

DR. LEOPOLD: Dr. Sie? Reasonable or not?

DR. SIE: No.

DR. LEOPOLD: Okay. Mr. Timlin?

MR. TIMLIN: I have no comment.

DR. LEOPOLD: Okay. Dr. Portis?

DR. PORTIS: I would say yes.

DR. LEOPOLD: They are reasonable?

DR. PORTIS: Reasonable.

DR. LEOPOLD: Okay. Lonsbury-Martin?

DR. LONSBURY-MARTIN: Yes.

DR. LEOPOLD: Dr. Connor.

DR. CONNOR: Barely. So I mean --

DR. LEOPOLD: Okay. That's on the fence. Dr. Norton?

DR. NORTON: No.

DR. LEOPOLD: Dr. Sininger?

DR. SININGER: It says some patients. It doesn't say how many. That's what's still bothering me.

DR. LEOPOLD: Well, they give percents here. They're all sort of between the 10 and 20 range.

UNIDENTIFIED SPEAKER: I didn't know we could vote barely. I thought it was one of two choices.

DR. LEOPOLD: He cheated.

DR. SININGER: I'd have to say yes.

DR. LEOPOLD: Okay. Dr. Sininger is a yes. Dr. Cheung?

DR. CHEUNG: No.

DR. LEOPOLD: No?

DR. HALL: Yes.

DR. CUEVA: Yes.

DR. LEOPOLD: Thank you. So Dr. Cueva says yes. Does that help you?

DR. EYDELMAN: Yes.

DR. LEOPOLD: Thank you very much. Can you read Question No. 6, please?

DR. CLUPPER: The applicant has proposed the following indication for use: The intended use of the Esteem is to alleviate hearing loss in adults by replicating the ossicular chain and providing additional gain. The Esteem is intended for patients with hearing loss that meet the following criteria: 18 years of age or older, stable sensorineural hearing loss, mild to severe hearing loss, speech discrimination test score greater than or equal to 40%, normally functioning Eustachian tube, normal middle ear anatomy, and adequate space for Esteem implant determine via CT scan.

a. The primary effectiveness endpoint data is available for 3 subjects with mild hearing loss, 41 with moderate loss, and 10 with severe loss. Please comment on the proposed Indications for Use

for this device for each category of hearing loss (mild, moderate, and severe). Are these data sufficient to support safety and effectiveness for each of these categories?

b. Do you have any additional recommendations regarding the proposed Indications for Use?

DR. LEOPOLD: So let's go around the table again. This is working.

(Laugher.)

DR. LEOPOLD: And I guess I want to know given the data we have, are the data -- are these items, these indications sufficient or would you like to add more. I guess those are the two questions I'd like to know. Dr. Norton, I'm going to give you the opportunity to start this time. And I guess if you want to add more, please tell us what they are.

DR. NORTON: Well, I think the indications are misleading, as we have talked about before, because a mild hearing loss across the board would not be appropriate. I'm not sure a rising hearing loss would be appropriate, and I'm not sure a profound loss would be appropriate. They have not separated out those patients with thresholds 70 to 90 from those 70 to 100. But certainly, those with

steeply sloping losses are in a different category than patients with flat losses. So the configuration must be specified and further analysis done.

DR. LEOPOLD: Okay. And Dr. Sininger?

DR. SININGER: Yeah. My only concern is with the term mild hearing loss. I think if they used moderate to severe hearing loss, that by most definitions of moderate loss, those high frequency losses would have an average loss that's in the moderate range. And so I don't think there's been enough data on the milds to demonstrate effectiveness. But other than that, I would just change that to moderate to severe.

DR. LEOPOLD: Okay. Dr. Cheung?

DR. CHEUNG: I would add that with the benefit of some of the results from the study, for instance, fibrosis, and whether it's really a single event or a long-term event, you can start to develop some hypotheses and then from that estimate sample size and the longevity of your follow-up to put that issue at a rest or continue to study it.

DR. LEOPOLD: Do you want to add any?

DR. CHEUNG: No.

DR. LEOPOLD: Dr. Hall?

DR. HALL: My only concern was the mild.

DR. LEOPOLD: Okay. Dr. Cueva?

DR. CUEVA: The same, just a clarification on that mild category to include the severe slope.

DR. LEOPOLD: Dr. Hirsch?

DR. HIRSCH: A few comments. One is that it just should be really clarified that this represents -- although you use the word mild, it should be severe sensorineural hearing loss. So in other words, you cannot include mixed loss or conductive. So that comes into your exclusions, but either this has to be mentioned as a positive, in other words, there's no mixed hearing loss or conductive component, or in the exclusion it has to be added.

I would add, as was brought out by Dr. Sininger, that this be assured that these are recorded test results in terms of preop and postop, so the 40% should say recorded.

And the other thing that I mentioned earlier was that, as part of the inclusion criteria, that a normal tympanic membrane be verified.

DR. LEOPOLD: Dr. Hood?

DR. HOOD: I agree. I have concerns about the lack of data related to mild hearing loss and rising hearing loss.

DR. LEOPOLD: Dr. Ishiyama?

DR. ISHIYAMA: I have the same concern. And one additional point is G00321 study said the inclusion criteria was speech recognition score greater than 60%. But with this current study, you dropped to 40%, and I wasn't too clear as to why it happened.

DR. LEOPOLD: I believe they commented that it was due to better efficiency of the machine and their good success in that first study.

Dr. Kenna?

DR. KENNA: Yeah. I agree with all the prior people. I'm concerned about the mild losses. I also wonder -- this doesn't specify bilateral hearing loss, but it seems to me that the current indication would only be for bilateral hearing loss.

DR. LEOPOLD: Dr. Kileny?

DR. KILENY: I echo the concern about the mild hearing loss. I'm also slightly concerned about the severe plus range, not because some patients haven't done quite well, but the comparison, the baseline, may not be completely relevant, and when you get over the 90 dB or maybe even below that, you're in cochlear implant territory. Cochlear implant criteria are based on sentence tests and not

word recognition, like in sentences. So then the comparison becomes very difficult as to at what point do you recommend an implant, at what point does this stop being effective. So I'm a little concerned about the baseline or the basis for comparison.

DR. LEOPOLD: Dr. Lalwani?

DR. LALWANI: My concerns are at mild and profound.

DR. LEOPOLD: Okay.

DR. ROSOWSKI: The same.

DR. LEOPOLD: Okay. Dr. Sie?

DR. SIE: The same about the degree of hearing loss and the bilaterality. I'm not sure exactly what constitutes the definition of stable sensorineural loss in adults. And I don't know if we want to clarify that. The other issue that I wonder about is whether we want to include a hearing aid trial for these folks. It doesn't say that they failed a hearing aid trial, and that may be something to consider, given the ramifications of a surgical intervention.

DR. LEOPOLD: Mr. Timlin?

MR. TIMLIN: I don't have any specific comment, but I would like to reiterate that in the proposed labeling, they talk about a normal tympanic

membrane, so that's one of the questions that's come up. Then also, they talk about a mild to severe hearing loss that falls within the indicated audiometric range, then provide a graph there. So I just hope that provides some clarification. And I think what I'm hearing is that, you know, some of the labeling might be able to be modified to make this approvable.

DR. LEOPOLD: Dr. Portis?

DR. PORTIS: I think a concern I had that could probably be answered by a Panel member, assuming a person is going to go bilateral and if their hearing loss progresses --

DR. LEOPOLD: I believe this is only for unilateral --

DR. PORTIS: This is only for unilateral?

DR. LEOPOLD: Yes.

DR. PORTIS: Well, even for unilateral, would that create any kind of medical complication for, then, if the person needs a cochlear implant?

DR. EYDELMAN: If I can just interject. Actually, the indications do not specify whether it's for unilateral or bilateral.

DR. LEOPOLD: Okay.

DR. PORTIS: So, then, from a medical

perspective, I would just wonder does that create any complications if this is no longer an effective treatment because the hearing loss progresses and the person would then need a cochlear implant? Does that create any type of medical complication?

DR. LEOPOLD: Dr. Lonsbury-Martin?

DR. LONSBURY-MARTIN: I agree with the eliminate the mild hearing loss, and I'd like the normal tympanic membrane mentioned.

DR. LEOPOLD: Dr. Connor?

DR. CONNOR: I agree with the questions about the demonstration -- effect in mild patients and also improved labeling on whether it's necessary to have bilateral hearing loss to be eligible.

DR. LEOPOLD: Dr. Eydelman, is this sufficient?

DR. EYDELMAN: Yes. Thank you.

DR. LEOPOLD: Can you read the next question, No. 7, for us?

DR. CLUPPER: Do the pivotal study data support reasonable assurance of safety and effectiveness for the Esteem system? In your discussion, please consider:

This device requires disruption of a normal intact ossicular chain and partial resection of the

incus. In cases when the device may need to be explanted, ossicular chain reconstruction surgery is required to restore hearing.

The device battery must be replaced in an outpatient surgical procedure following approximately 4.5 years of 24/7 device activity.

DR. LEOPOLD: So the questions we're asked to comment on here are does this hearing improvement device, is it appropriate in a safety manner and effectiveness manner to interrupt the ossicular chain with a surgical procedure and to have to change a batter every four to eight years, or whatever it is?

Dr. Kenna, you want to start, and we're going to go in the other direction.

DR. KENNA: Just if I start with the battery question first, it does say in the labeling, in the brochure that's included in their information, four and a half years. But several of the people who gave information today, patients said batteries were replaced within three years. So we might need to modify the labeling until the better batteries become available.

UNIDENTIFIED SPEAKER: That was the first study.

DR. KENNA: Right. But I'm just commenting

that, you know, anyway --

DR. LEOPOLD: And, in fact, if they use it a lot with high volume --

DR. KENNA: And they use it a lot.

DR. LEOPOLD: You even indicated that it would be 2 point something years. So --

DR. KENNA: Right.

MR. SPEARMAN: That was a different thing on the first battery --

DR. LEOPOLD: Okay.

MR. SPEARMAN: The Esteem 1, the 0203.

DR. LEOPOLD: Okay.

UNIDENTIFIED SPEAKER: But with the current battery, do you have four and a half year data?

DR. LEOPOLD: Can you come to the microphone?

MR. SPEARMAN: The same data we did to establish the two and a half to five years life of laboratory testing, the power consumption of the processor, the circuit, the input noise, was done with the new device. The new device draws much lower mAs in both the active and the quiescent state. And the battery was increased by 20% in size within the canister. So we have laboratory data to adequately demonstrate that these numbers -- these are worse

case scenarios at four and a half years.

DR. KENNA: Right. But you don't have four and a half year data yet, so I'm just commenting. That's all.

DR. LEOPOLD: Okay.

DR. KENNA: And the other question I guess you asked was intact ossicular chain. I think it would depend on the final recommendations for effectiveness whether it's worth disrupting the ossicular chain.

DR. LEOPOLD: Okay. Dr. Ishiyama?

DR. ISHIYAMA: I have no concern.

DR. LEOPOLD: Dr. Hood?

DR. HOOD: I agree.

DR. LEOPOLD: With no concerns?

DR. HOOD: Yes.

DR. LEOPOLD: Okay. Dr. Elliot -- Hirsch?

DR. HIRSCH: Again, if it's deemed to be effective and safe in the first go around and patients are aware that they may have a 5 plus percent chance that it won't work and either it has to be revised or if revision is unsuccessful that they may have to undergo OCR, I still think that it can be considered safe.

DR. LEOPOLD: Okay. And OCR would be

ossicular chain reconstruction?

DR. HIRSCH: Yes. Sorry.

DR. LEOPOLD: Dr. Kenna -- Cueva. Excuse me.

DR. CUEVA: Cueva. That's correct. I reiterate Dr. Hirsch's statement.

DR. LEOPOLD: Okay. Dr. Hall?

DR. HALL: It sounds good to me.

DR. LEOPOLD: Okay. Dr. Cheung?

DR. CHEUNG: In the reconstructed ears, were the word recognition scores comparable?

DR. KRAUS: Dr. Kraus. Yes. Actually, in three of them, the word recognition scores were either comparable or higher. One of them, the very first patient --

DR. CHEUNG: Thank you. I have no concern.

DR. KRAUS: Okay.

DR. LEOPOLD: Okay. Dr. Sininger?

DR. SININGER: So we're supposed to be discussing safety and effectiveness?

DR. LEOPOLD: Yeah. Can you click on? Yes, safety and effectiveness. In other words, is it worth -- in light of the fact that this needs -- we need to surgically operate on the ossicles and change a battery every four or more years, is it worth doing

this? Does the safety and effectiveness justify that?

DR. SININGER: I'm still concerned about the effectiveness.

DR. LEOPOLD: Okay. Dr. Norton?

DR. NORTON: I'm still concerned about the effectiveness.

DR. LEOPOLD: Got it. Dr. Connor?

DR. CONNOR: I agree with what Dr. Hirsch said.

DR. LEOPOLD: That you have no concerns except for -- got it. Okay. Dr. Lonsbury-Martin?

DR. LONSBURY-MARTIN: Ditto.

DR. LEOPOLD: With Dr. Hirsch?

DR. LONSBURY-MARTIN: Right. With Dr. Hirsch.

DR. LEOPOLD: Got it. Dr. Portis?

DR. PORTIS: I also feel the pressure to -- no, I agree with Dr. Hirsch. As long as the labeling provides clear informed consent, no concerns.

DR. LEOPOLD: Okay. Mr. Timlin?

MR. TIMLIN: I'm not sure if I'm really qualified to say, and you tell me whether as an industry rep whether this is even appropriate for me to answer.

DR. LEOPOLD: No.

(Laughter.)

DR. LEOPOLD: Dr. Sie?

DR. SIE: I think it's reasonably safe. I'm not completely convinced about effectiveness.

DR. LEOPOLD: Dr. Rosowski --

DR. EYDELMAN: If I can --

DR. LEOPOLD: Oh, sorry.

DR. EYDELMAN: Before you finish going around, I guess we wanted to hear one yes or no, whether it's reasonably safe and effective.

UNIDENTIFIED SPEAKER: Barely.

DR. LEOPOLD: It seems the Panel is unwilling to do that. Dr. Rosowski?

DR. ROSOWSKI: So I was going to echo that I think it's -- safety is okay, particularly if it's labeled as such, right? And, you know, it's all going to depend upon the labeling, that people are going to need to know this happens, and I also am on the fence as far as effectiveness. I'm sorry.

DR. LEOPOLD: Okay. Dr. Lalwani?

DR. LALWANI: Yes on safety. Question mark by effectiveness.

DR. LEOPOLD: Dr. Kileny?

DR. KILENY: Same.

DR. LEOPOLD: Dr. Eydelman, are you potentially happy?

(Laughter.)

DR. EYDELMAN: What --

DR. LEOPOLD: Yes or no?

DR. EYDELMAN: I guess you're going to revisit this when you vote, but I'm still not quite clear on the Panel's consensus.

DR. LEOPOLD: Okay. Can you read Question No. 8 for us?

DR. CLUPPER: The applicant has proposed a five-year continuation of the current pivotal study as a Post-Approval Study (PAS). No specific sample size, objectives or study hypothesis have been specified.

a. Given the currently available safety and effectiveness data, and if this device is approved, is a post-approval study recommended?

b. If a post-approval study is recommended, is the applicant's proposal of a five-year continuation of the current pivotal study appropriate?

c. Is a post-approval study of newly enrolled patients to evaluate the performance of the device under conditions of general use warranted?

d. If a post-approval study is recommended, what do you recommend for the following post-approval elements:

The objectives.

Clinical endpoints that address: firstly, the long-term effectiveness of this device to aid sensorineural hearing loss; also, the safety issues related to device implant once used in a larger and more diverse patient population; the different safety issues potentially associated with patients' clinical and socio-demographic characteristics (for example, age, gender, level of education, socio-economic status, etc.); the safety issues related to devices implanted by a group of newly trained surgeons (that is, surgeons with no previous experience implanting the Esteem system); and given the observed site variability in the pre-market pivotal study, would you recommend masking or blinding the audiologists conducting the post-implant evaluations?

Duration of follow-up of study subjects that address: the potential long-term effects of continuous vibration of the ossicles (for example, necrosis) with the Esteem system; and also the durability of the connection of the Sensor to incus/malleus, and the Driver to stapes, with the

1 EnvoyCem cement.
2 And, finally, any other specific issues you
3 would like to be addressed in the post-approval
4 study.
5 DR. LEOPOLD: Thank you.
6 DR. EYDELMAN: Dr. Leopold, before you go
7 around, perhaps I could ask that the Panel addresses
8 (a) before you proceed?
9 DR. LEOPOLD: Yes. I was going to ask
10 Dr. Connor if he would -- from your biostatistical
11 standpoint, give us sort of a framework as to what
12 you would suggest for a theoretical post study.
13 DR. CONNOR: Thank you for this
14 opportunity.
15 DR. LEOPOLD: You're welcome.
16 DR. CONNOR: So, first, I would say
17 definitely if this device is approved, I would like
18 to see more data on both the current cohort of
19 patients and future patients. For the current
20 cohort, you suggested following 50%. I would say
21 that it's important for that 50% to be a truly random
22 50%, meaning I would like to see the patient, you
23 know, in whom the device was removed or patients with
24 poor outcomes as well as patients who are doing well
25 because I think it's important that we understand

how, perhaps, you know, the next technology that comes along works in patients who have had this device or still have this device to make sure that it isn't, you know -- given everything we're hearing about, you know, was the current hearing aid optimized, and these sorts of things, I think, you know, a subsequent study, if this approved, with a more stringent criteria for getting, you know, the best possible outcomes with the hearing aid in would be warranted so we can truly judge the effect of this therapy or so that that can be applied, you know, potentially to the label once that, you know, better data is available.

DR. LEOPOLD: Okay. We were asked to consider Part (a) first. Any sort of general -- maybe we don't have to go around. Any sort of general discussion on Part (a), that is, if this device is approved, do we want a PAS. Is this something that we can generally say yes?

UNIDENTIFIED SPEAKERS: Yes.

DR. LEOPOLD: Okay. That's down. Let's do then Part (b). The recommendation from Dr. Connor is that if it's a recommended, the proposal would be to continue the current study at least for 50%? I think that number could be worked out. Everyone is in

agreement with that, that if it's approved, a subsequent study or continuing study on the current people is a good idea?

UNIDENTIFIED SPEAKER: Why would it not be 100%?

UNIDENTIFIED SPEAKER: Why not 100%, right.

DR. LEOPOLD: I will let the statisticians work that out, but a study on the current people is a good idea? Okay.

DR. KILENY: I would just say a statistically significant follow-up, so then 50%, 75%, 100%, whatever.

DR. LEOPOLD: Okay. Part (c). If --

DR. EYDELMAN: Part (b) was the length of the follow-up.

DR. LEOPOLD: And a five-year, is that an appropriate length of time to learn what we need to learn? I'm seeing a majority yes nods.

And Part (c), is a study on the newly enrolled patients appropriate?

UNIDENTIFIED SPEAKER: Yes.

UNIDENTIFIED SPEAKER: Absolutely.

DR. LEOPOLD: All of them, some of them, a statistical percentage? How do we want to say that? Dr. Lalwani?

1 DR. LALWANI: Anil Lalwani, New York. It'd
2 be ideal if there was a data sheet put together so
3 that every patient that underwent this procedure had
4 some baseline material that was submitted as part of
5 their procedure and --
6 DR. LEOPOLD: Some type of patient registry
7 thing?
8 DR. LALWANI: Right.
9 DR. LEOPOLD: Yes. Dr. Connor?
10 DR. CONNOR: Right. And to answer
11 questions like this, my preference is for, you know,
12 that we would articulate the concerns that we still
13 have that need to be addressed in a post-market study
14 and then let, you know, FDA and FDA statisticians
15 identify what that correct number is. So, you know,
16 if we say everyone, and this is a huge success, you
17 know, we don't really need everyone. But, you know,
18 if we say yes and, you know, it gets used
19 infrequently, then maybe we need all those infrequent
20 patients. So I think letting the FDA statisticians
21 identify the sample size is appropriate.
22 DR. LEOPOLD: Moving on to Part (d) of this
23 Question 8, if this post study is recommended, there
24 is a whole list of points. Can you each look at
25 those and determine if there are additional items

you'd like to add, if there are items there that are superfluous. Dr. Kenna?

DR. KENNA: I think one of the things we brought up is that as the study was initially planned, I think PTA was the only primary outcome, but meanwhile, there has been a lot of SRT and WRS and other data. So going forward to include other audiologic measures, I think, would be very, very important from the get-go rather than post hoc.

DR. LEOPOLD: Yes. Dr. Sininger?

DR. SININGER: Yeah. I'd like to recommend, as was stated, that in the newly enrolled patients, that there be an acceptable standard for a hearing aid fitting that is supplied to all the patients before they're enrolled in the study, something like the National Acoustics Laboratory results rather than the manufacturer's target so that you get this moving target. So pick one target that's acceptable, and give us some assurance that those patients are fit to those targets and for at least three months of time so they get acclimatized to the hearing aid, and then start them in the study.

DR. LEOPOLD: And thanks for giving us an example of that. Yes. Dr. Hirsch?

DR. HIRSCH: Given the earlier concerns

about safety and efficacy that was raised about hearing outcomes and facial nerve, one of the issues that's raised is what's the safety issues regarding new surgeons. So I think this has been done in the best of hands by you three from this pivotal study and probably the earlier one. So I mean, nobody has more experience in the United States than you three. Yet, you're going to open it up to new surgeons. So I can't emphasize enough that these outcomes have to be very carefully monitored both for hearing and facial nerve plus/minus on the tinnitus and the chorda tympani because it may be inherent with the procedure. But facial nerve and hearing are critical.

DR. EYDELMAN: I just wanted to remind the Panel that, in light of your comment, approvability -- in order for something to be approvable, it has to be found reasonably safe and effective based on the data up to date. So the PAS will not -- the post-approval study is not in lieu of having data which will help you make a decision about the device going to market today.

DR. LEOPOLD: Do you have enough answer to Question No. 8?

DR. SOLDANI: Which part of the question?

DR. LEOPOLD: The whole thing.

DR. EYDELMAN: All of it, Federic --

DR. SOLDANI: I would say no because actually many of this -- I mean, we don't have enough data currently, and actually many of these questions --

DR. LEOPOLD: No. My question is do we need to talk about No. 8 anymore?

DR. SOLDANI: Well, what about -- okay. I mean, what about the masking or blinding of the raters, of the audiologists because, I mean, for instance, while it has been an emphasized the issue of site variability --

DR. LEOPOLD: Let me handle that in a minute, okay?

DR. SOLDANI: Um-hum.

DR. LEOPOLD: Dr. Kileny, you're saying no? Paul Kileny. I don't believe you can do that because they will see the incision or the size of the incision.

DR. LEOPOLD: Dr. Kenna agrees. Blinding, rating the audiologist? Anybody from this side?

Dr. Hall?

DR. HALL: So what if an audiologist were brought in just to do the test, and the patient was

put into the booth, and the testing audiologist was not really aware of who was in that booth and just did the test? Would that be sufficient for a blinding study?

DR. LEOPOLD: I suppose if their hair was long, it might work.

(Laughter.)

DR. LEOPOLD: Because you're going to be putting on ear muffs and --

UNIDENTIFIED SPEAKER: Somebody else --

ARBITRATOR GOLDSTEIN: Yeah. Dr. Norton?

DR. NORTON: I would suggest that you have a strict standardized protocol for audiological evaluation and fitting of these patients, beginning with the pre-implant hearing aid and post-implant testing so we don't have individual audiologists deciding what is the minimum level they're going to test at.

DR. LEOPOLD: So given that you have the protocols, do we need to blind or somehow control the identity of these patients to the tester?

DR. NORTON: No.

DR. LEOPOLD: Dr. Sininger?

DR. SININGER: There's a lot of ways to do this. You can record their responses. The whole

issue is, is the person making a judgment about whether or not they repeated a word correctly. They could record those and have them rescored by, you know, someone who is blinded even if they knew what the situation was. But there are ways in which the company could justify that these scores were not being influenced by the scoring of the audiologist who would like to see a good outcome.

DR. LEOPOLD: Any other parts of Question 8 that are a concern?

DR. EYDELMAN: Thank you.

DR. LEOPOLD: Dr. Eydelman, you're happy? I think we've earned our break, and I'd like to make it a short one. If we could just take a ten-minute break, it's now 20 after 4. If we can begin our deliberations for voting -- for our summaries at 4:30, we'll see you back then.

(Off the record at 4:20 p.m.)

(On the record at 4:30 p.m.)

DR. LEOPOLD: I'd like to resume our meeting now. Dr. Clupper or Dr. Eydelman, do you have any comments from the FDA side?

DR. EYDELMAN: No. I just wanted to thank the Panel, and we look forward to your vote.

DR. LEOPOLD: Thank you.

DR. EYDELMAN: As a yes or no.

(Laughter.)

DR. LEOPOLD: Is there any further comment or clarification from the Sponsor? Any final comments?

MR. SPEARMAN: Just briefly. You know, when we first started developing the Esteem, and just a quick thing here, we looked at all the numbers like any manufacturer would and looked at the numbers of patients affected with hearing loss. We all know these numbers, 30 million people with hearing loss, 25 million with sensorineural loss, of which 6 million people have actually made the decision to purchase hearing aids and treat their hearing loss. And of those, we find that 17% of them don't even wear their hearing aids, 21% are dissatisfied, and countless others use them because it was the best they could get.

You know, in this study, we're having to compare to hearing aids. That's just the way the metrics work in these middle ear devices. We're not saying hearing aids are bad. We're just saying that the Esteem has a great technology. And when we looked at this, what we could bring to the industry, we really saw some very unique features, which even

step outside of just the audiometric metrics in terms of the quality of life, the total implantability, the patients being able to feel normal, and we really look forward to bringing that to the industry, knowing we had some abilities for improved gain, speech discrimination. That's the kind of things we're talking about here today.

But I must say the one thing that amazed us most during the study, and I think I speak on behalf of all the Envoy associates and, I should say, the clinical investigators, their audiologists, was the impact that this had on individuals and how it changed their lives almost to a T on every patient. And that's the kind of thing that's not really captured here.

For that, we want to thank the patients who made the trip here today just to share their experiences with us because that really is ultimately what this ultimately becomes, as a patient's choice to be able to have a choice for something that they feel is optimum for themselves.

On that note, too, we'd like to thank the Panel. This is quite a few more people than we expected here today, and we think it's fantastic that this many people actually made the trip here to --

1 for these deliberations. This has certainly been
2 extremely helpful, we think, in formulating the
3 labeling claims, which will give patients realistic
4 expectations of what they can expect with this
5 device.
6 And, finally, we'd like to thank the
7 Agency. They've been involved in this technology for
8 almost as long as we have, intimately for the last
9 five years during these clinical studies. And it's
10 been a lot of hard work on both sides to bring it
11 here today, to put it out here so that there could be
12 spirited discussions. And we appreciate the work
13 that they've done, and thank you again very much.
14 Thank you.
15 DR. LEOPOLD: Thank you. Before we move to
16 our voting, I would like to ask Dr. Portis, do you
17 have any -- as the consumer representative, do you
18 have any final comments to make about this product
19 and our deliberations?
20 DR. PORTIS: Well, the only thing I would
21 say would be, coming from my perspective, I was
22 executive director of a hearing health consumer
23 advocacy group for five years and traveled around the
24 country meeting a lot of consumers. And I know that
25 frustration with hearing aids, the care and the use

of hearing aids does suggest that there needs to be another alternative, particularly for people with moderate loss.

DR. LEOPOLD: Mr. Timlin, any comments?

MR. TIMLIN: No.

DR. LEOPOLD: Okay. Thank you. We're now going to move on for a vote. Dr. Kane, would you like to read your part?

DR. KANE: Before I read my part, I want to remind everybody that they should keep in mind that the discussion to conduct a post-approval study does not decrease the threshold of evidence required to find the device approvable.

The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable, publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

The definition for safety comes from 21 C.F.R. Part 860.7, Paragraph (d)(1). It reads as follows: There is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from the use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

The definition for effectiveness comes from 21 C.F.R. Part 860.7, Paragraph (e)(1), and it reads as follows: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The definition of valid scientific evidence comes from 21 C.F.R. Part 860.7, Paragraph (c)(2): Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies in objective trials without matched controls, well-documented case histories conducted by

qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Your recommendation options for the vote are as follows:

Approval, and that is if there are no conditions attached.

Approvable with conditions is your second choice. The Panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel.

The third choice is not approvable. The Panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or the data do not provide a

reasonable assurance that the device is effective under the conditions of these prescribed, recommended, or suggested in the proposed labeling.

Following the voting, Dr. Leopold will ask each Panel member to present a brief statement outlining the reason for his or her vote.

Dr. Leopold?

DR. LEOPOLD: Panel members, please refer to the voting procedures chart in your folder. It's this multi-colored one that we've seen before. We will be using this for our voting procedures. Are there any questions from the Panel about the voting process before we begin?

Seeing none, I would be willing to entertain a motion for approvability, and this would be a motion for either approval, approval with conditions, or not approval.

DR. CUEVA: I forward a motion for approval with conditions. Roberto Cueva.

DR. LEOPOLD: And this is Dr. Cueva?

DR. CUEVA: Yes.

DR. LEOPOLD: And we have a second?

DR. CHEUNG: I second.

DR. LEOPOLD: Okay. It has been moved and seconded that the -- so the conditions of approval

are amendments to the main motion of conditional approval. Approval conditions should be as specific as possible. It has been moved that the PMA be approved with conditions. Refer to the yellow portion of your voting procedure chart in your folder.

Remember, we are voting on the conditions of approval for this PMA application as it stands. We must first recommend a condition. The condition must be seconded, and there will be a discussion regarding the recommended condition as it was worded. There will then be a vote on that condition. If that condition is approved, it will be the first condition to the main motion, approvable with conditions. We will then move on to a new condition and repeat the process until there are no new conditions.

Finally, we will vote on the motion to approve the Esteem Totally Implantable Hearing System with all of the conditions we have just approved by a majority vote.

Does anyone wish to recommend a condition? Dr. Kileny?

DR. KILENY: Paul Kileny. I'd move that we introduce a condition that the indications would include moderate to severe hearing loss.

DR. LEOPOLD: Is there a second?

DR. SININGER: Second.

DR. LEOPOLD: Dr. Sininger seconds that. Any discussion on this first condition? Seeing none, we will now vote on the condition of including moderate to severe hearing loss. All in favor of this condition raise your hand for this. And, now, with your hands up, we need to go around so the record will have a note of this. We need to go around the room and just -- okay. It's unanimous, so we don't need to worry about it. Thank you. And there were no abstentions.

Okay. Is there a motion for another condition?

DR. LEOPOLD: Dr. Cueva?

DR. CUEVA: Dr. Cueva. Motion for changing in the labeling of the patient materials specifically relating to the incidence of facial nerve injury. The current patient materials indicate a 0.5% rate. I think that ought to be given a range of 1 to 5% based on some of the data that was presented by the Sponsor in regards to cochlear implant as an analogous procedure.

In addition, I would add that they should also quote a 15 to 20% incidence of taste disturbance

so patients are fully aware that they may very well have that and then maybe presenting some of that APHAB data that 20% of patients felt that their hearing aid performed better than the new device so they know going in that that may not -- you know, have about a 20% chance that it may not work out for them.

DR. LEOPOLD: So just to clarify, we got Condition No. 2, and would you read back what it is?

DR. HIRSCH: The labeling for the patient information related to the rate of facial nerve injury should indicate 1 to 5%. Taste disturbance should indicate 15 to 20%, and that prior subjects, 15 or 20%, based on APHAB results, did not like their implant as well as they liked their hearing aid.

DR. LEOPOLD: Is there a second? Yes?

DR. EYDELMAN: If I can just interject. You can just -- you don't need to specify a specific percentage. It can just say that these need to be in the labeling, and then we can work with the Sponsor to make sure that the appropriate numbers show up.

DR. LEOPOLD: Okay. So we will modify that to indicate facial nerve, taste -- and how do we say APHAB -- dissatisfaction with performance compared to a hearing aid.

DR. SIE: Can I also add that on Page 15, I think just all the discussion and listing of potential adverse events is very redundant and kind of scattered, and it needs to be tightened up, I think. Tinnitus is mentioned three times here in different spots.

DR. LEOPOLD: That'll be a recommendation that the FDA I think can handle. So is there a second?

UNIDENTIFIED SPEAKER: There's a second.

DR. LEOPOLD: So there's a second to the second motion? Thank you -- the second condition. Any other further discussion on this second condition? I would like to suggest that in the wording, that the taste concern is something that resolves much of the time, so that it may not be 10 or 20% long-term. Any other taste concern or facial nerve concerns?

(No response.)

DR. LEOPOLD: All in favor of adding No. 2? It looks unanimous to me. Okay. None against or no abstentions. So that's approved.

Is there a motion for a third condition? Dr. Kenna?

DR. KENNA: I don't know if we assumed it,

but the indication should be a bilateral sensorineural hearing loss. Currently, I just think it says sensorineural hearing loss. So bilateral moderate to severe sensorineural hearing loss.

DR. LEOPOLD: Second? Second by Dr. Norton. Discussion?

(No response.)

DR. LEOPOLD: All in favor? Dr. Cheung, you're not in favor of that?

DR. CHEUNG: No. I'm not in favor.

DR. LEOPOLD: Okay. So were you the only one not with a hand up?

UNIDENTIFIED SPEAKER: No.

DR. LEOPOLD: So we need to go around the room, and so all those in favor put their hands up, and we're just going to have you read your names as we go down the line.

DR. SIE: Kathy Sie, in favor.

DR. LEOPOLD: I guess as we're going in the line, we can probably say yes or no. Go ahead.

DR. ROSOWSKI: John Rosowski, not.

DR. LEOPOLD: John Rosowski is not in favor.

DR. ROSOWSKI: Thank you.

DR. LALWANI: Anil Lalwani, not in favor.

DR. KILENY: Paul Kileny, in favor.

DR. KENNA: Marly Kenna, in favor.

DR. ISHIYAMA: Akira Ishiyama, in favor.

DR. HOOD: Linda Hood, in favor.

DR. HIRSCH: Barry Hirsch, in favor.

DR. CUEVA: Bob Cueva, not in favor.

DR. HALL: Joe Hall, in favor.

DR. CHEUNG: Steven Cheung, not in favor.

DR. SININGER: Yvonne Sininger, in favor.

DR. NORTON: Susan Norton, in favor.

DR. CONNOR: Jason Connor in favor.

DR. LONSBURY-MARTIN: Brenda Lonsbury-Martin, in favor.

DR. LEOPOLD: So that passed 11 to 4. Okay.

Is there a motion for another condition? Dr. Cheung?

DR. CHEUNG: I move that the indications be restricted to one device per head, unilateral, not bilateral.

DR. LEOPOLD: Are we allowed to do that?

DR. EYDELMAN: Yeah.

DR. LEOPOLD: Okay. Do I have a second for that?

DR. ROSOWSKI: I'll second it.

DR. LEOPOLD: Dr. Rosowski? Any discussion?

DR. HIRSCH: Just the concern, I gather is that with bilateral implantation, the potential loss of the chorda tympani nerve raises the level of concern?

DR. CHEUNG: That's correct. I think we need more -- if this goes forward and approved with contingencies, that we really actually need to learn more about this chorda tympani nerve issue and whether bilateral chorda tympani nerve loss would be well tolerated.

DR. LEOPOLD: And just as a point of surgical practice, during stapedectomy, it is often routine to cut the chorda tympani nerve, and there are lots of people running around who have got bilateral stapes surgeries who have had both of their chordas cut. So this is actually a pretty common procedure -- just as a comment.

DR. CUEVA: Comment. I've got a lot of patients with bilateral canal -- mastoids have no chorda tympanis, and quite frankly, they don't really notice much taste disturbance themselves. I think if you inform the patient and allow them to make that decision, then they can go in with their eyes open

because really just the fact -- sweet, salt, bitter and sour, you have most of the other aspects of flavor that many patients really don't miss that.

DR. CHEUNG: Living in Northern California, everyone seems to know a lot about wine, and whenever I talk about any taste disturbance, it's a major consideration.

DR. CUEVA: Those patients may choose not to do it, then.

DR. LEOPOLD: We need a second on this motion. Dr. Kenna? Any other discussion?

(No response.)

DR. LEOPOLD: All in favor of this motion? I'm seeing one, two, three -- let's go around the room. And we'll start on this side. Dr. Lonsbury-Martin, do you want to start?

DR. LONSBURY-MARTIN: Not in favor.

DR. CONNOR: Connor, opposed.

DR. LEOPOLD: Dr. Norton?

DR. NORTON: So what's the motion?

DR. LEOPOLD: The motion is that we limit this to only one side; is that correct?

DR. CONNOR: Can I clarify if this is one at a time or one ever?

DR. LEOPOLD: I think it's one at a time

ever. Is that your understanding, Dr. Cheung?

(Laughter.)

DR. CHEUNG: One side per head at this time.

DR. CONNOR: So the patient could have two, just not two at once?

DR. LEOPOLD: No. I believe the intent of Dr. Cheung's comment is that he wants only unilateral --

DR. CONNOR: Okay. So the patients here who is looking forward to the other ear would never have that done under this label?

DR. LEOPOLD: Correct.

DR. CONNOR: Okay. Thank you. So I remain opposed.

DR. LEOPOLD: Let's start the voting again. Dr. Lonsbury-Martin?

DR. LONSBURY-MARTIN: Opposed.

DR. CONNOR: Opposed.

DR. NORTON: In favor.

DR. SININGER: Opposed.

DR. LEOPOLD: Can you say your names --

DR. SININGER: Sininger is opposed.

DR. LEOPOLD: And Norton was?

DR. NORTON: In favor.

DR. LEOPOLD: Okay. Cheung?

DR. CHEUNG: In favor.

DR. HALL: Hall, opposed.

DR. CUEVA: Cueva, opposed.

DR. HIRSCH: Opposed.

DR. LEOPOLD: Dr. Hirsch?

DR. HIRSCH: Opposed.

DR. LEOPOLD: Hirsch, opposed.

DR. HOOD: Hood, opposed.

DR. ISHIYAMA: In favor until more data is available.

DR. LEOPOLD: Ishiyama.

DR. KENNA: Marly Kenna, in favor.

DR. KILENY: Kileny, opposed.

DR. LALWANI: Lalwani, opposed.

DR. ROSOWSKI: Rosowski, opposed.

DR. SIE: Sie, in favor.

DR. LEOPOLD: And it failed, 10 to 6. Are there additional conditions that would like to be listed? Dr. Rosowski?

DR. ROSOWSKI: I'd like to place the condition that in the advertising or the labeling for this issue, that the claim that these are better than present hearing aids -- I don't mind -- as far as effectiveness goes, I'm perfectly happy with them

claiming to be as effective as present hearing aids. But as to whether they're better or not -- so my motion is that they remove from their advertising the claim that their device is better than hearing aids and maybe has a better SRT or whatever, but better thresholds --

DR. EYDELMAN: Let's limit the comments to the labeling, please.

DR. LEOPOLD: Yeah. In terms of using the word better, you have to be -- I think you have to say better something, you know, better length, better color, better something because better is -- you just can't give a blanket statement like that. So you're saying better SRT, but that's actually not true in the majority of patients, as I understand the data.

DR. ROSOWSKI: Well, I guess my concern is I don't necessarily -- until the question of the --

DR. LEOPOLD: Can we say it's not always better?

(Laughter.)

DR. ROSOWSKI: Yes. What I'm really interested in is the fact that there is some variability in --

DR. LEOPOLD: Dr. Eydelman, can you help us with this?

DR. EYDELMAN: Yes. We usually in the labeling present the data as it appeared in the trial. So it will actually reflect the actual percentage rather than making any conclusive statement.

DR. LEOPOLD: Does that make you happy or tolerable?

DR. ROSOWSKI: Yes.

DR. LEOPOLD: Thank you. Any other conditions?

DR. CONNOR: -- second it?

DR. LEOPOLD: It was withdrawn.

DR. SIE: I have a condition.

DR. LEOPOLD: Dr. Sie?

DR. SIE: To require a hearing aid trial as part of candidacy.

DR. LEOPOLD: Okay. Do we have a second for requiring a hearing aid trial as part of candidacy?

DR. LONSBURY-MARTIN: Second.

DR. LEOPOLD: Dr. Lonsbury-Martin seconds it. Discussion? Dr. Sininger, you have something on the tip of your tongue?

DR. SININGER: Yeah. I think it would need to be specified what a hearing aid trial means. You

know, there'd have to be some language as to, you know, what constitutes an appropriate hearing aid trial.

DR. LEOPOLD: And can the FDA handle a language about what a hearing aid trial would constitute?

DR. EYDELMAN: Yes.

DR. LEOPOLD: Given that wording, any other discussion? Yes, Dr. Lalwani?

DR. LALWANI: So I mean, I see this as sort of as an alternative to hearing aid, not necessarily something that is equivalent to hearing aid or something, so I don't personally see why somebody has to undergo a hearing aid trial to decide whether they want this particular device.

DR. LEOPOLD: So you're saying that somebody who comes -- who has a de novo hearing loss who doesn't want -- who wants to swim or whatever and absolutely won't wear something on their ear that's visible but would want this doesn't need to go through the trial to get there?

DR. LALWANI: I guess so. I mean, I guess I'm not sure exactly -- maybe you can clarify for me the purpose of the hearing aid trail, in terms of the process of undergoing Esteem implantation?

DR. SININGER: I would just think that in order to be an informed consumer that, you know, there are a lot of poorly fit hearing aids, a lot of -- you can buy hearing aids over the internet these days, and that sort of thing -- that anyone who wants to be an informed consumer should at least have some experience with a non-surgical hearing aid so that they can make that decision, you know, based on the performance as it could be rather than just this looks good and I want to try it.

DR. LEOPOLD: Dr. Cueva?

DR. CUEVA: Most hearing aid manufacturers give you a month and, you know, you previously mentioned maybe a three-month trial. The problem is the person spends $2,500 for a hearing aid --

DR. LEOPOLD: Or more.

DR. CUEVA: -- and then three months later -- or more -- and they go, wow, this is driving me crazy, I can't stand it, and now they've just spent a good chunk of change, and now they're going to have to face, you know, the cost of a surgical procedure, the implant, et cetera, et cetera. I agree with Dr. Lalwani. I think if you look at the unaided results and the benefit, they're at least as good as hearing aids, and I think that ought to be

kind of an equivalent option depending on where they want to spend their money, again, if they are adequately informed, knowing what they're facing in the way of risk. We all make those kind of choices as a consumer. I mean, if you want to go get a facelift or --

DR. SININGER: Well, we went through the same discussions with cochlear implants, but it has been historically appropriate to go for a non-surgical approach first and do the best you can with that before going on to a surgical. Now, I know that in a lot of cases, that's just ignored anymore.

DR. CUEVA: Part of that is because when you put a cochlear implant in, that ear won't hear naturally again. This you can at least reverse it if need be and reconstruct the ossicles, and at least they're where they started, or pretty darn close.

DR. LEOPOLD: Dr. Eydelman, you had a comment?

DR. EYDELMAN: I just wanted clarification in light of this discussion whether the Panel is recommending just a hearing aid trial or modification of indication so as to limit it to only individuals who have failed a hearing aid. Those are two distinct recommendations.

DR. LEOPOLD: Comments?

DR. SIE: My intention in the motion was to require patients to at least experience a hearing aid for a period of time so they could have some comparison point or understanding what a non-surgical option would do. As far as failure of a hearing aid trial, I think that opens up a whole 'nother kind of bag of worms, if you will, to define what failure is.

DR. LEOPOLD: Pursuant to Dr. Cueva's comments, is a one-month trial appropriate?

DR. SIE: I think for an adult, it might be appropriate.

DR. LEOPOLD: Okay. And that's what we're talking about here.

DR. SIE: Yes.

DR. LEOPOLD: So I think that's a yes. So we could put that in the wording? Is everyone in agreement that at least a one-month trial before using this would be appropriate? Dr. Lalwani?

DR. LALWANI: I'm not convinced that's really necessary at least as a point of discussion. That is, a stapedectomy is an analogous situation in my mind. A patient has, you know, three options, do nothing, put a hearing aid on, or have surgery. And even though I make that recommendation, plenty of

1 people decide not to undergo the process of doing a
2 hearing aid trial even though I strongly recommend
3 it. In the same way, I see this particular
4 prosthesis in a similar fashion. The patient is
5 trying to decide between not doing anything for their
6 hearing loss, putting a conventional hearing aid in,
7 or having a surgical intervention that kind of, at
8 best, at least replicates what a hearing aid does,
9 maybe slightly better, who knows? So in my mind, the
10 one-month trial, I'm not sure what the purpose -- I'm
11 not sure if it's necessary as a condition for
12 undergoing this procedure, at least in my mind.
13 DR. LEOPOLD: Other comments? Dr. Kenna?
14 DR. KENNA: I think that there is enough
15 concern or information out there or lack of
16 information, how effective this is in certain groups,
17 and it is a surgical procedure with a permanent
18 device in place, so I personally would be in favor of
19 a hearing aid trial because there are going to be
20 people who benefit and who won't need this, at least
21 not now. And that way, they will clearly be better
22 informed. So for me, personally, I think it is a
23 reasonable option.
24 DR. LEOPOLD: Dr. Kileny?
25 DR. KILENY: Just as a quick comment --

1 Paul Kileny -- I would expect that any ethical
2 clinician would discuss with his or her patient the
3 various options for hearing rehabilitation, which
4 includes conventional amplification, and then if this
5 is approved there. So I'm kind of on the fence about
6 this. I'm not sure that it's absolutely necessary.
7 DR. LEOPOLD: But we aren't going to put in
8 there that there has to be an ethical surgeon to use
9 the device.
10 (Laughter.)
11 DR. LEOPOLD: That'd be another indication.
12 Are we ready to vote? All in --
13 DR. NORTON: No, we're not --
14 UNIDENTIFIED SPEAKER: Mr. Chairman?
15 DR. LEOPOLD: We still need a second? I'm
16 sorry.
17 DR. NORTON: Susan Norton. I just want to
18 say -- I mean, we frequently get people coming in who
19 are what we call borderline cochlear implant
20 candidates, and we fit them with, you know, optimal
21 or better amplification than they have, and they
22 choose not to undergo that procedure because they do
23 much better. And so just because it's going -- I
24 mean, you can't predict how a person will perceive.
25 And if we look at the data here, someone -- those

people with good word rec scores, they didn't have as far to move. And the very best, two of the three didn't move, and one got much worse.

DR. LEOPOLD: Right. Dr. Connor?

DR. CONNOR: And it seems to me, if this is part of the trial, if a patient still wants this implant, they come in and can say they're unhappy with -- so I mean, I guess it solves the problem of someone who is surprisingly happy with their hearing aid. But it seems that if a patient wants this anyway that they can, you know, end up with the implant regardless.

DR. LEOPOLD: We need a second for this motion. Dr. Kenna? All in favor?

UNIDENTIFIED SPEAKER: State the motion again?

DR. LEOPOLD: The motion is that we require at least a one-month trial -- correct me if I get this wrong -- we require at least a one-month trial of a hearing aid properly prescribed prior to allowing this device to be utilized. All in favor? Let's go around the room. Dr. Sie, will you start again, please?

DR. SIE: In favor.

DR. ROSOWSKI: Rosowski, in favor.

DR. LALWANI: Lalwani, not in favor.

DR. KILENY: Kileny, opposed.

DR. KENNA: Kenna, in favor.

DR. ISHIYAMA: Ishiyama, in favor.

DR. HOOD: Hood, in favor.

DR. HIRSCH: Hirsch, in favor.

DR. CUEVA: Cueva, opposed.

DR. HALL: Hall, in favor.

DR. CHEUNG: Cheung, opposed.

DR. SININGER: Sininger, in favor.

DR. NORTON: Norton, in favor.

DR. CONNOR: Connor, opposed.

DR. LONSBURY-MARTIN: Lonsbury-Martin, in favor.

DR. LEOPOLD: So it passes -- what number did you get?

UNIDENTIFIED SPEAKER: I got 15.

DR. LEOPOLD: We have 15. Can the yes people please raise their hands again? One, two, three, four, five, six, seven, eight, nine, ten. And there's 15 people voting. So we're okay?

UNIDENTIFIED SPEAKER: The numbers are good.

(Laughter.)

DR. LEOPOLD: Okay. Are there any other

conditions that would need to be added? Yes, please?

DR. CONNOR: So I would motion -- I revisit Dr. Rosowski's comment that the label clearly say non-inferior to hearing aids, meaning it doesn't say superior. You know, the primary outcome, the lower bound was 7.1, and it needed to be higher than 5, but there are questions about site heterogeneity there. The FDA's analysis went all the way down to -9.4, which didn't even meet the non-inferior bound. I am comfortable saying it's non-inferior. So that's with respect to SRT. So I would say that is it non-inferior with respect to SRT and WRS, as opposed to superior to either or with respect to either of those. With WRS, you know, only essentially 30 out of 60, or half, showed an improvement, which means we can't reject the hypothesis that a majority improved. Well, actually, I'm sorry. I'm probably getting into my point. So I motion that the label clearly say non-inferiority with respect to SRT and WRS, not superior with respect to SRT and WRS.

DR. LEOPOLD: Did we get that down?

UNIDENTIFIED SPEAKER: That claim was voted down. That condition was not approved that Dr. --

DR. ROSOWSKI: I withdrew the motion, the condition. So I'll second it.

(Laughter.)

UNIDENTIFIED SPEAKER: Restate your condition?

DR. CONNOR: That the label clearly say it is non-inferior to hearing aids with respect to SRT and WRS, meaning it does not say that it's superior to hearing aids with respect to SRT and WRS.

DR. LEOPOLD: Did you get that? Okay. In part of the discussion, I would suggest that when we do put this in the patient literature, we put it in understandable language for non-statistical persons.

(Laughter.)

DR. LEOPOLD: Dr. Eydelman?

DR. EYDELMAN: Again, perhaps you just want to leave the general comments and leave the specifics to the statisticians on the FDA staff if you --

DR. LEOPOLD: But at least this gives them the idea of exactly what we want.

DR. CONNOR: Right. I'm always happy to let the FDA and especially the statisticians, you know, identify what we're recommending. But I want to be particular enough so you know what we're recommending. But of course, you know, the label would be up to you.

DR. LEOPOLD: Additional comments?

Discussion?

(No response.)

DR. LEOPOLD: All in favor? This is unanimous, as I can see it. Any other conditions that we -- yes. Dr. Cueva?

DR. CUEVA: Would this be where we talk about a post-approval study or is that --

DR. EYDELMAN: Yes.

DR. LEOPOLD: Yes.

DR. CUEVA: Okay. Then I recommend a condition being a post-approval study.

DR. LEOPOLD: Thank you. Is there a second on this? Dr. Sie? And as I was told before, what is in that post-approval study can be decided by the FDA based on the comments that have gone on here. So we don't need to go through and enumerate all the little things to be in that study. And that would be done per the wishes of what our discussion has been through the entire transcript of this meeting. So we need to have a discussion of whether -- of having a post-approval study. Comments? Yes?

DR. CONNOR: So I would recommend that it both track as many patients as possible of the current cohort, to follow both efficacy and safety outcomes that have been discussed, and include, as a

number decided by FDA and their statisticians, a number of new patients here going forward.

DR. LEOPOLD: Okay. Additional thoughts on a post study?

(No response.)

DR. LEOPOLD: All in favor of a post-approval study? That's unanimous. Other conditions? Yes, Dr. Hirsch?

DR. HIRSCH: I may be, you know, repeating myself, but again with the indication that it be defined as sensorineural hearing loss, the word recognition scores be recorded, and that normal tympanic membrane be part of the inclusion criteria.

DR. LEOPOLD: Is there a second? Dr. Kenna? Dependable. Thank you. Comments? Questions? Discussion?

DR. EYDELMAN: I believe that already is in the -- normal tympanic --

DR. LEOPOLD: Normal tympanic membrane, I believe, is already one of the things we've approved.

DR. HIRSCH: Okay.

DR. LEOPOLD: So we can scratch that. And so we're down to -- now, we already had sensorineural hearing loss, moderate to severe, I believe it was.

DR. HIRSCH: But it doesn't say

sensorineural at least on the FDA summary.

DR. LEOPOLD: But I believe the one we said was sensorineural.

UNIDENTIFIED SPEAKER: It was an earlier condition.

DR. EYDELMAN: It was in the inclusions, but not in the indications. So --

DR. LEOPOLD: Okay.

DR. EYDELMAN: Because the terminology keeps getting mixed up. Is the motion on the table to include these in the indications, which makes it very clear that only those with these are allowed to be?

DR. HIRSCH: Yes. But I'm trying to say there's no conductive component. This is purely sensorineural. So if we put that in the inclusions, that'll eliminate a conductive component.

DR. EYDELMAN: No. If you put it in the indications, it will, not in the inclusions.

DR. HIRSCH: Oh.

DR. EYDELMAN: Indications for use defines the population for which this device could be approvable.

DR. HIRSCH: And it's part of the indications?

DR. LEOPOLD: And we've had a second. And so we're down to sensorineural hearing loss, and there was one more? And WRS scores be recorded?

DR. HIRSCH: Be recorded.

DR. LEOPOLD: Yes. I can't hear you.

DR. SIE: And normal tympanic membrane.

DR. LEOPOLD: That's already in there. So any further discussion? Dr. Cheung?

DR. CHEUNG: Steven Cheung, UCSF. Can you specify how much conductive hearing loss is too much? Any conductive hearing loss --

DR. HIRSCH: I believe they had criteria where they said it was less than 10 dB at three frequencies. I'd have to look at the original exclusion criteria, but I think it was spelled out.

DR. CHEUNG: I think in our motion, we need to specify what we would like to see.

DR. LEOPOLD: Can we let the FDA decide that based -- and we're in agreement with what the original criterion were for this industry study?

DR. HIRSCH: Criteria and exclusions, yes.

DR. LEOPOLD: Yes? Okay. Any other discussion?

(No response.)

DR. LEOPOLD: All in favor? I'm seeing

that being unanimous. Any other conditions to be added?

Dr. Norton?

DR. NORTON: What do we want to do about profound hearing loss?

UNIDENTIFIED SPEAKER: It's excluded.

DR. NORTON: It's not excluded.

UNIDENTIFIED SPEAKER: We did.

DR. NORTON: We did?

DR. LEOPOLD: We said moderate to severe --

DR. NORTON: Moderate to severe. Okay. I just wanted to make sure because in their diagrams, they say severe, but it goes all the way down to 100.

DR. LALWANI: Anil Lalwani, NYU. I believe our earlier motions or conditions restricted it to moderate to severe sensorineural hearing loss. It could be unilateral --

UNIDENTIFIED SPEAKER: No, bilateral --

DR. LALWANI: The bilateral passed? Okay.

DR. LEOPOLD: Can we have a comment from the FDA, please?

DR. EYDELMAN: Yeah. Actually, keep in mind that the severity of hearing loss is based on the PTA at 500, 1,000, and 2,000. So based on this criteria, it is possible to have patients who have

profound hearing loss at high frequencies. And that's what I want to say.

DR. LEOPOLD: Okay.

DR. PENG: Just to clarify that profound --

DR. EYDELMAN: The clarification that's needed is whether the current indication reading -- they eliminated mild, but currently, it's still for moderate and severe.

DR. PENG: Yeah. Profound is not there, yeah.

DR. EYDELMAN: Thank you.

DR. LEOPOLD: We're all in agreement. Any other indications or conditions?

(No response.)

DR. LEOPOLD: Then, Dr. Norton, are you ready to --

DR. NORTON: Is this where it would go into about rigorous training for surgeons and audiologists?

DR. LEOPOLD: Sure, if you'd like to propose something like that?

DR. NORTON: I guess we could say there has to be rigorous training and a certification of surgeons and audiologists involved with this device and leave that up to the FDA and the manufacturer.

DR. LEOPOLD: And I believe the manufacturer already has that intention, but we can put that in certainly as a condition. Second by Dr. Lalwani. Any discussion?

(No response.)

DR. LEOPOLD: All in favor? That's 100% Any other conditions?

(No response.)

DR. LEOPOLD: I believe we're ready to now go back and vote on the main discussion, the main motion. Is that your understanding?

It has been moved and seconded that the PMA 090018 for the Esteem Totally Implantable Hearing System be found approvable with conditions, and there are eight conditions. Voting members who are raising their hands indicating that they concur with the recommendation that the above-stated PMA is approvable with those stated conditions are -- now we get a show of hands --

UNIDENTIFIED SPEAKER: Just summarize the conditions before --

DR. LEOPOLD: Okay. So the conditions are -- should be limited to moderate to severe hearing loss. That's No. 1. No. 2 is labeling changes to include facial incidence, taste

disturbance incidence, hearing aid may perform better than the APHAB results. No. 3 is indications should be limited to bilateral hearing loss. No. 4 is require one-month hearing aid trial, properly prescribed, for candidacy. No. 5 is label clearly states not inferior to hearing aids with respect to SRT and WRS. No. 6 is we want a post-approval study. No. 7, indications reflect the WRS be recorded and that it be for sensorineural hearing loss, and I believe the conductive levels as indicated by the manufacturer. And 8, rigorous training and certifications for surgeons and audiologists.

So we will now have a show of hands. For everyone who is in favor of this proposal, raise your hand. And then we will go around the room and -- well, this is unanimous. Do we still need to go around the room?

Okay. There are no abstentions and no removals. So it is the recommendation of the Panel to the FDA that PMA 9090018 for Esteem Totally Implantable Hearing System be found approvable with stated conditions.

I will now ask each Panel member to state the reason for his or her vote, starting with Dr. Lonsbury-Martin. You're welcome.

DR. LONSBURY-MARTIN: I think this is a very worthwhile project. I did have concerns about the variability across sites. And I'm pleased with the conditions that were put on for the future of this work, in terms of, I'd say, a post-application study being approved and all the other conditions that we talked about seemed relevant. As a physiologist, it makes good sense to do this kind of work, and I approve of it as long as it's held to a rigorous standard.

DR. LEOPOLD: Dr. Connor? Thank you.

DR. CONNOR: I think this is a promising treatment, and I think that the data I've seen proves it's safe and effective, sufficiently safe and effective so that patients should have this as an option to treat their hearing loss.

DR. LEOPOLD: Dr. Norton?

DR. NORTON: I believe it's a promising treatment. I believe it's safe. I think the data are okay.

(Laughter.)

DR. LEOPOLD: Thank you. Dr. Sininger?

DR. SININGER: Yeah. I also think it's a very promising technology, and I'm glad to see us coming forward with new technology, and I think the

data showing effectiveness still outweighs my questions about some of the ways that subjects were selected. And so I'm still convinced that this is probably going to provide benefit for the majority of the patients and outweigh the risks of the surgery.

DR. LEOPOLD: Dr. Cheung?

DR. CHEUNG: I congratulate the Envoy team for their perseverance to really take on this very difficult project. I would say that the data analysis and data exposition could have been better and that they would exercise good judgment on when they would like to have bilaterally implanted patients.

DR. LEOPOLD: Dr. Hall?

DR. HALL: I think it's not easy to draw conclusions comparing this device to hearing aids, but I think it's a promising device, and it seems safe and effective.

DR. LEOPOLD: Dr. Cueva?

DR. CUEVA: Dr. Cueva. I think the device is certainly safe in the plan to make sure that the future operating surgeons are going to do safe surgery as well. It appears to me that the device is at least effective as hearing aids, in terms of the auditory measures, I think, in terms of quality of

life. From what we heard from the patient testimony, I think it's going to be a significant benefit. Thank you.

DR. LEOPOLD: Dr. Hirsch?

DR. HIRSCH: In the right hands, I think this has been shown to be an effective device that adds a level of quality to sound that we can't measure. But, again, this must be done in the right hands and in the right setting.

DR. LEOPOLD: Dr. Hood?

DR. HOOD: Linda Hood. I think that this is a promising technology, and I look forward to it moving field of patient care ahead. I look forward to more information for the sake of patients making decisions related to the effectiveness.

DR. LEOPOLD: Dr. Ishiyama?

DR. ISHIYAMA: Yes. I'd like to also congratulate the Envoy team for coming up with this promising technology. My only concern has been intra-site variability of the outcome, but I'm sure that those are going to be all worked out once more data is generated. We're going to probably find a lot of patients who will be very happy with the outcome of the procedure.

DR. LEOPOLD: Dr. Kenna?

DR. KENNA: Yes. I think this is really very promising. There is certainly a group of patients who don't seem to benefit optimally from their hearing aids. And so in the correctly chosen patients and correctly trained surgeons and audiologists, this does seem to be very exciting.

DR. LEOPOLD: Dr. Kileny?

DR. KILENY: Dr. Kileny. I feel this is a promising technology. It's a great alternative for the hearing impaired population. In the right hands, this is going to work great. And I'm just going to add this to the list of stuff I never learned in school.

(Laughter.)

DR. LEOPOLD: Dr. Lalwani?

DR. LALWANI: So I think it's a new frontier in terms of totally implantable hearing aids. I do hope that the post-studies, in fact, bear this out. And I hope that its implementation is prudent in terms of who gets to implant it, where it's implanted, and the audiologists participating in the process.

DR. LEOPOLD: Dr. Rosowski?

DR. ROSOWSKI: So I think this is a promising device. It's clear that there are people

1 who have received it who are receiving great benefit
2 from it. And I'm also glad that we've arrived at
3 some conclusions where it's -- that not only the
4 benefits, but the potential risks are clearly
5 communicated to whoever is considering having this
6 device.
7 DR. LEOPOLD: Dr. Sie?
8 DR. SIE: My main concerns about the device
9 and studies are the intra-site variability and the
10 long-term problems/issues with people potentially
11 undergoing ten battery changes and soft tissue issues
12 that might arise. And so I do have concerns about
13 bilateral devices. Though overall, I think it's an
14 incredibly exciting technology. And I'd like to
15 thank the patients for coming at this time of year
16 and giving their stories because I think that is
17 something that's very compelling, that we really
18 don't have ways to measure. And I think that has
19 really helped us come to this conclusion. So thank
20 you.
21 DR. LEOPOLD: Mr. Timlin, any comments?
22 MR. TIMLIN: No.
23 DR. LEOPOLD: Okay. Dr. Portis? No? I
24 would like to thank the Panel, who have worked very
25 hard on this. I appreciate all of your insight, your

intellect, and I want to again thank you very much for all the work you've put into this and for helping to move this technology forward. I personally think this is opening the door to a whole generation of new technology, which will allow us once we're in the middle ear to move forward and make some great strides. So I'm quite excited about this.

Dr. Eydelman, last words?

DR. EYDELMAN: Just once again to thank all of you coming out here to D.C. a week before Christmas -- we know -- and to put all your effort, we really appreciate it, and Dr. Leopold for moving this along. We're very close to schedule, which is very impressive with a Panel this size. And last but not least, I want to thank my team who has really worked well beyond the call of duty to make today as smooth as possible. Thank you guys.

DR. LEOPOLD: Thank you.

(Applause.)

(Whereupon, at 5:30 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

EAR, NOSE AND THROAT DEVICES PANEL

December 18, 2009

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY ATKINSON, JR.

Official Reporter