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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICE EVALUATION AND RESEARCH

ORTHOPEDICS AND REHABILITATION DEVICES

ADVISORY COMMITTEE

Thursday, July 20, 2000

9:30 a.m.

Holiday Inn Gaithersburg
Walker/Whetstone Rooms
Two Montgomery Village Avenue
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
735 8th Street, S.E.
Washington, D.C. 20003

at

PARTICIPANTS

Barbara D. Boyan, Ph.D., Chairperson
Hany Demian, M.S., Executive Secretary

VOTING MEMBER

Michael J. Yaszemski, M.D., Ph.D.

CONSULTANTS DEPUTIZED TO VOTE

Albert J. Aboulafia, M.D.
Edward Cheng, M.D.
Maurean Finnegan, M.D.
Robert Goldman, M.D. (Session 1)
Kinley Larntz, Ph.D.
Peter A. Lewin, Ph.D.
Stephen Li, Ph.D. (Session 2)
John Lyons, M.D. (Session 2)
Glenn B. Pfeffer, M.D. (Session 2)
John Robinson, M.D. (Session 1)
Douglas G. Wright, M.D.

INDUSTRY REPRESENTATIVE

Raymond Silkaitis, Ph.D.

CONSUMER REPRESENTATIVE

Velia Butcher, J.D.

FDA

Celia Witten, Ph.D., M.D.

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1 P R O C E E D I N G S

2 **Opening Remarks/Conflict of Interest**

3 MR. DEMIAN: Good morning, everybody. We are
4 ready to begin this meeting of the Orthopedic and
5 Rehabilitation Devices Panel. My name is Hamy Demian. I am
6 the Executive Secretary of this panel and senior reviewer in
7 the Orthopedics Devices Branch.
8 I would like to remind everyone that you are
9 requested to sign in on the attendance sheets which are
10 available outside the doors. You may also pick up and
11 agenda and information about today's meeting including how
12 to find out about future meeting dates through the advisory
13 panel phone line and how to obtain meeting meetings or
14 transcripts.
15 I will now read two statements that are required
16 to be read into the record. The first one is a deputization
17 of temporary voting members statement. Pursuant to the
18 authority granted under the Medical Device Advisory
19 Committee Charter dated October 17, 1990 and as amended
20 August 18, 1999, I appoint the following individuals as
21 voting members of the Orthopedic and Rehabilitation Device
22 Panel for this meeting on July 20, 2000; Kinley Larntz, John
23 Robinson, Peter Lewin, Robert Goldman, Glenn Pfeffer,
24 Douglas Wright, Maurean Finnegan, Stephen Li and John Lyons.
25 For the record, these individuals are special

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1 government employees and consultants to this panel or other
2 panels under the Medical Device Advisory Committee. They
3 have undergone the customary conflict of interest review and
4 have reviewed the material to be considered at this meeting.
5 This is signed by Linda Kahn for Dr. David Feigal dated July
6 12, 2000.
7 The second statement that I have to read is the
8 conflict of interest statement. The following announcement
9 addressees conflict of interest issues associated with this
10 meeting and is made part of the record to preclude even the
11 appearance of any impropriety. To determine if any conflict
12 exists, the agency reviewed the submitted agenda for this
13 meeting and all financial interests reported by the
14 committee participants.
15 The Conflict of Interest Statute prohibits special
16 government employees from participating in matters that
17 could affect their or their employer's financial interests.
18 However, the agency has determined that participation of
19 certain members and consultants, the need for whose services
20 outweighs the potential-conflict of interest involved is in
21 the best interest of the government.
22 Therefore, waivers have been granted for Drs.
23 Edward Cheng, Kinley Larntz, John Lyons and Stephen Li for
24 their interest in firms that could potentially be affected
25 by the panel recommendations. Copies of these waivers may

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1 be obtained from the agency's Freedom of Information Office,
2 Room 12A-15 of the Parklawn Building.
3 We would also like to note for the record the
4 agency has taken into consideration other matters regarding
5 Drs. Barbara Boyan, Michael Yaszemski, Edward Cheng and
6 Stephen Li. Each of these panelists reported current or
7 recent interest in firms at issue but in matters that are
8 not related to today's agenda.
9 The agency has determined, therefore, that they
10 may participate fully in all discussions. In the event that
11 the discussions involve any other products or firms not
12 already on the agenda for which an FDA participant has a
13 financial interest, the participant should excuse him or
14 herself from such involvement and the exclusion will be
15 noted for the record.
16 With respect to all other participants, we ask, in
17 fairness, that all persons making statements or
18 presentations disclose any current or previous financial
19 involvement with any firms whose products they may wish to
20 comment upon.
21 Before turning this meeting over to Dr. Boyan, I
22 would like to introduce our distinguished panel members who
23 are generously giving their time and help to help FDA at
24 matters being discussed today, and other FDA staff seated at
25 this table. So we will simply go around the room. Give

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1 your name and your affiliation and your areas of interest.

2 Dr. Boyan.

3 DR. BOYAN: I'm Barbara Boyan. I am a professor

4 and director of orthopedic research at the University of

5 Texas Health Center at San Antonio. My specialty is bone

6 and cartilage biology.

7 DR. CHENG: My name is Edward Cheng. I am with

8 the University of Minnesota Department of Orthopedic

9 Surgery. My interests are in reconstructive surgery,

10 osteonecrosis and musculoskeletal tumors.

11 DR. WRIGHT: Douglas Wright. I am in Baltimore.

12 I am in private practice. I am affiliated with Johns

13 Hopkins Bayview. My interest is fracture surgery and foot

14 and ankle surgery.

15 DR. PFEFFER: Glenn Pfeffer, San Francisco,

16 Orthopedic Surgeon in private practice. I am assistant

17 clinical professor at the University of California, San

18 Francisco. My practice is limited to the foot and ankle.

19 DR. SILKAITIS: Hi. My name is Raymond Silkaitis.

20 I am the industry rep for the panel, a non-voting member of

21 the panel. I work for Gliatech and have a Ph.D. in

22 pharmacology and am a pharmacist.

23 MS. BUTCHER: My name is Vickie Butcher. I have

24 previously served on the FDA Consumer Consortium helping to

25 choose people to serve on panels on such as this. My

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1 background is in teaching of the law and I represent the
2 consumer as a non-voting member.
3 DR. WITTEN: I am Dr. Celia Witten. I am the FDA
4 representative at the table. I am the Division Director of
5 the Division of General Restorative Devices.
6 DR. ABOULAFIA: My name is Albert Aboulafia. I am
7 an orthopedic surgeon. I am currently at University of
8 Maryland and Sinai Hospital in Baltimore. My areas of
9 interest are bone and soft-tissue sarcomas, musculoskeletal
10 oncology.
11 DR. GOLDMAN: My name is Robert Goldman. I am a
12 physiatrist practicing at the University of Pennsylvania
13 with research interests in wound healing in clinical
14 practice and wound healing in general physiatry and tech
15 transfer.
16 DR. ROBINSON: John A. Robinson, Associate Dean
17 for Research at Loyola University Medical Center with the
18 academic practice of rheumatology.
19 DR. LEWIN: I am Peter Lewin. I am from Drexel
20 University in Philadelphia. I am Professor of Electrical
21 and Biomedical Engineering. My specialty is shock waves,
22 lithotriptors and anything that has to do with acoustic
23 waves.
24 DR. LARNTZ: Kinley Larntz, Professor Emeritus,
25 University of Minnesota. My field is statistics. I am

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1 interested in research design, analysis of data, all those
2 fun things.
3 DR. FINNEGAN: Maurean Finnegan. I am from the
4 University of Texas, Southwestern Medical Center in Dallas.
5 My interests are trauma and sports.
6 DR. YASZEMSKI: Michael Yaszemski. I am from the
7 Departments of Orthopedic Surgery and Biomedical Engineering
8 at Mayo Clinic, Rochester, Minnesota. On the orthopedic
9 side, I do total joint replacements and spine surgery. On
10 the research side, I work in bone and cartilage tissue
11 engineering.
12 MR. DEMIAN: Thank you.
13 At this time, I would like to turn the meeting
14 over to our chairperson, Dr. Barbara Boyan.
15 DR. BOYAN: Good morning. My name is Dr. Barbara
16 Boyan. I am the Chairperson for this meeting. Today, we,
17 the panel, will be making recommendations to the Food and
18 Drug Administration regarding two premarket approval
19 applications.
20 In the morning, the committee will discuss and
21 make a recommendation for a lithotriptor used for heel pain
22 while, in the afternoon, the committee will discuss and make
23 a recommendation for a ceramic-on-ceramic total hip
24 arthroplasty.
25 I would like to note for the record that the

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1 voting members present constitute a quorum as required by
2 21 CFR, Part 14. Before we begin, I would like to ask Dr.
3 Witten to make a special announcement.
4 DR. WITTEN: Thank you. Actually, I have two
5 special announcements which is two plaques I would like to
6 present to members of the panel who have helped us so much
7 in the past couple of years with our work and who are going
8 to be rotating off their current responsibilities in the
9 panel.
10 The first one is for you, Barbara. It is a
11 certificate of appreciation in recognition of distinguished
12 service. It says here on the plaque, "Term: May 14, 1995 to
13 August 31, 2000." So it is five years of distinguished
14 service and it is signed both by our Center Director, Dr.
15 Feigal and by Jane Henney, the Commissioner of Food and
16 Drugs.
17 I would like to read the letter signed by Jane
18 Henney to you. "I would like to express my deepest
19 appreciation for your efforts and guidance during your term
20 as a member and chair of the Orthopedic and Rehabilitation
21 Devices Panel of the Medical Devices Advisory Committee.
22 The success of this committee's work reinforces our
23 conviction that responsible regulation and consumer products
24 depends greatly on the participation and advice of the non-
25 governmental health community."

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1 I would just like to echo her thanks from all of
2 us here at FDA and CDRH for the work that you have done over
3 the past several years helping us with our work. Without
4 the panel's participation, we would lose, really, a very
5 valuable part of the insight that we need to do our jobs.
6 I also want to mention that, although you are
7 going to be rotating off as chairman, you are still on the
8 panel's consultants and we look forward to seeing you at
9 future meeting.
10 [Applause.]
11 DR. BOYAN: Thank you very much.
12 DR. WITTEN: The other person that I want to thank
13 today is Ray Silkaitis who is our industry representative on
14 the panel. Dr. Silkaitis also has provided very valuable
15 perspective for us. I think that the panel benefits greatly
16 from the perspective from its industry representative.
17 In particular, Dr. Silkaitis, you really have done
18 a great job with providing that perspective for this panel
19 as it does its work. So I want to just take a moment to
20 thank you. Your certificate of appreciation, term from
21 February, 1997 to August of 2000, also signed by Dr. Feigal
22 and Dr. Henney.
23 The letter says, "I would like to express my
24 deepest appreciation for your efforts and guidance during
25 your term as the industry representative member of the

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1 Orthopedic and Rehabilitation Devices Panel of the Medical
2 Devices Advisory Committee. The success of this committee's
3 work reinforces our conviction that responsible regulation
4 of consumer products depends greatly on the participation
5 advice of the non-governmental health community."
6 I would just like to echo, again, the thanks in
7 this letter because we do find the industry representative a
8 valuable member of the panel and we appreciate your work
9 over the past couple of years.
10 [Applause.]
11 DR. SILKAITIS: Thank you very much.
12 DR. WITTEN: I do have one other thing I want to
13 mention which is we have a new--although we are not really
14 providing a formal update, there is a new ODE Director who
15 started this past Monday. I am hoping that he may be able
16 to stop by so we can introduce him. It is Dr. Bernard
17 Statland. Some of you met him during the panel training.
18 He has a distinguished record both as a pathologist and has
19 experience both as a practicing pathologist and also
20 industry experience as well.
21 So we are looking forward to him providing
22 leadership to us in the next couple of years. There are
23 actually two panel meetings going on in this building. If
24 he manages to stop by from this one, I will introduce him at
25 that time.

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1 DR. BOYAN: Thank you very much, Dr. Witten. As
2 long as we are at this part of the ceremony--I was going to
3 save it until the end, but I would like to express my thanks
4 to you for giving me this opportunity. It has been one of
5 the most rewarding experiences of my career, and I have had
6 the opportunity to work really closely with two wonderful
7 executive secretaries, one of which is with us today, Hamy
8 Demian.
9 Altogether, it has been a real learning experience
10 for me and I have had a great time and I will miss seeing
11 you all. But now I understand that it is a never-ending--
12 torture.
13 So, at this time, I would like to proceed with the
14 open public hearing session of this meeting.
15 **Open Public Hearing**
16 DR. BOYAN: I would ask at this time that all
17 persons addressing the panel come forward and speak clearing
18 into the microphone as the transcriptionist is dependent on
19 this means of providing an accurate record of this meeting.
20 We are requesting that all persons making
21 statements during the open public hearing of the meeting
22 disclose whether they have financial interests in any
23 medical device company. Before making your presentation to
24 the panel, please state your name, your affiliation and the
25 nature of your financial interests, if any.

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1 Is there anyone wishing to address the panel at
2 this time? Since there are no requests to speak at the open
3 public hearing, Mr. Demian will summarize three letters he
4 received regarding this meeting.
5 MR. DEMIAN: I received three letters from
6 individuals supporting the approval of the HealthTronics
7 OssaTron Premarket Approval Application for the treatment of
8 plantar fasciitis. It is estimated that between 2 and
9 6 million people suffer from this product each year. Each
10 letter urges the committee to approve this product because
11 of limited alternative treatment options which include
12 orthotics, stretching, antiinflammatories and cortisone
13 shots.
14 The only other treatment currently available is
15 surgery which can have a 50 percent failure rate and
16 possible ruin a person's ability to walk for the rest of
17 their life. It is believed that this treatment has shown
18 success in Europe and in Canada for many years and has
19 proven to be an effective and safe treatment to reduce pain
20 and, in some cases, provide 100 percent cure. Unlike
21 surgery, the lithotriptor treatment for plantar fasciitis
22 carries with it no great risks.
23 Dr. Boyan.
24 DR. BOYAN: Thank you, Mr. Demian.
25 We will now proceed to the open session for the

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1 first PMA of the day.

2 **Session 1: PMA for HealthTronics OssaTron**

3 DR. BOYAN: This is P990086, HealthTronics

4 OssaTron Lithotriptor used for the treatment of heel pain.

5 We will now consider the premarket approval application for

6 HealthTronics OssaTron. I would like to remind the public

7 observers at this meeting that, while this portion of the

8 meeting is open to public observation, public attendees may

9 not participate except at the specific request of the panel.

10 We are now ready to begin the sponsor's

11 presentation followed by an FDA presentation. I would like

12 to ask that each speaker state his or her name and

13 affiliation to the firm beginning their presentation.

14 Sponsor, are you ready? We will have the

15 sponsor's presentation now for HealthTronics, Inc. There

16 will be three presenters: George DeMuth, who is the

17 biostatistical consultant and President of StatTech

18 Services; Marie Marlow, from HealthTronics; Dr. Reinhart

19 Schultheiss who is also for HMT OssaTron.

20 Then we will have a question and answer--actually,

21 we are not going to have a question-and-answer period until-

22 -are any of your physicians going to speak in this portion?

23 MS. MARLOW: They are here for your convenience.

24 DR. BOYAN: We will save that until after your

25 presentation, then.

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1 **Introduction**

2 MS. MARLOW: Good morning, Dr. Boyan, members of
3 the Panel, Dr. Witten and FDA staff.
4 [Slide.]
5 I am Marie Marlow. I am the Vice President of
6 Clinical and Regulatory Affairs for HealthTronics. I would
7 like to thank all of you for the time and effort you have
8 taken in reviewing our PMA for the OssaTron, an
9 extracorporeal shock-wave system indicated for use to treat
10 chronic heel-pain syndrome.
11 To address the financial-disclosure requirements,
12 I am a HealthTronics employee, an officer and a shareholder
13 and I have a financial interest in our company.
14 [Slide.]
15 I will take a brief minute to introduce everyone
16 who will be speaking to you today during our presentation.
17 After my introductory remarks, you will be hearing from Dr.
18 Reiner Schultheiss of HMT High Medical Technologies in
19 Lingwil, Switzerland. Dr. Schultheiss holds a Ph.D. in
20 physics and he is one of the developers of the OssaTron. He
21 headed up the Science and Applications Department of HMT
22 before taking on his current responsibilities as the
23 Director of Sales and Marketing. He will be summarizing the
24 technical characteristics of the OssaTron and the non-
25 clinical testing that was included in our PMA.

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1 Next you will hear from George DeMuth who is a
2 biostatistician and President of StatTech Services. His
3 organization prepared the statistical analyses of our data
4 and he will be summarizing that information from the PMA for
5 you.
6 And I will be summarizing the clinical findings
7 from our study.
8 Once we have completed the presentations, we
9 welcome the opportunity to answer your questions. Our
10 medical monitor and the primary investigator for the study
11 are here with us today to help answer your questions.
12 Dr. John Ogden is the medical monitor for all of
13 HealthTronics OssaTron projects. He is the Director of
14 Orthopedic Education at Atlanta Medical Center and he was
15 recently named President Elect of the International Society
16 for Musculoskeletal Therapy at their recent meeting in
17 Naples, Italy.
18 Dr. Richard Alvarez served as our primary
19 investigator for this study. He is a member of the Foot and
20 Ankle Society. He is Past President of the Foot and Ankle
21 Club and he is in private practice in Chattanooga,
22 Tennessee. He is an associate professor at the University
23 of Tennessee, Department of Orthopedics.
24 With these introductions completed, I will start
25 with the summary of our PMA.

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1 [Slide.]

2 HealthTronics is the initial distributor for the
3 OssaTron in the United States and, as such, we sponsored the
4 PMA. The OssaTron is manufactured by HMT who maintains an
5 ISO 9000 certified facility and, over the past three years,
6 they have successfully completed three FDA quality-systems
7 inspections, most recently in April.

8 HMT is also the manufacturer of HealthTronics
9 LithoTron, the kidney lithotriptor for which we received PMA
10 approval in July of 1997.

11 I will briefly review just a little background
12 information about extracorporeal lithotriptor devices used
13 for kidney stones since the OssaTron is almost identical to
14 these devices. The first ESW system indicated for use in
15 lithotripsy was granted PMA approval in 1984, so there is
16 about twenty years of clinical experience with
17 lithotriptors. In fact, your colleagues on the
18 Gastroenterology and Urology Devices Panel recently voted to
19 reclassify ESW lithotriptors as class II devices when they
20 are used as indicated to treat upper urinary-tract-calculi.

21 Extracorporeal shock-wave technology is well-known
22 and well-documented, and there is a wealth of information in
23 the clinical and scientific literature about shock waves
24 interact with all sort of human tissue.

25 This is a good time for me to turn the

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1 presentation over to Reiner Schultheiss who can speak to you
2 with experience about the research that has been done on
3 shock-wave devices. He will also provide you with a more
4 detailed description of the OssaTron and he will talk about
5 the testing that was done to characterize the device.

6 **Device Description**

7 DR. SCHULTHEISS: Dr. Boyan, members of panel,
8 ladies and gentlemen. My name is Reiner Schultheiss. I
9 hold a Ph.D. in physics. I am working for HMT, High Medical
10 Technology, in Lingwil, Switzerland. I have to disclose
11 that I have a financial interest in HealthTronics and at
12 present, I am a shareholder of that company.

13 I have the opportunity today to speak to you. I
14 am a little bit nervous because it is the first time I am
15 part of a panel meeting. I am very happy to give you some
16 technical description and some technical information of the
17 OssaTron, the special device we developed for treating
18 orthopedic diseases which we thought is not possible to do
19 with the normal kidney lithotriptor. That is why we
20 developed that special device.

21 First of all, I want to give you an overview of
22 the functional components of the device and show you a
23 video. It will take about three minute.

24 Can we start the video, please.

25 [Video.]

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1 The HealthTronics OssaTron is an extracorporeal
2 shock-wave system designed specifically for orthopedic use.
3 The OssaTron ESW System utilized spark-gap technology to
4 generate shock waves. The OssaTron system incorporates all
5 device components into a single, transportable unit.
6 The major components include the control cabinet,
7 the control console and the therapy head. The control
8 cabinet is the main body of the device. It connects to a
9 standard hospital main 120 VAC power supply. The control
10 cabinet is mounted on a locking wheel base and has six
11 subcomponents; the charging unit, the shock-wave generator,
12 electrical module, the water supply and valve units, and the
13 motor drive units.
14 The control console includes a touch-pad user
15 interface with LED display and a hand-held shock-wave
16 release button. The control console houses the two-positive
17 key switch for turning the power supply to the device on and
18 off. The pressure of the coupling membrane is adjustable
19 via a control knob. Touch keys are provided for selecting
20 the desired shock-wave energy and frequency.
21 The control console display shows these settings
22 along with the total number of shocks delivered per
23 procedure. The operating state of the device is indicated
24 by the LED display panel. Movement of the therapy head and
25 locating bow are driving from the control console.

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1 The therapy head integrates the brass ellipsoid,
2 the coupling membrane, the ELC 114 single-use electrode and
3 the locating bow. The therapy head is coupled to the
4 patient via the water-filled coupling membrane covering the
5 brass ellipsoid.
6 The ELC 114 electrode fits into the therapy head
7 and extends into the ellipsoid. The electrode receives a
8 high-energy current from the shock-wave generator across the
9 electrode tips which produces the shock wave. The wave is
10 then focused by the ellipsoid and transmitted through the
11 coupling membrane.
12 A locating bow affixed to the therapy head allows
13 for approximating the location of the shock-wave focus and
14 aligning it with the desired target area. The locating bow
15 can be rotated in two planes via the control console. The
16 therapy-head unit is connected to the control cabinet via an
17 arm with 350 degree rotation capability.
18 Safety features of the device include the anti-
19 collusion hood on the therapy head, an emergency off-switch
20 located on the control cabinet and standby mode for all
21 device operations when the shock-wave release button is
22 engaged.
23 So far for the technical description of the
24 device.
25 [Slide.]

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1 Coming back to the most interesting part of the
2 device, which I think is the shock-wave-generating system
3 and, as mentioned already in the video, we see, here, an
4 electrode plug which is plugged into an ellipsoid and is
5 charged with high-voltage. Between the tips--I hope I am
6 not too nervous to show that--between the tips of that
7 electrode, when we put the high voltage on it, up to 28 kV
8 and a high current is crossing an igniting spark, we have a
9 vaporization of the water there, an explosive wave which is
10 a spherical wave--I will show later how we think the
11 focussing is working.
12 This is the production of a regular shock wave,
13 then. We use that electrode for 2000 shocks and then it has
14 to be replaced with a new one.
15 [Slide.]
16 Now I can show the ellipsoid where the electrode
17 is put inside. The electrode is put inside in a way that
18 the tips of the electrode are located on the first focal
19 point of that ellipsoid. So whenever radiation is radiated
20 or emitted from that, it is reflected by the walls of the
21 ellipsoid and it is converged or focussed in the second
22 focal point.
23 [Slide.]
24 In this slide I can show you the details. We
25 have, again, the ellipsoid over here. Then we have the

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1 electrode. And now we make the shock wave release. Now you
2 can see this spherical wave. And now we see the focused
3 wave traveling to the focal point.
4 Now we have the focal point where the spheropoidic
5 sender is located. Again. So focussing. Now we hit the
6 spheropoidical area.
7 [Slide.]
8 So far for the principles. Some technology
9 properties from the bench testing of the device.
10 [Slide.]
11 Most important, we have a penetration depth of the
12 focal area ranging from 0 mm to 100 mm that says we can
13 start treatment from right on the skin to about 10 cm
14 penetration depth where the focal size 5.5 mm to 16 mm--that
15 means the site of the focal point is about the size of a
16 small finger, something like that, where we have a maximum
17 pressure of 49 MPa which means 490 bars.
18 The rise time of the shock wave, itself, is 33 ns,
19 which is a very fast process in physics, as well, and it is
20 very hard to measure. The pressure pulse width is 280 ns.
21 [Slide.]
22 We characterize that according to an FDA guidance
23 document which was released in 1991 and suggested the
24 information how to provide to FDA for lithotripsy
25 measurements. We used the same protocol for that.

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1 [Slide.]

2 This is one of the examples from those pressure
3 measurements. This is the distribution of the amplitude in
4 the direction of the beam. So the ellipsoid is located
5 somewhere here. We are coming to the focal point which is
6 located at the set position of 0. This is the amplitude
7 distribution of the focussing process.

8 This data we use to extract the length of the
9 focal point where 61 mm was extracted from that plug.

10 [Slide.]

11 Other type of testing we did is electrode testing.
12 We tested samples at 80 kV, 23 kV, 28 kV, looked that they
13 showed no misfiring, that they performed very well, that the
14 insulation stays intact, that there is no mechanical damage
15 to the electrode.

16 We do to all devices a final performance testing.
17 Some examples are conductor resistance testing, leakage
18 current, safety circuits, emergency stop, shock-wave
19 performance.

20 [Slide.]

21 To give you an overview of the nonclinical
22 testing.

23 [Slide.]

24 The standard HMT is working and producing devices,
25 so we are an ISO-9000 certified company which is inspected

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1 by the LGA in Nuremberg, which is the modified body in
2 Europe. Then OssaTron is inspected according to the IST
3 standards, electromagnetic compatibility testing, software
4 verification and validation, which is a guidance document by
5 FDA. Shock-wave testing, as I mentioned before, and a final
6 test for each device before CE labeling.
7 [Slide.]
8 What I want to give at the final end of my
9 presentation is a short conclusion about the studies with
10 the information in Europe. So I will conclude that shock-
11 wave treatment of kidney stones is reported to be an
12 effective and safe treatment modality. Laboratory studies
13 of shock-wave application to bones and tendons in Europe
14 have shown that low side effects might be caused by
15 mechanical shock-wave energy or capacitation generation.
16 Bone growth and new blood-vessel formation has
17 been reported in those articles, and healing signs have been
18 found after some days in the exposed area.
19 Thank you for much for your attention. Now, I
20 will transfer, again, to Marie Marlow.
21 **Clinical Study**
22 MS. MARLOW: Thank you.
23 [Slide.]
24 Our study of the OssaTron was a multicentered,
25 randomized, double-blinded, placebo-controlled clinical

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1 trial. The primary objective of the study was the determine
2 the safety and effectiveness of the OssaTron for performing
3 the ESW treatment for chronic heel-pain syndrome.
4 [Slide.]
5 The study also had two secondary objectives. We
6 wanted to look at the durability of results, to a minimum of
7 six months post treatment, and we wanted to collect
8 sufficient preliminary safety and effectiveness data so that
9 we could develop appropriate contraindications, warnings and
10 precautions for the device labeling.
11 [Slide.]
12 The complete list of inclusion and exclusion
13 criteria are described in our study protocol and basically
14 included the requirements that each patient had to have had
15 symptoms for at least six months and had to have failed to
16 respond to at least prior attempts at conservative
17 treatment.
18 The investigator assessment of heal pain had to be
19 more than 5.0 on a 10 cm Visual Analogue Scale, VAS. The
20 subject's self assessment of pain during the first five
21 minutes of walking in the morning had to be more than 5.0 on
22 a 10 cm VAS. Other causes of heel pain must have been ruled
23 out such as clinically significant vascular insufficiency of
24 neuropathy of the lower extremities. And, concomitant
25 pathophysiologies must have been ruled out.

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1 In other words, we were targeting the patients
2 with moderate to severe recalcitrant heel-pain syndrome who
3 had exhausted nonoperative management. We wanted to enroll
4 the same patients who would be considering surgery to
5 include quality of life or to return to work.
6 [Slide.]
7 To meet our study objectives--that is, to look
8 primarily at safety and effectiveness, but then also to look
9 at durability of results--we looked at findings at several
10 intervals to 12 months post treat-treatment. We did this
11 because of what is known about the natural history of
12 chronic heel-pain syndrome.
13 We assigned the initial success/fail status at
14 12 weeks post-treatment because we believe that this is a
15 long enough time for the complete healing process and,
16 therefore, the full benefit of treatment to occur.
17 But we also know that, because of the known
18 natural history of the condition, some of the study patients
19 might get better on their own during the course of study
20 participation even in this recalcitrant patient population.
21 So we decided to make the primary success/fail assignment at
22 12 weeks post-treatment because we felt that this interval
23 would be most likely to let us measure outcome as a direct
24 response to treatment.
25 We thought that a patient's status after a longer

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1 interval, such as 6 months or 1 year, could arguably be
2 attributed to the natural history of the condition rather
3 than to the ESW treatment.
4 As I said, we also wanted to look at the issue of
5 repeat treatment. We knew from reports of clinical series
6 in Europe that multiple treatments were sometimes advocated,
7 so we wanted to collect enough information to assess how
8 this might apply to the OssaTron.
9 So, if a patient failed the initial treatment,
10 whether active or placebo, the patient was allowed the
11 option of a repeat treatment. Patients who initially had a
12 placebo treatment could then have a primary ESW treatment
13 and the active-treatment patients could have a repeat
14 treatment.
15 The protocol requirements continued to apply. The
16 success/fail status was assigned at 12 weeks and then follow
17 up continued through 6 and 12 months to see if the results
18 of treatment changed.
19 [Slide.]
20 In addition to our clinical investigators, the
21 study participants included our medical monitor, Dr. John
22 Ogden, who we introduced to you earlier. We also appointed
23 an independent reviewer who periodically reviewed our study
24 findings and advised us as to the interpretation of clinical
25 significance of the findings. This was Dr. Sally Rudicel of

at

1 the New England Medical Center, Department of Orthopedics,
2 Foot and Ankle Section.
3 [Slide.]
4 These are the seven investigational sites that
5 participated in the study. I will point out that Baylor
6 College of Medicine, the final site that was approved for
7 participation in the study, had not enrolled any patients at
8 the time the database was closed to prepare the PMA and so
9 patients from this site were not included in any the
10 analyses in our PMA.
11 [Slide.]
12 We were approved to enroll 300 randomized and
13 50 nonrandomized study patients. The purpose of enrolling
14 the nonrandomized patients was so that we could train the
15 nonblinded investigator at each site how to do the study
16 procedure.
17 At the time we closed the database to prepare the
18 PMA, we had enrolled a total of 314 patients in the study.
19 Of these 314, 302 had undergone the study procedure at the
20 time we closed the database including 42 nonrandomized
21 patients and 260 randomized patients. The remaining 12 were
22 completing pretreatment lab and X-ray requirements or were
23 simply waiting for the scheduled treatment date when we
24 closed the database.
25 Five of the 302 patients, or 1.7 percent, withdrew

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1 from the study or were lost-to-follow-up prior to the 12-
2 week follow-up visit. One of the five was a nonrandomized
3 patient and the remaining four are nonrandomized patients.
4 At the time we closed the database to prepare the
5 PMA, 276 of the 297 remaining subjects were eligible for and
6 had completed 12-week follow up. There were 21 patients
7 continuing the study participation who simply had not
8 reached 12 weeks post-treatment at the time we closed the
9 database.
10 [Slide.]
11 The study population was predominantly female and
12 the subject's ages, at the time of study enrollment, ranged
13 from 20 years to 79 years. Our subjects were predominantly
14 Caucasian.
15 [Slide.]
16 The study protocol required that each subject must
17 have had symptoms of heel pain for at least six months prior
18 to study enrollment. The mean duration of symptoms for the
19 active-treatment subjects was 2.65 years, for placebo
20 subjects it was 2.95 years. For the nonrandomized-subjects,
21 the mean was 2.58 years.
22 [Slide.]
23 In our study, the OssaTron treatment was completed
24 in an average 17 minutes for active-treatment patients,
25 16 minute for the placebo patients, and 19 minutes for the

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1 nonrandomized patients. All of the procedures were
2 performed at 1500 shocks delivered at a power setting of
3 18 kV and the overwhelming majority of procedures was
4 performed with a local anesthetic or ankle block.
5 [Slide.]
6 We applied a very stringent composite scoring
7 system to our study findings. The success/fail status was
8 assigned to each subject at the 12-week follow-up visit
9 according to four parameters. Those included the
10 investigator's assessment of pain--the exact description is
11 up on the slide--the subject's self-assessment of pain, the
12 subject's self-assessment of activity, and the use of pain
13 medications.
14 A subject had to meet all four of these criteria
15 in order for the composite endpoint of success to be
16 assigned. I am first going to go over the findings for each
17 of these individual parameters and then I will give the
18 overall success/fail status.
19 [Slide.]
20 The investigator who was blinded to randomization
21 assignment assessed the patient heel pain by applying
22 pressure to the heel at the insertion of the plantar fascia
23 on the medial calcaneus. This is according to the
24 definition of heel-pain syndrome from Dr. Pfeffer in Jahss'
25 text book.

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1 Investigator assessment is probably the most
2 clinically significant measurement of outcome of the four
3 that we used and it was also the most significant in our
4 statistical analyses, as George DeMuth will talk about in
5 few minutes.
6 This may be because this evaluation is "the" one
7 of the four evaluation parameters that is the least affected
8 by such other factors as the patient's attempt to compensate
9 for heel pain or the patient's perception or correct
10 recollection of pain or activity.
11 [Slide.]
12 62 percent of the active treatment patients were a
13 success according to the investigator assessment following a
14 single treatment compared to 44 percent success rate in
15 placebo patients.
16 For the sake of full disclosure, here are the
17 findings for the nonrandomized or training patients. Please
18 keep in mind that the results for these patients are not
19 included in the statistical analyses of our findings.
20 [Slide.]
21 For the self-assessment of pain, we asked the
22 patients to report the amount of pain they had had during
23 the first few minutes of walking in the morning. This was
24 also reported according to a 10 cm VAS.
25 60 percent of the active treatment patients were a

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1 success for this parameter following a single treatment with
2 48.2 percent of the placebo patients meeting the success
3 criteria. Again, for the sake of full disclosure, here are
4 the findings for the nonrandomized patients.
5 [Slide.]
6 The subject's self-assessment of activity was
7 measured in two ways; according to the distance and to the
8 length of time the patient could walk. Overall, 71.4
9 percent of the active treatment patients met success
10 criteria for the combined activity self-assessments and 67.7
11 placebo treatment patients met the success criteria for this
12 parameter.
13 Again, for the sake of full disclosure,
14 87.8 percent of the nonrandomized subjects met the success
15 criteria for this parameter.
16 [Slide.]
17 Finally, we asked each patient to report the
18 medications he or she was taking for pain at the initial
19 study enrollment visit and, thereafter, to keep track of all
20 medications taken for pain throughout the course of study
21 participation. In order to be assigned the status "success"
22 for this parameter, the patient's use of pain medication for
23 any indication must be classified as none or rare at the 12-
24 week visit and prior to the 12-week follow-up visit, the
25 subject must have taken on pain medications for twice the

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1 half-life of the medication taken which was usually about
2 24 hours.
3 69.7 percent of the active treatment patients and
4 64.6 percent of the placebo patients were a success for this
5 parameter. For the nonrandomized patients, it was
6 80.5 percent.
7 [Slide.]
8 Once again, we will go over the success/fail
9 criteria and, again, the subjects had to meet four of four
10 criteria to be assigned an overall final status of
11 "success." So it is investigator assessment, subject self-
12 assessment, self-assessment of activity and use of pain
13 medications according to the limits described on the slide.
14 47.1 of the active treatment patients met all four
15 criteria compared to 30.2 percent of the placebo patients.
16 This is a difference of 56 percent between the active and
17 placebo patients. Of the 41 nonrandomized patients,
18 58.5 percent met all criteria.
19 [Slide.]
20 One of our secondary objectives in this study was
21 to collect information about the durability of treatment
22 results. All the patients who were a success at 12 weeks,
23 whether placebo or active, had to continue follow up through
24 the 6 and 12-month visits.
25 In the case of the failed subjects who didn't

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1 withdraw from the study to have some other form of treatment
2 for heel pain, we also asked these subjects to voluntarily
3 continue follow up through the 6 and 12-month visits.
4 88 percent of the active subjects maintained the "success"
5 status at the 6-month visit compared to 71 percent of the
6 placebo patients.
7 The other secondary objective was to look at the
8 issue of repeat treatments. Again, we knew from reports of
9 European clinical series that repeat or serial treatments
10 had been recommended. So this is the data that we collected
11 about this. Only 43 percent of the active treatment
12 patients who failed the primary treatment chose to have a
13 repeat OssaTron procedure.
14 It is unclear why the remaining 57 did not opt for
15 retreatment. This may say something about the study
16 success/fail criteria versus patient satisfaction with
17 outcome, especially since many of the failed active-
18 treatment patients volunteered when asked to stay in the
19 study and continue to be followed without undergoing any
20 further treatment for heel pain.
21 Compared to the 57 percent in the active-treatment
22 group who opted for retreatment, 70 percent of the patients
23 in the placebo group opted for the primary OssaTron
24 treatment. In the group of patients originally randomized
25 to active treatment, the success rate following repeat

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1 treatment was 52.4 percent

2 [Slide.]

3 We also looked at how the subjects originally

4 randomized to placebo treatment responded to the primary ESW

5 treatment and the success rate there for four-of-four

6 criteria was 54.1 percent.

7 [Slide.]

8 Our analysis of safety parameters includes data

9 for each of the 302 patients who had a study treatment,

10 whether randomized or nonrandomized and whether or not 12-

11 week follow-up data were available. A total of 38

12 complications were reported in these 302 patients who had a

13 total of 273 active ESW treatments and 130 placebo

14 treatments. We have had no unanticipated adverse events, no

15 serious device-related events in any patient participating

16 in this investigation.

17 All the complications that have occurred have been

18 temporary in nature in all the results and all have resolved

19 spontaneously without intervention.

20 [Slide.]

21 In the active-treatment group, there were 18 total

22 complications. Ten were procedure-related and eight were

23 not related to the OssaTron procedure. In the placebo

24 group, there were a total of fifteen complications, thirteen

25 following the placebo treatment, eight of which were related

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1 and eight unrelated to the placebo procedure and then an
2 additional two complications that occurred after an active
3 ESW treatment in a placebo patient. Among the nonrandomized
4 training patients, there were four procedure-related
5 complications and one nonrelated complication.
6 [Slide.]
7 The most commonly reported procedure-related
8 complications were post-treatment pain and mild numbness or
9 tingling in the treated foot. Pain was reported following
10 1.5 percent of the active ESW procedures and 3.1 percent of
11 the placebo procedures. 2.2 percent of the active treatment
12 patients had numbness or tingling after the procedure and
13 0.8 of the placebo patients reported this complication.
14 Two patients who had active ESW treatment
15 sustained midsubstance plantar fascia tears during the
16 course of study participation. In both cases, the
17 investigators determined the tear to be unrelated to the
18 study procedure and the medical monitor confirmed this
19 determination.
20 Two late complications occurred including an
21 exacerbation of heel pain at six months in a nonrandomized
22 patient and localized tingling at the site of ankle-block
23 injection at 12 weeks post-treatment in an active-treatment
24 patient. Both of these late complications resolved
25 spontaneously without intervention.

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1 At this point in time, I will turn things over to
2 George DeMuth to give you the statistical analyses of these
3 findings.

4 **Statistical Summary**

5 DR. DeMUTH: Thank you, Marie.

6 [Slide.]

7 I am George DeMuth. I am President of StatTech
8 Services, LLC. We provided statistical consulting and
9 support on the project. I am not a shareholder and I don't
10 have a financial interest in the HealthTronics aside from
11 them being a client for this project.

12 [Slide.]

13 This slide gives you an overview of what I am
14 going to talk about and just go over the statistical testing
15 results. We start with tests of baseline homogeneity, look
16 at the evaluation of 12-week response, look at the primary
17 efficacy endpoint and the components. I have a couple of
18 secondary efficacy analyses that I am going to look at and
19 there is an evaluation of covariates and a brief comment on
20 the SF36.

21 [Slide.]

22 These are the factors we looked at to evaluate
23 baseline homogeneity. What we were trying to do is evaluate
24 whether they were distributed homogeneous across the sites
25 and treatment. So we fit either our logistic model or a

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1 general linear model, depending upon the endpoint, as a
2 function of site and treatment.
3 This is a randomized trial so we really don't
4 expect to see an association of treatment except by chance.
5 [Slide.]
6 This is a table of p-values, actually. Sites
7 actually significantly associated with these, are they are
8 associated with sites. Gender is actually somewhat
9 associated with treatment. This would be of interest if
10 these were predictive and there was a site effect.
11 [Slide.]
12 I am going to turn to the analysis of primary
13 efficacy results. You saw these numbers early. This is the
14 composite endpoint at 12 weeks. There was a 47 percent
15 response in the OssaTron active group and a 30 percent
16 response in the placebo. Now, we actually did one interim
17 analysis and so we have a O'Brien-Fleming correction. Our
18 p-value reference for an alpha is 0.043.
19 We constructed a likelihood ratio test fitting a
20 model that included the site. And then, looking at the
21 difference between non or mild and the treatment difference
22 fit, and we got a p-value of 0.008, somewhat adjusting for
23 site.
24 Then we had relative risk; this is not an adjusted
25 relative risk, 1.56, indicating about 56 indicating about

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1 56 percent better response in the OssaTron than placebo.

2 [Slide.]

3 These are just some additional test statistics.

4 The first one is our main test. This other is the Cochran-

5 Mantel test controlling for site controlling for site. The

6 p-value is almost identical, 0.009. These last two don't

7 adjust for study site, 0.008 and 0.011 for the Fisher's

8 Exact is a little more conservative.

9 We looked at the Breslow-Day test which is a test

10 of homogeneity odds ratios across the study sites. It is a

11 somewhat interaction test and it is not significant, 0.247.

12 [Slide.]

13 These are the four components of success.

14 Actually, for the composite, you had to be successful on all

15 these. These are the individual components. We actually

16 see a trend towards the OssaTron on all the measures. This

17 is an unadjusted chi-square test. In the investigator

18 assessment, it was 0.005. Pain on walking is marginal,

19 0.08. While there is a trend in activity level and

20 medication use, they are not statistically significant.

21 So just the main efficacy endpoint was a

22 significant result, 0.008 when compared with 0.043 that we

23 needed because of the interim analysis. We got most of our

24 activity or significance out the investigator suspect.

25 [Slide.]

at

1 I want to turn to a couple of secondary analyses.
2 This is a kind of failure analysis. What we did is
3 constructed, starting at 12 weeks, if you failed to meet the
4 composite endpoint, you are a failure. So these 12-week
5 results match our primary efficacy. Then if patients become
6 a failure at a later time point, then they become an event
7 as a failure. People that are not followed up are censored
8 in this.
9 This was an attempt to get at a durable response
10 and also attempt to see if we could sort of root out a
11 nondurable placebo response. If we saw a placebo response
12 that didn't maintain as well as a OssaTron response, we
13 would expect these curves to deviate and come apart.
14 Hopefully, the OssaTron doesn't go down very much.
15 It is pretty much what we see. We actually get
16 wider here at the six month. If you look at the bottom, it
17 is a log-rank test. The p-value is 0.002. It is more
18 significant than our original primary efficacy.
19 Before we go on, I want to show the results for
20 the six months, but you have to consider them in the context
21 of that they are only for patients that were survivors at
22 12 weeks.
23 [Slide.]
24 As we noted before, for these patients, we got
25 about 71 percent response in placebo versus 88 in the

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1 OssaTron group. It is not statistically different,
2 significantly different, but it is partly we are going
3 through a reduction in the sample size because only
4 survivors can make it here.
5 [Slide.]
6 This slide shows the investigator VAS scale. We
7 are actually looking at the other end of the curve here.
8 This was our most sensitive measure. What we saw if we
9 looked at the four-week visit is we got significance already
10 in this measure. It is also significant here. I apologize.
11 There is a little error on the slide. These bars are in the
12 wrong place. This is statistically significant as well.
13 I tabbed this slide three times and then I forgot
14 to get it fixed. So I apologize. But the key thing here, I
15 think, is noting that we had actually an early response in
16 this and the other second evaluation of the time-to-failure
17 gave some evidence of a sustained response; at least the
18 curves certainly did not go together.
19 [Slide.]
20 I am going to turn to some evaluation of
21 covariates. We analyzed these using the likelihood ratio
22 tests. We used models along the same line that we did our
23 primary analysis. We fit the covariate first and then we
24 looked to see if treatment difference was significant after
25 then. Then we also looked at the interaction.

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1 There are three reasons that we did it. One was
2 to look for predictive factors. The next was to sort of
3 validate that treatment was still significant after the
4 covariate and to look for potential interactions.
5 [Slide.]
6 This slide, is, again, I'm sorry, of p-values.
7 But there are some things about it. We did get some
8 significant factors; age, back pain, baseline pain, duration
9 of pain. It doesn't really matter if you get a very
10 significant treatment effect. There is one marginal
11 interaction in back pain.
12 I am going to look at two of these in detail. I
13 am going to look at duration of pain just because it is the
14 most significant, and I am going to look at the back pain
15 because there was this interaction term.
16 [Slide.]
17 This slides shows the response by duration of
18 pain. All I did was actually split by median. Not
19 surprising, I think, that we see these patients did not
20 respond as well as the patients that have the shorter
21 duration of pain, but I think what was nice to see here is
22 the treatment effect didn't really go away.
23 This is about 21 percent versus 39 percent.
24 Actually, the difference is about the same. It is almost
25 two-fold.

at

1 [Slide.]

2 This is the response by back pain. This is

3 actually an ad-hoc parameter. We looked at it just sort of

4 by inspection of the data. We got this marginally

5 significant interaction.

6 There is absolutely no difference in the placebo

7 response. It was 0.31 versus 0.30. Back pain, itself, is

8 actually less than 20 percent of the population. So I am

9 not sure whether this is actually an artifact of the data or

10 it is real. But it is clear we got this marginal

11 interaction, so I wanted to present it.

12 Those are what I am going to talk about for the

13 covariates. Now, I think our treatment effect remained

14 robust, at least in terms of p-values, although we did have

15 this one marginal interaction.

16 [Slide.]

17 I have one last analysis I am going to talk about.

18 This is the SF-36 composite score, percent change from

19 baseline, mental and physical composites, at, of course,

20 4 weeks, 8 weeks and 12-weeks. Now, a higher value is

21 better here as percent improvement OssaTron and better as--

22 it is a trend, but none of these were significant on a t-

23 test. It is sort of like these other measures where we see

24 some trend towards the OssaTron, but they are not

25 statistically significant.

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1 [Slide.]

2 I have a concluding slide here. The primary
3 efficacy result, 12 weeks, was significant, 0.008 relative
4 to 0.043. Active there was 56 percent better than placebo.
5 The investigator was the most sensitive measure, and it
6 actually showed some sensitivity early on even though maybe
7 those patients were not successes at that point in time.

8 There is some evidence of sustained effect and the
9 effect was across the all the populations. The study
10 results support a treatment effect, shows strong evidence of
11 the treatment effect.

12 Thank you.

13 **Summary**

14 MS. MARLOW: Thank you.

15 [Slide.]

16 Our study showed that a single ESW procedure with
17 the OssaTron is a safe and effective treatment for chronic
18 heel-pain syndrome. We studied patients who would otherwise
19 be candidates for surgery. They had moderate to severe
20 heel-pain syndrome for at least six months. They had failed
21 three prior courses of conservative treatment.

22 Following a single OssaTron procedure,
23 62.2 percent were a success according to the blinded
24 investigator assessment and 60 percent were a success by
25 their own self-assessment. 47.1 percent of the subjects

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1 randomized to active treatment met all four-of-four success
2 criteria compared to only 30.1 percent in the placebo group,
3 a difference of 56 percent that is significant at a p-level
4 of 0.008.
5 [Slide.]
6 We see no reason to recommend routine repeat
7 treatment. In our study, far fewer subjects than we
8 expected chose to have a repeat treatment. Less than half
9 of the patients who failed a primary ESW treatment chose to
10 have a second treatment.
11 The number of subjects who chose to have a
12 retreatment seems to be more closely related to the number
13 of subjects who failed according to the investigator and
14 subject self-assessments rather than to the number of
15 subjects who were eligible for retreatment based on the
16 four-of-four criteria. It appears that retreatment has
17 about the same success rate as a primary treatment.
18 The results of a single ESW treatment appear to be
19 durable through six months post-treatment. 88 percent of
20 the active treatment subjects were still a success for all
21 four evaluation parameters at the six-month visit.
22 The risks associated with the OssaTron treatment
23 were acceptable in consideration of the benefit of
24 treatment. No study subject has experienced an
25 unanticipated or serious device-related adverse event during

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1 the course of study participation.

2 All of the procedure-related complications were

3 temporary in nature and all resolved spontaneously without

4 any intervention. The most common complications were

5 transient numbness or tingling which occurred in 2.2 percent

6 of the active-treatment patients and in 0.08 percent of the

7 placebo treatment patients, and persistent pain, post-

8 treatment, which occurred in 1.5 percent of the active

9 treatment and in 3.1 percent of the placebo patients.

10 Therefore, based on the safety and effectiveness

11 data collected and analyzed as described, the following

12 indications, contraindications and precautions were included

13 in the draft labeling for the OssaTron.

14 [Slide.]

15 Our indication for use is worded that, "The

16 OssaTron is indicated for use for performing extracorporeal

17 shock-wave ESW treatment in patients with chronic heel-pain

18 syndrome who have failed to respond to conservative

19 treatment. Chronic heel-pain syndrome is defined as pain in

20 the area of the insertion of the plantar fascia on the

21 medial calcaneal tuberosity that has persisted for six

22 months or more.

23 [Slide.]

24 Our contraindications include patients who have

25 not yet reached skeletal maturity, patients with bleeding

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1 disorders and patients who are taking medications that may
2 prolong blood clotting in pregnant women.
3 [Slide.]
4 We have included the precaution in our labeling
5 that the OssaTron treatment should be performed by a
6 physician with experience in the care of patients with foot
7 and ankle disorders. We have also stated that the OssaTron
8 may only be performed by a physician who has completed a
9 training course in the use of the OssaTron for heel-pain
10 syndrome, and HealthTronics will be providing the training.
11 training courses. The training will include information
12 about device use and about appropriate patient selection.
13 We will inform the users that anesthesia is
14 required for OssaTron procedures and that the overwhelming
15 majority of clinical study procedures were performed with
16 local or regional anesthesia. Of course, we recognize that
17 the choice of anesthesia always remains at the discretion of
18 the physician.
19 We will warn about the risk of injury to nerves or
20 blood vessels, and we will warn that the OssaTron should be
21 carefully positioned by the physician throughout the
22 treatment to avoid these structures.
23 We will warn that patients should be carefully
24 screened for concomitant problems such as tarsal-tunnel
25 syndrome or other nerve-entrapment disorders, diabetic

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1 neuropathy, calcaneal fracture, significant peripheral
2 vascular disease, rheumatoid arthritis and other similar
3 conditions that could be possible causes of heel pain.
4 Finally, we will include the warning that patients
5 with a history of current or recent direct therapy that
6 interferes with tissue healing such as immunosuppressant
7 agents or long-term corticosteroids should be evaluated
8 carefully prior to treatment with the OssaTron since the use
9 of such medications may reduce the effectiveness of ESW
10 treatment.
11 Dr. Boyan and panel, we have been intentionally
12 brief. As you know from the materials that FDA provided,
13 you know there is a lot more information in our PMA. So we
14 will be happy to answer any questions you may have. Thank
15 you very much for your attention during the presentation.
16 DR. BOYAN: Thank you very much, Ms. Marlow.
17 Since this is my last act as chairman and they
18 can't get mad at me and punish me in any way, I am going to
19 now put into effect the things that I always wanted to do
20 for the past five years, and that will make this go more
21 quickly and painlessly.
22 So, rather than have it be open to questions and
23 answers now, what I would like to do is get all positions
24 out on the floor and then I will invite you back,
25 HealthTronics, to make any last comments you might want to

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1 make in rebuttal. And then we will have the general
2 discussion.
3 So I am going to turn this over now to the FDA and
4 ask the lead reviewer, Sankar Basu, to make his
5 presentation.
6 It is with great trepidation I tell you this next
7 little thing. Do not--you have no permission to--get up and
8 leave the room at this time. But the FDA presentation is
9 available in hard copy outside and if you really just have
10 to have it, you can sneak out the back way. But it will be
11 up on the screen and we can all follow along.
12 Then, if you would like to take a copy of it home,
13 certainly, there are copies available for you.
14 **FDA Presentation**
15 **Introduction**
16 DR. BASU: Good morning.
17 [Slide.]
18 I am Sankar Basu. I am with the General Surgery
19 Devices Branch, being trained in physics. I will briefly
20 describe the OssaTron technological characteristics and the
21 principle of shock wave generation.
22 [Slide.]
23 OssaTron is a device, a shock-wave device, which
24 is intended for use in chronic heel-pain syndrome, but this
25 company has a similar device, LithoTron, which was cleared a

at

1 few years ago for fragmentation of the kidney stone.

2 Characteristics of the shock waves are they build

3 up a high pressure gradient which can go up to 100 mPA which

4 is close to one kbar, 1000 bar of pressure, which will

5 exceed the comprehensive strain of the tissue material.

6 Shock wave energy is generated extracorporeally by an

7 underwater capacitor discharge, which is know as spark-gap

8 technology, can be propagated to the target tissue without

9 any energy loss or damage to the body tissue when it is

10 highly focused.

11 [Slide.]

12 This can be focused precisely by integrating the

13 energy source into a suitable reflecting system which is a

14 metallic reflector which is ellipsoid in nature. Dr.

15 Schultheiss has described previously that it has two foci.

16 One of the foci contains a pair of electrodes and the other

17 foci is the target material.

18 The shock wave is generated by underwater

19 discharge of the capacitor can reproduced any time.

20 [Slide.]

21 Histopathological evaluation; this is based on the

22 European studies. No evidence of marked damage to tendon

23 and adjacent tissues for energy densities used up to

24 0.28 mJ/mm2 was noted. This is based on the animal studies

25 in the Achilles tendon of the rabbit.

at

1 At energy densities of 0.60 mJ/mm2, the tendon and
2 the paratendon showed marked damage. Increase in tendon
3 diameter, fibroid necrosis and inflammatory reaction had not
4 completely disappeared after four weeks of the treatment.
5 [Slide.]
6 The sonographic evaluation; three levels of
7 sonographic evaluation was made. Level 0 is a difference in
8 diameter of up to 0.5 mm. Level 1, the difference in
9 diameter between 0.5 and 1.0 mm. Level 2 is the difference
10 in diameter greater than 1.0 mm compared to the baseline.
11 Now, the conclusion was, at 0.28 mJ/mm2, three
12 cases of Level 2 and 0.8 mJ/mm2, a few of Level 1 thickening
13 were observed. No damage to muscle or body structure was
14 noted.
15 [Slide.]
16 The principle of shock-wave generation; shock wave
17 for OssaTron is generated by underwater electrical discharge
18 caused by the passes of 18,000 Volts or above. Typically,
19 they use 14 kV to 28 kV, but, for treatment purposes, 18 kV
20 is used across the spark gap.
21 [Slide.]
22 Energy densities can be divided into three areas;
23 Low energy is considered to be 0.08 to 0.28 mJ/mm2. Medium
24 energy is from 0.28 to 0.60, and high energy is greater than
25 0.6. High energy is typically used for stone fragmentation,

at

1 but low energy between 0.8 to 0.28 is normally used for pain
2 relief as was used in the chronic heel-pain syndrome.
3 [Slide.]
4 This is a graph which shows the cellular repair or
5 damage potential plotted against the energy density. You
6 can see the mJ/mm2 energy density is plotted along the
7 X axis and the damage potential is along the Y axis. These
8 energy densities are divided into four parts; 0.12, 0.24,
9 0.36 and 0.48 where the arrows are shown.
10 The increased permeability of the cell starts at
11 0.12 to 0.14 mJ/mm2 and, at the extreme end, you will see
12 the damage of the cellular nucleus occurs at 0.48 mJ/mm2.
13 If you go beyond these, then stone fragmentation energy
14 density will be reached.
15 For pain therapy, it is pretty much within 0.08 to
16 0.47 of 0.48 in the scale.
17 [Slide.]
18 The conclusion is the energy produced is below the
19 energy for stone-breaking lithotriptors and the shock-wave
20 technology is well understood.
21 Thank you very much.
22 The next speaker will be Neil Ogden who will
23 present our clinical findings.
24 **Clinical Data**
25 MR. OGDEN: Thank you, Dr. Basu.

at

1 [Slide.]

2 First off, I would like to say that originally

3 this panel meeting was scheduled to be held in May and some

4 issues came up with the possibility of some integrity issues

5 with the data. I would like to state for the record that

6 those issues have been completely resolved. There are no

7 issues with the integrity with this data for this PMA.

8 As you can see, I am the Branch Chief for the

9 General Surgery Devices Branch. This product has been

10 reviewed in my branch.

11 [Slide.]

12 The indication for use, as you have heard, for the

13 OssaTron are for extracorporeal shock-wave treatment of

14 chronic heel-pain syndrome in patients who have had symptoms

15 for a minimum of six months and who have failed to respond

16 to conservative treatment.

17 [Slide.]

18 The study design was a randomized, prospective,

19 multicenter clinical trial consisting of a maximum of

20 300 patients with an additional 50 nonrandomized patients

21 for investigator training and seven investigative sites.

22 There was a minimum of two investigators at each

23 site. One investigator was actually doing the treatments on

24 patients. The other investigator was blinded and was doing

25 the evaluations on those treated patients.

at

1 Patients were randomly assigned to the active or
2 placebo treatment groups. Baseline and outcome assessments
3 included localized heel pain--10 cm on the VAS scale--
4 walking heel pain--and 10 cm on the VAS scale--time and
5 distance activity level and pain medication usage.
6 Each patient was followed for 12 weeks following
7 treatment. The success and failure of the treatment was
8 determined at the 12-week endpoint.
9 [Slide.]
10 Success, as you have previously heard, was defined
11 as meeting all four of the following criteria at the 12-week
12 endpoint: the investigator assessment of heel pain was
13 greater than 50 percent improvement over baseline and a VAS
14 score of less than or equal to 4; the subject's self-
15 assessment of pain, greater than 50 percent improvement over
16 baseline and a VAS score of less than or equal to 4; the
17 subject's self-assessment of activity, improvement of 1
18 point on a 5-point scale or maintenance of a baseline score
19 of 0 or 1; and use of pain medications, no pain medications
20 for heel pain.
21 [Slide.]
22 Inclusion criteria for the study: symptoms of
23 moderate or severe pain in the affected heel at the
24 insertion of the plantar fascia on the medial calcaneal
25 tuberosity that had persisted for at least six months prior

at

1 to the study enrollment; failure to respond to at least
2 three attempts at conservative treatment, two prior courses
3 of noninvasive treatment including physical therapy and use
4 of an orthotic device, and one prior course of pharmacologic
5 treatment such as NSAIDs or cortisone injections;
6 investigator pain assessment greater than or equal to 5 cm
7 on a 10 cm VAS scale at the medial calcaneal tuberosity;
8 pain self-assessment greater than or equal to 5 cm after the
9 first five minutes in the morning; greater than 21 years of
10 age; of course, informed consent; and male or female.
11 [Slide.]
12 The exclusion criteria were: pregnancy; other
13 cause of heel pain such as vascular insufficiency or
14 neuropathy; severe osteoarthritis, rheumatoid arthritis,
15 osteoporosis, metabolic disorders, malignancies, Paget's
16 disease, acute, subacute or chronic osteomyelitis or
17 systemic infection, fracture of the affected foot or ankle.
18 These were determined by patient history,
19 capillary refill, tibular artery pulse testing, gross
20 sensory evaluation and a baseline radiograph prior to
21 treatment.
22 One thing I would like to mention is that our
23 statistician will note in his review that, based on these
24 inclusion/exclusion criteria, and the patient results that
25 were provided, it was noted that patients with a shorter

at

1 time of pain and a lesser degree of pain seemed to do better
2 with this treatment and, also, he will comment on the fact
3 that, even though the study objective for this study was
4 12 weeks, if you look at some of the other time points, some
5 of the patients that had a good outcome at the 12-week
6 endpoint may have been above or below an improvement at the
7 other time endpoints prior to that in the study.
8 [Slide.]
9 We have a question or an issue that we would like
10 the panel to think about and we have a question later on,
11 after the presentations. We noted that the indication for
12 use includes the term "chronic heel-pain syndrome." We have
13 noted from the inclusion/exclusion criteria and the patients
14 treated in the study that pain seems to be coming from
15 plantar fasciitis so that the FDA believes that chronic heel
16 pain, in this study, equals plantar fasciitis.
17 [Slide.]
18 Please note the trial design and the data provided
19 do not allow analysis of the retreatment results or the
20 durability of the treatment. I know the sponsor has
21 presented an opinion on this and the FDA believes there are
22 not enough patients that were followed up to the 6-month or
23 12-month period to allow any statistically significant
24 information to be gathered from those time points.
25 [Slide.]

at

1 Patient accountability; we are just putting this
2 slide up to show that there was pretty good patient
3 accountability. We don't really have any issues with the
4 number of patients that made it through the 12-week time
5 point.
6 [Slide.]
7 Safety analysis. This slide shows that, for the
8 treated groups, there was an approximately equal amount of
9 complications, 13, 10 and 12 percent in each of the arms.
10 The placebo group also had 10 percent. But what we would
11 really like you to focus on is the procedure-related
12 complications.
13 [Slide.]
14 For the active-treatment group, this includes both
15 the nonrandomized and the randomized group. There were
16 seven nerve complications, either nerve rotation or
17 numbness. There were two plantar fascial tears. I would
18 like to note that the sponsor did not include the plantar
19 fascial tears in their active-treatment adverse events. But
20 we consider these to be potentially from the treatment.
21 There was one ecchymosis on the dorsum of the
22 toes, one mid-foot pain and one decreased sensation in the
23 medial heel for the active-treatment group.
24 The placebo group also had some intermittent
25 numbness in the lateral heel radiating to the lateral foot,

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1 increased heel pain, one nerve irritation or numbness.
2 There were a couple of other placebo patients put into the
3 complications from the treatment group and those were
4 considered by our clinician to be nonsignificant.
5 We will have a question on this for the panel at
6 the end of our presentations.
7 [Slide.]
8 This slide shows the investigator assessment of
9 heel pain and the VAS scores. From this, you can see that
10 there does seem to be a trend toward reduction in the VAS
11 scores, both in the placebo arm and in the active-treatment
12 arm.
13 [Slide.]
14 This is a brief slide showing the 12-week success,
15 the number of patients that met all four of the success
16 criteria, 47 percent for the active group and 30 percent for
17 the placebo group. Our statistician will go into greater
18 detail on this issue.
19 [Slide.]
20 So that is our brief conclusion of our brief
21 presentation of the clinical information. We have three
22 questions for the panel members at the end of our
23 presentations, all the presentations. One is concerning
24 safety of this treatment. The other is the effectiveness or
25 the clinical benefit. A third would be whether this is a

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1 heel-pain-syndrome-type of device or should it be a plantar-
2 fascia-treatment-type of device.
3 Thank you for your attention. Now, Dr. Gerry Gray
4 will present the statistical analysis for the FDA.
5 DR. WITTEN: Before Gerry Gray makes his
6 presentation, I just want to introduce Dr. Statland,
7 identify him, our new ODE Director.
8 Dr. Statland, I have already introduced you in
9 absentia, but I thought people might want to associate a
10 face with a name.
11 DR. STATLAND: Thank you very much.
12 **Statistical Analysis**
13 DR. GRAY: Good morning.
14 [Slide.]
15 My name is Gerry Gray. I would like to present a
16 summary of the statistical results for the HealthTronics
17 OssaTron device.
18 [Slide.]
19 I am going to start out with a slide that you have
20 already seen about five-times; the endpoints and success
21 criteria for the student. The overall success for a given
22 patient was determined by the success of each of the
23 individual components, independent pain assessment, self-
24 assessment of heel pain, and activity score, use of pain
25 medications.

at

1 There were four components to the overall success
2 for a given patient.
3 [Slide.]
4 This table shows a summary of the overall results
5 with the success being a patient meeting all four of those
6 criteria. 47 percent of the OssaTron patients and 30
7 percent of the sham patients met that criteria at the 12-
8 week point. Statistically, this is very significant.
9 This was the prespecified primary endpoint. There
10 was a single interim analysis. These results are similar
11 with or without any adjustment for centers. You can analyze
12 these data in various ways, but it always gives you pretty
13 much the same p-value.
14 [Slide.]
15 This table summarizes the safety-related endpoint.
16 This is the number of patients with device-related adverse
17 events for the two devices. You can see that eight of the
18 OssaTron and five of the placebo patients had device-related
19 adverse events. This is not statistically significantly
20 different.
21 This study was not designed, wasn't powered, to
22 detect any difference this small. Based on this data, all
23 we can really is that the OssaTron adverse-event rate is
24 less than 9 percent higher than the sham rate. That is
25 based on a one-sided confidence interval. It also does not

at

1 consider any relative severity of the different adverse
2 events.
3 [Slide.]
4 Just digging a little deeper into the overall
5 endpoint, you recall that 47 percent of the OssaTron and 30
6 percent of the sham patients were successes at 12 weeks.
7 You can break that down and look at each of those separate
8 components individually.
9 The general trend is that the OssaTron is superior
10 to the sham. For each of those endpoints, it had a higher
11 proportion of successes. The majority of the overall
12 effects seem to have come from the independent VAS
13 assessment that had a p-value, as you see in the last
14 column, of 0.005.
15 The self-assessed VAS score was marginal and the
16 other two endpoints were statistically not different between
17 the two. So I am going to dig a little bit further into the
18 independent VAS scores to see if we can get some insight
19 into what is going on here.
20 [Slide.]
21 This graph shows the mean score for each of the
22 two groups, the sham and the OssaTron group, at baseline for
23 8 and 12 weeks. As you can see, there is a decline between
24 baseline and 4 weeks after treatment, and then, beyond that,
25 the two groups stay pretty much the same distance apart and

at

1 there is a gradual decline between 4 and 12 weeks.

2 My best estimate of that difference is 1.1 units.

3 So you could interpret that as treatment with the OssaTron

4 device, on average, will reduce the VAS pain score by one

5 unit on a scale of 0 to 10. There is a general slope

6 between 4 and 12 weeks, a decline of 0.2 units per week, so

7 it looks like there is some maybe natural healing going on.

8 Patients continue to get better even after they have been

9 treated, regardless of whether it was the sham or the

10 OssaTron device.

11 [Slide.]

12 This graph shows the trend in the mean, the means

13 of these time points, but the means don't really tell the

14 whole story so I am going, in the next few slides, dig a

15 little further into what is really going on.

16 [Slide.]

17 This graph shows--again, the guideline is the same

18 as on the previous slide. The thin segmented lines show the

19 traces for each of the 130 patients, or the 116 patients, I

20 believe, who were treated with the sham device, at baseline

21 and after 12 weeks.

22 A couple of things become immediately apparent

23 when you see this slide. One is that there is a lot of

24 variability. There is a lot of variability within and

25 between patients. A patient can go from a very low score to

at

1 high and back again between the successive measurements.

2 The decline from the baseline to the 4-week point

3 could be explained with any combination of regression to the

4 mean, just the natural healing or some amount of placebo

5 effect. You can't really tell.

6 [Slide.]

7 Contrast the to the next slide which shows the

8 OssaTron treatment, the same slide for the patients who were

9 treated with the OssaTron device. Again, the same kind of

10 trends. There is a lot of variability, the main difference

11 being that there is a sharper decline in the baseline and

12 the 4-week point.

13 There is a difference between these two slides

14 that might not be immediately apparent, but if you look

15 towards the bottom of this slide, you will see there is sort

16 of a more dense band of lines. There is more what you might

17 call responders.

18 If you look at the previous slide, in that slide

19 you see, especially at the 12-week point, which is the

20 predetermined endpoint, there is much more of a uniform

21 distribution. On this slide, you will see how there is a

22 more dense band at the bottom.

23 Those are patients that I would call responders to

24 the treatment. That is what seems to be driving the

25 difference between the mean for the two different patient

at

1 groups.

2 [Slide.]

3 The next slide shows this a little more clearly.

4 This is a set of four side-by-side histograms at each of the

5 time points that show, basically, the same data we just saw

6 in a different way. The point to notice here is that, in

7 the upper left-hand corner, are the two distributions of

8 baseline pain scores, the green being the OssaTron device

9 and dashed bars being the placebo sham device.

10 At baseline, they had almost identical

11 distribution between scores. As you go from 4 to 8 to the

12 12-week graph in the bottom right-hand corner, what you see

13 emerging on the bottom is a set of patients who have a VAS

14 score of 0, a very low VAS score.

15 That patient group of responders appears under

16 both treatment groups. There are some responders in the

17 OssaTron and some in the placebo. What is driving the

18 difference is basically the bar for the OssaTron is much

19 larger. There is a higher proportion of responders in the

20 OssaTron group.

21 So when you see that, you start thinking about can

22 I predict which patients those are? It would be great if we

23 could know who were the responders before we do the

24 treatment. So the sponsor conducted some analyses to try to

25 determine that in the next slide.

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1 [Slide.]

2 What came out as predictive factors for overall
3 success were patients who were older, who had less baseline
4 heel pain, who had shorter duration of heel pain who also
5 had back pain. There was an interaction, as was mentioned,
6 where the OssaTron subjects, with back pain, had a
7 relatively higher success rate.

8 So there are some predictive factors in the data
9 we have. I am not sure that is useful to the clinician or
10 not. They seemed to me to be more common sense than
11 anything else. But that is all we know about why people
12 respond to the treatment.

13 [Slide.]

14 I would like to shift gears for a second. I am
15 going to look at the data in a slightly different was that
16 we haven't seen before. Again, looking at the independent
17 VAS score, this table shows the observed improvement over
18 baseline for each of the two devices, the proportion of
19 patients who had an observed improvement of 0. 2.5, 5.0 or
20 7.5 units.

21 So, for example, 89 percent of the OssaTron
22 patients had some improvement in VAS score over baseline.
23 73 percent had an improvement of 2.5 units or more, and
24 54 percent had an improvement of 5.0 units or more.
25 37 percent of the sham patients had an improvement of 5.0

at

1 units or more.

2 Based on these data, we can make a prediction for

3 the future concerning, say, the 54 percent and 37 percent.

4 We could expect that, for similar patients, at least

5 46 percent of the OssaTron and 30 percent of the sham

6 patients will have an improvement of more than 5.0 units on

7 the VAS scale at 12 weeks.

8 [Slide.]

9 Looking at that same data in yet another way, we

10 can test for the difference in improvement over baseline.

11 We can do a statistical Wilcoxin or Mann-Whitney test.

12 Again, it has a value of 0.5, the p-value is 0.014, very

13 similar to what we have already seen.

14 The advantage of looking at it this way, there is

15 an interpretation of that statistic, 0.59, and you could say

16 that, for a particular patient, there is a 59 percent chance

17 that if you treat them with the OssaTron, they will do

18 better than if you had treated them with the sham device.

19 For comparison, is the device is totally ineffective, you

20 would be able to say the 50:50 chance of doing better.

21 [Slide.]

22 To summarize, then, based on the prespecified

23 primary analysis, the OssaTron is statistically superior to

24 the sham device. That result holds up under various other

25 alternative analyses. The difference is due primarily to

at

1 the difference in the independent pain evaluation, the VAS
2 score, and that is driven by a higher proportion of what I
3 would call responders in the OssaTron group.
4 The predictive factors that were identified for
5 overall success were age, baseline and duration of heel pain
6 and back pain.
7 Thank you very much.
8 DR. BOYAN: Is that the end of the FDA
9 presentation?
10 DR. WITTEN: Yes.
11 DR. BOYAN: We are going to now move to the
12 reviewers, the lead reviewers, from the panel and have them
13 present their review. Then we will move to general
14 questioning of all who are here.
15 So I would like to ask Dr. Lewin to present his
16 preclinical review of the application.
17 **Panel Reviews**
18 DR. LEWIN: Thank you. I primarily looked into
19 the technical specifications. I am an expert in shock-wave
20 technology. I have to say that I was actually impressed
21 with the data which the company provided. The measurements
22 were done according to the FDA guidelines and they are
23 showing everything they should.
24 I do have a couple of questions. I don't know
25 whether it is appropriate to raise them right now but you

at

1 will tell me.

2 DR. BOYAN: You can ask no questions.

3 DR. LEWIN: Okay; no questions right now.

4 Otherwise, overall, technically, it seems to be a very solid

5 application.

6 DR. BOYAN: Thank you.

7 Could I then have Dr. Robinson present the

8 clinical review.

9 DR. ROBINSON: I can be brief also. I reviewed

10 this from the perspective of the clinical perspective of

11 taking care of this type of patient. I was impressed with

12 the sponsor's ability to do at least a 12-week assessment of

13 really a chronic-pain syndrome and done by the, should I

14 say, current gold standard of clinical investigation

15 including the sham procedure. These are studies that are

16 always very difficult to do.

17 I also have a few questions which I will not ask

18 at this time. I, again, thought the 12-week data was

19 convincing. The data after that, I am in agreement with

20 some of the reviewers, cannot really be assessed in a

21 substantial manner. However, maybe later on, we can discuss

22 using patients as their own controls.

23 So, overall, I thought it was a well-conducted

24 study to the point of the primary endpoint. I will leave it

25 at that for the moment.

at

1 DR. BOYAN: Thank you.

2 Finally, Dr. Larntz, could you present your

3 assessment of the statistical analysis.

4 DR. LARNTZ: I won't be quite as brief. It is a

5 randomized, two-arm study really designed only to look at

6 12-weeks data. The planned follow up after 12 weeks was not

7 appropriate to make any statements about duration. The

8 follow up at 6 months is horrid. I don't think you can put

9 up numbers of success after 6 months and believe them.

10 So that is my opinion on duration.

11 The 12-week data is compelling and really due only

12 to that assessment of pain relief by the physician, maybe a

13 little bit from the patient's self-assessment. There is a

14 big site-to-site variation in that, as expected, because you

15 are having different physicians doing that. So any

16 statistical analysis should correct for that site-to-site

17 variation.

18 But Dr. Gray pointed out, and everyone else has

19 pointed out, no matter what you do to these data, the 12-

20 week data look statistically significant. And they are. So

21 there is no question about that. So, at 12 weeks, you have

22 got a 12-week response.

23 There is some missing data there. 12 weeks isn't

24 a very long period of time and over 10 percent of the

25 patients were missing--although not missing lost-to-follow-

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1 up, if I heard right, only a few were lost-to-follow-up. So
2 something went wrong with the assessments somewhere along
3 the way. I didn't hear about why they didn't get scores for
4 those, but 25 patients in the study didn't have assessments
5 as 12 weeks.
6 The repeat tests; patients were self-selected to
7 do the repeat tests. There is no statistical validity in a
8 self-selected population. Sorry; nothing I can gain from
9 that so I don't think that--it was nice that the numbers
10 came out to be successful and the rates that they did,
11 because they were similar to the others. That is
12 informative, to some extent, but there was a self-assessment
13 of the patients.
14 So, basically, anything after 12 weeks I don't
15 think has any statistical validity, poor execution and
16 follow up. There is lots of missing data. I think there is
17 an FDA slide that wasn't shown that shows that, in fact,
18 that shows a tremendous amount of missing data at 6 months.
19 And they were only intending to follow the successes to that
20 6-month period, at least that was that part of it.
21 You have to think, I am a statistician, so I will
22 be careful here. Why would someone not come back at
23 6 months? About half the patients didn't come back. I
24 don't know. Do you know why patients don't come back?
25 Because they are all doing so great or because they don't

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1 want to see you again. You tell me. I don't know. I am a
2 statistician.
3 MS. MARLOW: That was rhetorical; right?
4 DR. LARNTZ: We are asking no questions here.
5 Finally, two final comments. I am not a great fan of
6 composite endpoints. You have a composite success/failure.
7 I understand some people in the FDA are fans of composite
8 endpoints. I think it was very nicely done by both the
9 company and Dr. Gray pointing out the component of that
10 composite endpoint that shows the difference. I think that
11 was nicely done and it is that immediate, that pain relief
12 component, because the quality of life, duration of walking,
13 those kinds of things, there is really no difference in
14 those effects.
15 Pain is what you are relieving and that is what
16 you get with this device. You get some pain relief and that
17 is what you see statistically. Again, I don't know anything
18 about clinical things, but statistically, that is what we
19 see.
20 Finally, on the covariates, the interaction--can I
21 be technical? I would blow that off. I don't think that is
22 any big deal, one interaction. It was in the right
23 direction. That big spike for people with back pain. You
24 see a lot of variation. I understand the covariate analysis
25 and why you do it. If it is a randomized study, the

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1 covariate analysis is not necessary for validity. In fact,
2 I think Dr. Gray pointed out, it probably showed some
3 common-sense outcomes as opposed to anything that may be
4 useful, certainly not useful for assessing the validity of
5 the conclusions. You certainly have a valid conclusion at
6 12 weeks.
7 That's it. Thank you.
8 DR. BOYAN: Thank you very much.
9 Now what we will do is we go back and we will
10 begin the general discussion period.
11 **Panel Discussion**
12 DR. BOYAN: We will ask the lead reviewers to,
13 again, come forward in that order and ask their questions
14 that they are aching to ask. Then we will go around the
15 room, each person having an opportunity to ask questions
16 that they might like to ask.
17 If you are asked a question by one of the panel
18 members, please come forward to the podium, state your name
19 and, again, your affiliation, whether you are with
20 HealthTronics or whatever, or with you are with the FDA. If
21 you are a new person that we have not heard from, like one
22 of the physicians, then you need to, again, state your
23 financial interest in the company or any other device
24 company, as appropriate.
25 So let's begin now, again, with Dr. Lewin. It is

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1 now your opportunity to go.

2 DR. LEWIN: Thank you very much. I can see that

3 this is my possibility to get the answer to those aching

4 questions. Actually, it is scientific curiosity, a little

5 bit, and some other issues associated with quality control.

6 I have about four questions. I don't know if you would like

7 to write them down, or should I repeat them.

8 One of them is are you monitoring the acoustic

9 output--in other words, the parameters of the shock wave

10 when you start the treatment? In other question, a follow

11 up--

12 DR. BOYAN: Do you want them to answer that one?

13 DR. LEWIN: Okay.

14 DR. BOYAN: Dr. Schultheiss, that sounds like your

15 question.

16 DR. SCHULTHEISS: That is obviously a good

17 question for me. Dr. Lewin, thank you for that question.

18 The monitoring is done when the device is finally tested and

19 it is done during the safety check once a year or if a

20 malfunction occurs. We do not measure by a hydrophone. We

21 measure with the power by disintegration of artificial

22 stones. So we do tests according to a lithotriptor to

23 measure what is the potential of disintegrating, so to

24 measure the acoustical energy.

25 DR. LEWIN: But will you do it before you start

at

1 the treatment or you trust the device--

2 DR. SCHULTHEISS: It is on a periodical basis,

3 only.

4 DR. LEWIN: So, theoretically, you could have a

5 situation that your discharge in the capacitor fails and you

6 do not know about it.

7 DR. SCHULTHEISS: It is the same process for the

8 lithotriptors. We are doing the same we are doing for the

9 lithotriptors with more than ten years experience.

10 DR. LEWIN: Are you changing the electrode for

11 each patient? How many shocks can the electrode--it is

12 2500; right? 2500 shocks is the life of the electrode. How

13 many shocks do you use per patient?

14 MS. MARLOW: 1800. HealthTronics has labeled the

15 electrode for this indication for use "single patient use

16 only."

17 DR. LEWIN: How is the focal volume controlled?

18 You mentioned by little finger. Again, it seems to be a

19 fairly large volume.

20 DR. SCHULTHEISS: It is defined by the measurement

21 according to the guidance document, the minus-60D curve.

22 This is the measurement we did for that. It depends very

23 much on what is large and what is small, so this is done--

24 this is just a physician definition.

25 DR. LEWIN: No; that I understand. But you don't

at

1 have any other possibility to control the focal volume. It
2 is fixed.
3 DR. SCHULTHEISS: No; it is only pressure
4 measurement. There is no other chance to control the focal
5 volume.
6 DR. LEWIN: Then, in one of the--maybe not in your
7 slides, but there was a comment that the interaction between
8 the shock waves and the tissue is very well known. I would
9 like to ask you, would you be able to illuminate me on what
10 is the mechanism of the pain relief.
11 DR. SCHULTHEISS: This might not be a good
12 question for a technician or physicist like me. Maybe I can
13 transfer over that question to Dr. Ogden. He might answer
14 it better from a standpoint of a physician.
15 DR. OGDEN: I hope so.
16 DR. BOYAN: Dr. Ogden, don't forget to give your
17 whole personal history here.
18 DR. OGDEN: I am Dr. John A. Ogden from Atlanta.
19 I am the medical monitor for this project. I have been
20 compensated for such by HealthTronics. I have had
21 compensation for my residency program and support for them.
22 And I am a shareholder in the company.
23 The basic line is we do not know exactly how it
24 works.
25 DR. LEWIN: Thank you.

at

1 DR. OGDEN: There is an hypothesis that it affects
2 membrane potential and the release of a number of chemicals
3 like substance b and calcitonin gene-related peptide. I
4 think only by doing research at a molecular level will we
5 get that answer.
6 DR. LEWIN: Thank you very much. This is
7 precisely what I was looking for. I think that the
8 statement on one of those slides was a little bit
9 optimistic. Thank you.
10 I have no further questions. Thank you very much.
11 DR. BOYAN: Thank you very much.
12 Dr. Robinson, do you want to ask some questions?
13 DR. ROBINSON: Yes. I have two questions for the
14 sponsor, the more important one first. Can someone address
15 how you do evaluate your training program? It seems to me
16 that a site for mischief for this in the real world is
17 pointing it in the wrong direction.
18 I am sure the site investigators were trained
19 intensively, but how are you going to deal with it outside
20 of sites?
21 MS. MARLOW: We have spent a lot of time and
22 effort in putting together a training program. As a matter
23 of fact, we have a couple of backup slides on that because
24 we were hoping someone would ask us this question. We are
25 very proud of the work we have done.

at

1 Dr. Richard Alvarez, who is the primary
2 investigator for our study, and Cherita Lanham, who works
3 for HealthTronics--she is the application specialist--are
4 the two people that have the most information about this.
5 Depending on the level of detail you want me to
6 get into, I can have them come up and answer anything you
7 would like. But the training program that we used for the
8 investigators was our pilot for the training program we
9 intend to use in the real world.
10 DR. ROBINSON: So you can't tell me how it is
11 going to work in the real world. I understand that, but--
12 MS. MARLOW: I actually can; yes. If you want us
13 to go into that detail, I would be glad to bring them up.
14 DR. ROBINSON: If the panel would bear with me, I
15 would like hear that.
16 DR. BOYAN: Why don't you have Dr. Alvarez come
17 up.
18 DR. ALVAREZ: I am Dick Alvarez from Chattanooga,
19 Tennessee. I have some stock in HealthTronics. I am in
20 clinical practice, an orthopedist. I only do foot and ankle
21 surgery. I am also an associate professor at the University
22 of Tennessee.
23 What we plan to do with the training is to have a
24 didactic program to explain a little bit about the physics
25 of it at a basic level for physicians. We then will go

at

1 through a hands-on training so that they will know exactly
2 where we put the machine in relation to how much the ballast
3 is fielded, the water field where the shock is delivered. I
4 think that will take, we feel, somewhere around two patients
5 or maybe more. We feel that the training will be quite
6 reliable.
7 DR. BOYAN: Thank you. Did you want to add any
8 other comments from HealthTronics?
9 MS. LANHAM: Cherita Lanham. I am an employee of
10 HealthTronics and I am a shareholder. We do intend to have
11 hands-on with the physician with an anatomical model and
12 cover the didactics in a workbook and include the physicians
13 on this before we give certification.
14 DR. BOYAN: Dr. Finnegan? Is this related to
15 this?
16 DR. FINNEGAN: Yes.
17 DR. BOYAN: Okay.
18 DR. FINNEGAN: Are you going to have your sales
19 managers doing this out in the field or are you going to
20 have a central area for this.
21 MS. LANHAM: We hope to use a central area in the
22 future, but, in the beginning--
23 MS. MARLOW: Cherita; I am so sorry, but the sales
24 managers will not--
25 MS. LANHAM: No; it will be by the investigators.

at

1 DR. FINNEGAN: By the investigators.

2 MS. LANHAM: Initially; yes.

3 DR. FINNEGAN: Will it be mandatory?

4 MS. LANHAM: Yes.

5 DR. BOYAN: Dr. Robinson, any other questions?

6 DR. ROBINSON: One more, a simple one.

7 Osteoporosis was one of your exclusions. Could you be a

8 little bit more specific about that? Was it minus 2Z or

9 minus two standard deviations, or whatever? How were you

10 planning to advise exclusions for osteoporosis where I

11 think, not understanding any physics, but guessing that

12 there could be a potential clinical problem there? How are

13 you going to recommend that exclusion?

14 MS. MARLOW: Let me repeat back the question so I

15 understand it correctly. In our exclusion criteria for the

16 study, we simply stated that patients with osteoporosis

17 should be excluded. Are you asking about the exclusion for

18 the study or contraindications in our labeling?

19 DR. ROBINSON: Maybe just the exclusions for the

20 study, as a starter.

21 MS. MARLOW: I'm sorry. I am going to have to

22 have you repeat the question.

23 DR. ROBINSON: In other words, it was an eyeball

24 assessment made and just--

25 MS. MARLOW: By medical history; yes.

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1 DR. ROBINSON: Okay.

2 DR. BOYAN: Let's then go to Dr. Larntz and see if
3 there are any specific questions that he would like to
4 address.

5 DR. LARNTZ: No specific questions.

6 DR. BOYAN: We can now begin with general
7 discussion from the panel. I would like to start over there
8 on the right with Dr. Aboulafia. Are there any specific
9 questions you would like to ask?

10 DR. ABOULAFIA: I am going to defer any specific
11 questions right now.

12 DR. BOYAN: Just continue on down around the room.
13 Dr. Goldman?

14 DR. GOLDMAN: Thank you very much. This is my
15 first time on the panel and I want to thank everyone for the
16 honor it is to be on this panel.

17 With respect to the--just as I reviewed the
18 material and the potential labeling issues and from
19 experience in my practice, when I reviewed this my focus was
20 on how a clinician would decide that a patient would be
21 appropriate, more than the obvious physical characteristics.

22 My first question is, and I probably have three or
23 four--it goes back to the issue of the potential
24 complications being different between the placebo-controlled
25 and the treated groups. Between the treated groups, there

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1 were some neuropathic complications that related to
2 transient numbness that disappeared after a month or two.
3 There were allusions to possibilities of vascular problems.
4 I also noted that, in the initial assessment, the
5 assessment of vascular problems was by pulses only. I know
6 what bounding pulses feel like. I feel a lot of pulses.
7 But there were a few cases where pulses were not bounding.
8 The other issue concerns neuropathy. Neuropathy
9 was done by gross touch or sensation. I am curious, since
10 the complication rate is different, whether the company
11 could speak to possibility that--I don't know how to phrase
12 this--that there may have been some cases of peripheral
13 neuropathy either missed or underreported related to their
14 assessment.
15 I guess this would be for the clinician in the
16 study.
17 MS. MARLOW: If I got your questions correctly,
18 you wanted us to address the complications that we had as
19 far as any kind of nerve problems post-treatment.
20 DR. GOLDMAN: -Yes; and the vascular.
21 MS. MARLOW: And then also to speak to the
22 assessment pretreatment of vascular insufficiency and any--
23 DR. GOLDMAN: Yes. And I may ask some follow-up
24 questions, if the panel will indulge me.
25 MS. MARLOW: As far as the complications with

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1 nerve problems go, if I heard you correctly, you are correct
2 that there are a variety of different types of problems.
3 Some of them may have been associated with the injection,
4 the ankle block. Some of them may have been a direct result
5 of the shock wave. Some of them may have been--there are
6 similar symptoms to what you see in a patient with an
7 orthosis that is irritating the foot or perhaps not fitted
8 correctly.
9 It is unfortunate that we didn't anticipate those
10 variations when we designed the study protocol and we don't
11 have enough information to differentiate. I will be happy
12 to then turn things over to Dr. Ogden and Dr. Alvarez. They
13 can speak to their personal experience with some of these
14 things. Again, let me know how much detail you want because
15 I appreciate that you are trying to move things along.
16 DR. GOLDMAN: I don't know how far to press this,
17 but I would have liked to have seen a more objective
18 measurement of peripheral neuropathy. A very simple one,
19 which is extremely inexpensive, is the Semmes-Weinstein
20 5.07 monofilament test.
21 MS. MARLOW: After the study had started, that
22 issue came up during a meeting with FDA. We do have some
23 Semmes-Weinstein data.
24 Dr. Ogden, can I have you speak to that since you
25 were personally involved?

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1 DR. OGDEN: Obviously, our patients were not
2 subjected to detailed neurologic studies, EMGs, things like
3 that. But we did recognize the potential problems and the
4 easiest way, as we said, to detect this is the Semmes-
5 Weinstein. Not every patient had it down, but, after we
6 instituted it, it certainly was done in virtually every
7 follow up.
8 We did not pick up, once we instituted in it in
9 pre-treatment screening, any patients that had not been
10 screened out by history where we could find that kind of a
11 variation detectable by the monofilament.
12 As Ms. Marlow said, the majority of the patients
13 that had the complications, as we looked into it, some were
14 probably related to the technique of giving the block
15 anesthesia or the local anesthesia. Some were directly
16 traceable along the lines of a rigid orthosis that they were
17 allowed to continue to wear afterwards, and we think there
18 may have been subtle shifts in weigh-bearing as they were
19 relieved from the pain in the middle of the heel where the
20 plantar fascia attaches-and shifted their weight-bearing
21 axis.
22 As far as the comment on the vascular studies, we
23 did do capillary-refill studies as well as pulse testing so
24 we did look for small-vessel refill as well as major-vessel
25 inflow.

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1 The patient with the discoloration on the toes
2 probably, with detailed questioning, had an injury that they
3 did not attribute to this and that there was some ecchymotic
4 bruising, discoloration. It happened several weeks after
5 the treatment, and it did disappear.
6 The two patients with plantar fasciitis which were
7 in the treatment group as opposed to the placebo group, one
8 had had a cortisone injection five weeks prior to the
9 treatment. The rupture occurred several weeks after the
10 treatment when she was dancing wildly at a wedding.
11 The other patient had had multiple cortisone
12 injections and it is well recognized that cortisone
13 injections do predispose to premature rupture, just actual
14 rupture, of the plantar fascia.
15 I hope that answers it.
16 DR. GOLDMAN: Thank you very much. The other
17 thing is with a doppler and a blood-pressure cuff on the
18 thigh, you can do an ankle brachial index which is a very
19 objective and inexpensive way. These are just things that I
20 might think of as objective reliable ways to look at, in
21 prospect, not in retrospect, issues related to neuropathy
22 and vascular disease because we don't know much more about
23 the patients.
24 Thank you. I will defer at this point.
25 DR. BOYAN: Thank you. The next three are our

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1 reviewers. We will give Dr. Finnegan an opportunity here.

2 DR. FINNEGAN: Dr. Ogden, don't sit down.

3 Actually, to follow up on the neurologic question. Usually,

4 neurologic testing sensation is relatively subjective and

5 more objective would be motor. I didn't see any suggestion

6 that you looked for subtle clawing of the toes, either

7 clawing post, at the six-month period, or asymmetric clawing

8 between feet.

9 We know from gunshot wounds that shock waves and

10 the velocity of the shock wave can significantly injure

11 nerves over a period of time.

12 DR. OGDEN: I'm sorry; at six months?

13 DR. FINNEGAN: At 12 weeks or at 6 months, did you

14 look--was there any documentation or did people look for

15 clawing of the toes? You are fairly close to your two

16 plantar nerves.

17 DR. OGDEN: We looked for the overall appearance

18 of the foot. A complete exam was done on range of motion of

19 the toes as part of testing for mid-foot pain and any

20 changes that may have occurred in the plantar surface where

21 we did the shock waves. We did not specifically put on the

22 questionnaire that the evaluating physician filled out

23 whether they had clawing, but that would have been picked up

24 as part of the testing of range of motion.

25 DR. FINNEGAN: The second question is, as was

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1 asked earlier and I think is an appropriate question,
2 patients don't come back for two reasons; one, you made them
3 better or two, that was the worst experience of their life
4 and they don't ever want to come back.
5 This sounds like it probably has some significant
6 pain associated with. Was there any attempt to quantify why
7 patients did not come back?
8 DR. OGDEN: We tried to call a lot of patients.
9 We do have one problem in Atlanta. It is called traffic.
10 They don't like to come downtown. But the reality is that
11 many patients, when contacted by phone, did have improvement
12 that they were satisfied with and did not want to come for
13 long-term follow-up. The short-term patients, out to 12
14 weeks, I think there were, again, problems in getting
15 compliance because the patients had had the treatment.
16 They had responses that, to some extent, they were
17 happy with and that they did not want to come in for
18 additional follow up. It is a problem that I think you have
19 in any study where you do these things. It is very
20 difficult to say whether they are better or whether they are
21 unhappy with what has been done.
22 We are dealing with a patient population that is
23 having to deal with chronic pain. The average length of
24 symptoms in the patients is two-and-a-half years. They are
25 often frustrated. I agree. If they don't get better, they

at

1 are probably going to seek alternative.

2 DR. FINNEGAN: Did you quantify why people

3 wouldn't have a second treatment?

4 DR. OGDEN: We didn't quantify it, but a lot of

5 the patients expressed that they were better, that they had

6 some satisfaction with the treatment and that they did not

7 want to go ahead with the retreatment because it meant going

8 through all the stages of the protocol again, and they were

9 willing to wait and see what happened.

10 That was the general response that we saw in most

11 of the centers.

12 DR. FINNEGAN: My last question is to follow up on

13 the question on osteoporosis. Now, as part of preventative

14 care or wellness, people are getting bone-density studies

15 which will suggest that they are "osteoporotic." Are you

16 going to have a definition of osteoporosis, or will it be

17 anybody who has bone-density studies that are not normal?

18 DR. OGDEN: Shall I defer that to you? I will

19 give that to Marie.

20 MS. MARLOW: I have to be honest that we did not

21 consider that point. I think that some good points have

22 been raised here about how that issue should be addressed.

23 One thing that I will disclose is that you may

24 know, from other things that are in our PMAs, that we do

25 have studies ongoing about the effects of shock waves in

at

1 bone.

2 We are looking at--we have an investigator at the

3 University of Rochester looking at bone-density changes in

4 our OssaTron patients at that site. Rather than having a

5 detrimental effect, there is some very early, preliminary

6 evidence that there may, in fact, be a beneficial effect.

7 So I am not sure right now exactly what statement we should

8 make about patients with or without osteoporosis.

9 The reason we excluded them in the study is we

10 just thought that this would be a confounding factor in

11 analyzing results. As far as it being a contraindication

12 because there is evidence that it would be harmful, I am not

13 sure that--

14 DR. FINNEGAN: My question is basically for the

15 person who is using it as to how they decide whether

16 somebody is really, truly osteoporotic. Is that their

17 definition? I think you need a clearer definition; i.e., if

18 your bone-density study is normal or not normal, then you

19 are osteoporotic or then you are excluded or not excluded.

20 MS. MARLOW: I think that is a very good thing for

21 us to consider when we are talking about final labeling with

22 FDA. I appreciate the comment.

23 DR. BOYAN: I would like to also just follow up on

24 that a little bit because it actually is a question that I

25 had lurking, and that is that is you are to be definitely

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1 complimented, I think, on identifying factors, risk factors,
2 and identifying a population of patients that actually is a
3 preferred responder.
4 In fact, many of these osteoporotic individuals
5 may fit very nicely into your category of preferred
6 responders. I would hate to see them eliminated if they are
7 the group that really would benefit. Unfortunately, you
8 don't have any data to show that--
9 MS. MARLOW: Not yet.
10 DR. BOYAN: Since you eliminated them from the
11 clinical study. It is very, very difficult to determine who
12 really and truly has osteoporosis and a medical history
13 showing that a woman was taking pamidromate or some other
14 drug is hardly an indication, since that is now a freely
15 given drug.
16 So I also would encourage you to carefully think
17 about how, if you have excluded them because you thought
18 they might confound, you excluded them because you thought
19 that maybe it isn't a good idea. That may not be the case
20 at all.
21 MS. MARLOW: Again, I think these are all very
22 good comments. I think it is absolutely appropriate that
23 when we are talking about final labeling, we will work with
24 FDA on that very carefully.
25 DR. OGDEN: I would just like to add something.

at

1 One of the issues, obviously, a person with something that
2 would affect the study in a potentially negative way, where
3 we don't know the response, we wanted to keep out of the
4 study. But I share your concerns about should those
5 patients now be excluded from treatment.
6 There is good evidence from the studies that we
7 have done with fracture healing and in Europe that the
8 OssaTron, at the higher levels which we don't use for,
9 obviously, the plantar fasciitis, is osteogenic. It may
10 have a positive response in improving bone density in the
11 calcaneus as well as other bones if it is properly applied
12 and we use the right energy levels.
13 I think we have to be careful about necessarily a
14 contraindication for a patient with osteoporosis.
15 DR. BOYAN: I think we agree.
16 Dr. Finnegan, any other comments?
17 DR. FINNEGAN: No; I am done.
18 DR. BOYAN: Dr. Yaszemski?
19 DR. YASZEMSKI: I have a comment that doesn't
20 necessarily require an answer although please feel-free to
21 answer if you would like to. I guess I would ask us all to
22 consider caution in labeling that will require training.
23 I could consider two ends of a spectrum, one where
24 I might be a solo practitioner, think it is a good idea,
25 have never used it before and would greatly benefit from

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1 training. In that case, if it were offered, I, personally,
2 would take it.
3 On the other end of the spectrum, perhaps I would
4 the fifth or sixth person who joined a group, all the rest
5 of whom have been using it in their office for quite a while
6 and could likely get the training locally from my
7 colleagues, like we do with many other surgical and medical
8 procedures.
9 I guess my cautious note would be training,
10 perhaps, offered by not required.
11 MS. MARLOW: You have brought up some of things
12 that we have addressed in designing the training program.
13 Please correct me if I am wrong, but there is a provision in
14 our training program that once the first members of a group
15 have been adequately trained and have done X number of
16 patients, then it is appropriate for them to train their
17 partners.
18 What we are trying to avoid is this device being
19 used by a brand-new user with absolutely no experience.
20 Those that are familiar with lithotripsy know that the
21 precedent there was before lithotripsy became so commonplace
22 and taught in residency programs, it had to be the
23 responsibility of the company to make sure that the device
24 was used properly.
25 So, again, the training program for us has been a

at

1 very complicated, arduous task to design something that is
2 appropriate, but that exact issue has been addressed.
3 DR. YASZEMSKI: Thank you.
4 DR. BOYAN: Dr. Cheng?
5 DR. CHENG: First of all, I would like to thank
6 the company for bringing a very nice study to our attention
7 that a lot of companies have stated it is difficult to do.
8 There is no doubt it is difficult, but you have demonstrated
9 it is possible.
10 I have a couple of questions which I would like
11 maybe some clarification and that is that you have
12 mentioned, for anesthetic purposes, a local block was
13 performed, but, also, you said, another option was local
14 anesthesia. Does that mean an injection in the area of
15 local anesthesia to the planar fascia identified to be a
16 factor that might affect the outcome, if that was done.
17 MS. MARLOW: As far as affecting the outcome,
18 theoretically, any more fluid in the heel pad would aid in
19 transmitting the shock waves. There is no evidence it would
20 interfere with the shock waves, so there is no
21 contraindication that injecting it into the heel pad. The
22 reason that we didn't do it in the study again was because
23 we thought it might confound study findings if we injected
24 directly in the area where we were going to direct shock
25 wave.

at

1 Am I interpreting your question correctly?

2 DR. CHENG: So you are saying local anesthesia was

3 not--

4 MS. MARLOW: It is not contraindicated at all. It

5 is used in Europe.

6 DR. CHENG: No; in terms of the study, was it used

7 for any study patient?

8 MS. MARLOW: Yes? I know that Dr. Alvarez'

9 patients were a direct local.

10 DR. CHENG: So if one feels that that might

11 influence the outcome, as you just mentioned, how was that

12 controlled for in the study?

13 MS. MARLOW: All the patients that were blinded

14 are treated exactly the same. The retreatments and

15 nonrandomized subjects, we eased up on some of the

16 requirements. As you saw throughout the PMA, there were a

17 lot of deviations within the nonrandomized group. Once we

18 are not concerned about the patient being blinded to active

19 or placebo such that all the treatment procedures had to be

20 identical, the requirements for giving the anesthesia didn't

21 affect the evaluation of outcome. So those patients could

22 be treated with either a block or a local.

23 DR. CHENG: If there is a factor which will

24 influence the outcome, ideally one would try and stratify

25 for that at the time of randomization.

at

1 MS. MARLOW: Right.

2 DR. CHENG: So I guess I would wonder how many
3 patients--do you know how many patients in each treatment
4 group received the local anesthesia versus the block,
5 itself?

6 MS. MARLOW: All the patients in the randomized
7 group were treated exactly the same way. So there shouldn't
8 be any patients that were not given an ankle block for the
9 primary treatment. In the nonrandomized group and in the
10 repeat treatments, I don't have the data immediately in
11 front of me, how many patients had the local and how many
12 had the ankle block. Nor did we analyze it.

13 But, again, we are talking about a situation where
14 we have the one group of patients randomized, treated
15 identically, followed to 12 weeks. And then we have other
16 parts of the study, as you have heard about, where we had
17 nonrandomized patients that we used just for training
18 purposes to learn how to do the OssaTron procedure.

19 Then, once the blind is broken and a patient has
20 come back for a repeat treatment, we don't have the issue
21 with trying to make sure that all the patients are treated
22 identically. So the physician could use discretion as to
23 what kind of anesthesia at that point in time.

24 DR. CHENG: Let me just clarify so I understand
25 correctly. You are telling me all the patients in the

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1 randomized treatment groups had the placebo or treated group
2 received an ankle block and no local anesthesia; is that
3 correct?
4 MS. MARLOW: To my best knowledge; yes. That was
5 the protocol for it and yes, that is what is on the case
6 report.
7 DR. CHENG: I see. Okay. The other question I
8 had was were any steroid injections given during the study
9 or were those just steroid injections prior to the
10 initiation of the study?
11 MS. MARLOW: No steroid injections were given to
12 any patient continuing follow up in the study. If a patient
13 didn't get relief from the OssaTron or placebo treatment,
14 they were free to withdraw from the study to have other
15 treatment, and there are some patients that had cortisone
16 injections after they were determined to be a failure.
17 But none of the patients that continued follow up
18 had any sort of concomitant or active treatment after the
19 OssaTron or placebo treatment.
20 DR. CHENG: So, at twelve weeks, the patients that
21 had results in satisfying the four criteria that were
22 outlined earlier, none of those received any steroid
23 injection; is that correct?
24 MS. MARLOW: Not after the treatment. Of course,
25 there are patients that received it before they were

at

1 enrolled in the study. But if a patient had any secondary
2 treatment, any adjunct treatment for heel pain, they were
3 out of the study.
4 DR. CHENG: Does that include analgesics, as well?
5 MS. MARLOW: No; I'm sorry. That does not.
6 DR. CHENG: So they were free to use analgesics ad
7 lib?
8 MS. MARLOW: They were free to use analgesics, and
9 that is what is recorded in our four-of-four criteria, if
10 they were using pain medications.
11 DR. CHENG: So you used that as a judgment of
12 response, then.
13 MS. MARLOW: Yes.
14 DR. CHENG: I noticed in one of your slides that
15 you had mentioned that steroid usage, you thought, decreased
16 effectiveness of the treatment. I didn't see any data in
17 that regard, but, perhaps, there is something else that you
18 know about it?
19 DR. OGDEN: I think the slide you are referring to
20 is where we had what we feel will be contraindications or
21 limitations on the use of the device. What we intended
22 there is not a single cortisone injection because,
23 certainly, a lot of patients who qualified for this study
24 did have it four weeks or longer before they had the
25 treatment.

at

1 We wanted to put forth caution in a patient who is
2 on chronic cortisone treatment for other diseases, some type
3 of, say, Addison's disease or something like that where they
4 just have a drug on board that is known to affect a person's
5 ability to initiate and maintain tissue healing.
6 I think it is just a precautionary item that we
7 want to have in there the same way with an immunosuppressive
8 drug. Some of those patients who are on various drugs for
9 treatment of things like cancer obviously are going to be at
10 risk to develop heel pain for reasons unrelated to their
11 primary problem.
12 While we may recognize that they may not respond
13 as well, I don't think we should necessarily preclude them
14 from having access to this treatment if that is what is
15 necessary.
16 DR. CHENG: Okay. My last question is why do you
17 recommend a single treatment or how is that determined?
18 DR. OGDEN: The purpose of this study was to see
19 if a single treatment was effective. There are different
20 devices that have been used in Europe that require,
21 sometimes, multiple treatments. Our feeling was that if a
22 patient could have a single treatment and gain the relief
23 that they want, that would be the ideal method to utilize.
24 Obviously, a single treatment did not work in
25 every patient in our study. And many patients opted for a

at

1 second treatment.

2 I think in any clinical situation, obviously the

3 more precise, the more concise, we can be with treatment so

4 that the patient gets the relief that they want or the cure

5 that they want with a single treatment, that obviously,

6 ought to be our goal but it is not attainable in every

7 patient in anything that we do.

8 DR. CHENG: So, if this device is approved for the

9 use of chronic heel pain, I would foresee it evolving to

10 off-label usage for people who have a less than six-month

11 history of heel pain. Do you have any opinion on whether

12 this device would be useful for people with acute, in the

13 sense of, perhaps, those with plantar fasciitis?

14 DR. OGDEN: I don't think it will be the treatment

15 of choice for the person who initially presents with plantar

16 fasciitis; no. I think there are studies that have not made

17 it to press in Europe that show that patients with acute

18 changes, and particularly one that was presented at the

19 International Musculoskeletal Shock Wave Society two years

20 ago.

21 They had a number of patients in Germany who

22 presented to the physician's office who treated their

23 chronic problem on one side with acute problems, now, on the

24 opposite side, had the treatment and the efficacy of the

25 treatment was not as great.

at

1 I think they have to exhibit a certain amount of
2 chronic change, a certain amount of thickening of tissue, a
3 certain amount of decreased vascularity in tissue,
4 dysfunction in tissue, changes in ground substance, glycose
5 aminoglycands, collagen, whatever, in order to have the
6 effect of the shock waves to break up some of this and to
7 encourage revascularization, elaboration, perhaps, of
8 various growth factors and more appropriate tissue ingrowth
9 to accommodate the healing.
10 So, in the acute case, I think you have to go with
11 the more characteristic ways of treating heel pain.
12 DR. CHENG: Thank you.
13 DR. OGDEN: Thank you.
14 DR. BOYAN: Dr. Wright, do you have any questions
15 you would like to ask?
16 DR. WRIGHT: I guess I just have a brief question
17 regarding, also, off-label usage. I realize that in the
18 protocol that people who had had previous surgery were
19 excluded. Do you see this as a potential for people who had
20 had failed surgery? A lot of people I see have had surgery
21 and still have pain. Do you think that is an option, number
22 one.
23 Number two, do you see any adverse effects from
24 treatment relating to when people fail this treatment, some
25 of them go on to surgery? Do you think this impacts on the