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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

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SIXTY-THIRD MEETING

OPEN SESSION

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MONDAY,
JANUARY 29, 2001

The meeting was held at 9:17 a.m. at the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Blvd., Gaithersburg, Maryland, Dr. Jorge D. Blanco, Panel Chair, presiding.

PRESENT:

JORGE D. BLANCO, M.D.	Chair
RALPH B. D'AGOSTINO, Ph.D.	Temporary Voting Member
MICHAEL P. DIAMOND, M.D.	Temporary Voting Member
CINDY DOMECUS, R.A.C.	Industry Representative
GRACE M. JANIK, M.D.	Voting Member
DAVID F. KATZ, Ph.D.	Voting Member
BARBARA LEVY, M.D.	Temporary Voting Member
MICHAEL NEUMAN, M.D., Ph.D.	Temporary Voting Member
NANCY C. SHARTS-HOPKO, Ph.D.	Temporary Voting Member
GERALD SHIRK, M.D.	Temporary Voting Member
DIONY S. YOUNG	Consumer Representative
ELISA HARVEY, D.V.M., Ph.D.	Executive Secretary
JOYCE WHANG, Ph.D.	Incoming Executive Secretary

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(9:17 a.m.)

DR. BLANCO: Can we go ahead and start getting settled in, please? All right. Let's go ahead and call the meeting to order. I think we're settled in. I want to remind everyone who's at the meeting that there's a sign-in sheet outside of the door, if you would please sign in, so that we know who is present at the meeting.

I'd like to just go over some of the ground rules, and issues that have come up before. When we ask for audience comments, please allow yourself to be recognized by the Chair, come up to the microphone, and use the microphone for any speaking.

And please, at least the first time that you come up to speak, give your name, any full conflict of interest disclosure, including any payments, travel, per diem, or any relationship with any of the companies, either having business before this Panel, or that might be related, or a competing company before this Panel.

At this time, I'd like to go ahead and have the Panel members introduce themselves. We can go ahead and start on my left side. Cindy?

MS. DOMECUS: Hi, I'm Cindy Domecus,

1 Senior Vice-President of Clinical Research and
2 Regulatory Affairs for Conceptus, and I'm the industry
3 representative on the Panel.
4 MS. YOUNG: I'm Diony Young. I'm Editor
5 of the journal, "Birth." And I'm the consumer member
6 on the Panel.
7 DR. KATZ: I'm David Katz. I'm a
8 Professor in the Department of Biomedical Engineering
9 at Duke University.
10 DR. D'AGOSTINO: Ralph D'Agostino from
11 Boston University, Biostatistician.
12 DR. O'SULLIVAN: Mary Jo O'Sullivan,
13 University of Miami, OB/GYN.
14 DR. SHIRK: Gerald Shirk. I'm in private
15 practice in Cedar Rapids, Iowa, and a Clinical
16 Associate Professor at the University of Iowa.
17 DR. JANIK: Grace Janik, Reproductive
18 Endocrinologist, Medical College of Wisconsin, and
19 Associate Clinical Professor.
20 DR. BLANCO: I am Jorge "George" Blanco,
21 with PeriNatal Associates of Texas, Magella Health
22 Corporation.
23 DR. HARVEY: And you're the Panel Chair.
24 DR. BLANCO: Oh. I think they'll figure
25 that out.

1 DR. HARVEY: I'm Elisa Harvey, and I'm the
2 Executive Secretary for the OB/GYN Devices Panel. I'm
3 the outgoing Executive Secretary.
4 MS. LONG: I'm Joyce Long, and I'm a
5 reviewer and Executive Secretary to be of this Panel.
6 DR. LEVY: I'm Barbara Levy. I'm a
7 Clinical Gynecologist and Clinical Assistant Professor
8 of OB/GYN at the University of Washington and at Yale
9 University School of Medicine.
10 DR. NEUMAN: I'm Michael Neuman. I'm a
11 Professor of Biomedical Engineering at the Memphis
12 Joint Program in Biomedical Engineering of the
13 University of Memphis, and the University of
14 Tennessee.
15 DR. DIAMOND: I'm Michael Diamond. I'm a
16 Professor of Obstetrics and Gynecology, Professor of
17 Physiology, Wayne State University, Detroit, Michigan.
18 DR. SHARTS-HOPKO: I'm Nancy Sharts-Hopko,
19 Professor of Maternal, Infants, and Women's Health in
20 the College of Nursing at Villanova University.
21 DR. SCHULTZ: I'm Dan Schultz. I'm Deputy
22 Office Director in the Office of Device Evaluation,
23 and I guess, soon to be ex-Division Director of this
24 Division.
25 DR. BLANCO: Thank you. I also would like

1 to point out that Dr. Schultz is the FDA press contact
2 for this Panel meeting. And lastly, before I hand it
3 back to Elisa, please let's make sure you are
4 recognized before you make any comments. And we'll
5 stay with the Panel, and we'll try to make sure to be
6 on time.
7 DR. HARVEY: I wanted to reiterate that
8 Dr. Whang will be the Executive Secretary for this
9 Panel from this point forward after today. So she
10 will be the contact if you have any questions about
11 Panel matters, and she's already done a great job
12 putting most of this meeting together for me. So
13 thanks, Joyce.
14 I wanted to announce the remaining meeting
15 dates for 2001 that are tentatively set. Monday and
16 Tuesday, May 21st and 22nd, Monday and Tuesday, July
17 16th and 17th, Monday and Tuesday, October 15th and
18 16th.
19 At this time, I'd like to read the
20 conflict of interest statement, and our appointment to
21 temporary voting status. Pursuant to the authority
22 granted under the Medical Devices Advisory Committee
23 Charter, dated October 27, 1990, and amended April 20,
24 1995.
25 I appoint the following people as voting

1 members of the Obstetrics and Gynecology Devices Panel
2 for the duration of this Panel meeting on January 29,
3 2001: Dr. Ralph D'Agostino, Dr. Michael Diamond, Dr.
4 Barbara Levy, Dr. Michael Neuman, and Dr. Gerald
5 Shirk.
6 For the record, these people are special
7 government employees, and are consultants to this
8 Panel. They have undergone the customary conflict of
9 interest review, and they've reviewed the material to
10 be considered at this meeting. And it's signed by Dr.
11 David Feigal, the Director of FDA Center for Devices
12 in Radiological Health.
13 This is the conflict of interest
14 statement. The following announcement addresses
15 conflict of interest issues associated with this
16 meeting, and is made part of the record to preclude
17 even the appearance of an impropriety.
18 To determine if any conflict existed, the
19 agency reviewed the submitted agenda for this meeting,
20 and all financial interest reported by the Committee
21 participants. The conflict of interest statutes
22 prohibit special government employees from
23 participating in matters that could affect their or
24 their employer's financial interest.
25 However, the agency has determined that

1 participation of certain members and consultants, the
2 need for whose services outweighs the potential
3 conflict of interest involved, is in the best interest
4 of the government.
5 Therefore, waivers have been granted for
6 Drs. Michael Diamond, Barbara Levy, and Nancy Sharts-
7 Hopko for their interest in firms that could
8 potentially be affected by the Panels'
9 recommendations. The waivers allow these individuals
10 to participate fully in today's deliberations.
11 Copies of these waivers may be obtained
12 from the agency's Freedom of Information Office, Room
13 12A-15, of the Parklawn Building. We would also like
14 to note for the record, that the agency also took into
15 consideration certain matters regarding Drs. Levy and
16 Sharts-Hopko.
17 These Panelists reported past and or
18 current financial interest in firms at issue, but in
19 matters not related to today's agenda. The agency has
20 determined, therefore, that theymayparticipate fully
21 in today's deliberations.
22 In the event that the discussions involve
23 any other products or firms not already on the agenda,
24 for which an FDA participant has a financial interest,
25 the participant should excuse him or herself from such

1 involvement. And the exclusion will be noted for the
2 record.
3 With respect to allotherparticipants, we
4 ask in the interest of fairness, that all persons
5 making statements or presentations disclose any
current or previous financial involvement with any
7 firm whose products they may wish to comment upon.
8 I just wanted to also note that
9 transcripts and videos will be available after the
10 meeting. There should be notices out front on the
11 table for the transcripts and videos. And if there
12 are any presenters to the Panel who have not already
13 done so, you should provide FDA with a hard copy of
14 your remarks, including any overhead.
15. Mike Kuchinski at the table here will take
16 these from you at the podium. Okay. I think we're
17 ready. Go ahead, Dr. Blanco.
18 DR. BLANCO: All right. First, to begin,
19 I'd like to introduce Colin Pollard, the Chief of
20 Obstetrics and Gynecology Devices Branch.
21 MR. POLLARD: Before we get going, I'd
22 like to acknowledge not only Dr. Harvey stepping down
23 as Executive Secretary after this meeting, and Dr.
24 Schultz, who will, probably by the next time this
25 meeting convenes, will no longer be Division Director.

1 We have a number of the Panel members who
2 are rotating off. And I think we'd like to just
3 acknowledge them. Dr. Chapman is not here today, but
4 he's rotating off. Diony Young, our Consumer
5 Representative, this is her last meeting.
6 And to acknowledge the fine work that
7 she's done, we would like to present her with a
8 plaque. This is a certificate of appreciation from
9 the Commissioner of the FDA, in recognition of her
10 distinguished service.
11 I would also like to acknowledge the
12 wonderful help and work over the years from Dr. Grace
13 Janik, who is also rotating off. And we will present
14 her with a certificate of appreciation from the
15 Commissioner of the FDA in recognition of her
16 distinguished service.
17 And finally, to acknowledge the wonderful
18 help over 'six years in extended service, from our
19 industry representative, who has done a wonderful job,
20 Ms. Cindy Domecus, a certificate of recognition from
21 the Commissioner of the Food and Drug Administration,
22 in recognition for her distinguished service.
23 Before we get into the agenda for the day,
24 I'd like to make a couple of general announcements,
25 just to catch the Panel and the audience up on a

1 couple of items since our last Panel meeting, January
2 of 2000.
3 At that time, the Panel reviewed the PMA
4 from Nelcore, for its OxyFirst fetal oxygen saturation
5 monitoring system. In May of last year, FDA approved
6 that PMA.
7 FDA also participated in June of last
a year, in an ongoing effort -- in a jointly sponsored
9 conference to look at condom effectiveness for
10 prevention of sexually transmitted diseases, in a
11 collaboration with the NIH and the CDC.
12 And consequent to that, we've been engaged
13 in a condom labeling review. And that is something
14 that we probably will bring back to the Panel sometime
15 later this year.
16 Let's move to today's main agenda item.
17 Go to the next slide. Today the Panel will consider
18 a PMA submitted by CryoGen. For its first option,
19 cryosurgical system for the treatment of abnormal
20 uterine bleeding -- that is, non-malignant -- causes.
21 Next slide.
22 I'd like to briefly review a few
23 background points to help put this PMA into
24 perspective. Women suffering from abnormal uterine
25 bleeding must first go through a workup regimen to

1 rule out uterine malignancy, as well as to get a focus
2 on the cause of the problem.
3 The first line of treatment is often
4 hormonal. But if this is unsuccessful, or the patient
5 cannot tolerate the long term medication, surgical
6 options are then considered.
7 Before 1980, this generally meant
8 hysterectomy, although, DNC sometimes offered
9 temporary relief. However, in the '80s, techniques in
10 operative hysteroscopy were developed for endometrial
11 ablation. Next slide.
12 In 1981, Milton Goldrath, using a
13 neodimiumide laser fiber, introducedvia hysteroscopy,
14 was able to successfully perform endometrialablation.
15 A few years later, Michael Baggish, using an RF
16 electrosurgical electrode, was able to do the same
17 thing.
18 Instrumentation for performing endometrial
19 ablation these ways were cleared for market through
20 the 510(k) pre-market notification pathway. Next
21 slide.
22 Starting about seven or eight years ago,
23 manufacturers began to approach FDA with ideas for
24 achieving similar results to operative hysteroscopy,
25 using technologies that were re-engineered for this

1 clinical application.

2 In general, these represented a new

3 intended use for these technologies, and raised new

4 types of safety and effectiveness questions. And FDA,

5 from a regulatory perspective, directed these new

6 devices on to the PMA approval pathway, rather than

7 510(k) pre-market notification. Next slide.

8 The rationale for our thinking is that

9 these new devices present a technological features

10 that represented a real change from how endometrial

11 ablation had been done. They're probe or catheter

12 based systems, using a variety of different energy

13 sources.

14 They are much faster, compared to

15 operative hysteroscopy. And special software and

16 hardware controls and fail-safes were typical. The

17 clinical implications of these technological advances

18 were multi-fold.

19 The procedures themselves were much

20 shorter, and with much simpler surgical technique.

21 The risk of fluid intravasation, associated with

22 distention of the uterus for the hysteroscopic

23 procedure, have been minimized or eliminated all

24 together.

25 But on the other hand, a good deal of the

1 traditional surgeon feedback, both in terms of the
2 feel as well as visual feedback, has also been
3 minimized. Next slide.
4 About five years ago, in late 1995, FDA
5 brought this issue before this Panel for its advice.
6 The Panel listened to input from experts, as well as
7 presentations from manufacturers developing these
8 technologies.
9 The Panel recommended a staged clinical
10 study plan, first with pre-hysterectomy safety
11 studies, then pilot safety and effectiveness studies,
12 and finally, a controlled clinical trial against
13 operative hysteroscopy.
14 Issuing an IDE/PMAguidance document early
15. the next year, FDA implemented this policy, and called
16 for clinical investigations for such devices. The
17 branch here at CDRH has worked diligently with the
18 many manufacturers using our informal pre-IDE process
19 to help ensure that the studies conducted are
20 scientifically sound, and answer the key questions
21 needed for PMA approval. Next slide.
22 AS you know, many of -- many devices of
23 this sort are under development. However, we will not
24 bring all of them before the Panel. Today's PMA, for
25 CryoGen's First Option system, is the first

1 cryosurgical system to come before FDA for
2 consideration for endometrial ablation.
3 As a different energy source for this
4 procedure, compared to what you have seen before, we
5 decided that it is important that this PMA be
6 considered by the Panel. You will see that we have
7 posed certain questions, in your set of discussion
8 questions, that looked specifically at some of the use
9 aspects of endometrial cryoablation.
10 You should know that FDA has worked
11 closely with the manufacturer to ensure that it's
12 pivotal clinical study was designed to answer the
13 kinds of questions that the Panel has indicated in the
14 past are important.
15 When the PMA was submitted, we put
16 together a review team that you will be introduced to
17 later this morning, to go over all of the material.
18 I hope the review findings will be helpful, as you
19 consider the material before you.
20 We will be asking you for a recommendation
21 on this PMA, and your recommendation must take one of
22 three forms. Dr. Harvey will go over this again with
23 you later in the afternoon, but I think it's
24 worthwhile reviewing.
25 You will either recommend an approval, an

1 approval with conditions or not approval. Next slide.
2 To reach that kind of conclusion, you must consider
3 only valid scientific evidence. And I've listed up
4 here on this slide, various forms that that may take.
5 Well-controlled studies, partially
6 controlled studies, studies in objective trials
7 without match controls, well-documented case
8 histories, and reports of significant human history.
9 You will be asked -- next slide -- to consider the
10 safety and effectiveness of the device, where the
11 safety represents the -- that the benefit is
12 outweighing the risks.
13 And that the effectiveness really means
14 that the PMA has shown a clinically significant
15 result. As for the agenda today, we'll have an open
16 public hearing. The sponsor will present its PMA, the
17 FDA review team will present its findings, there will
18 be time for Panel deliberations, there will be time
19 later in the afternoon for the sponsor and the
20 audience to comment.
21 And then we'll ask the Panel to address
22 the discussion questions and arrive at its
23 recommendation. Thank you, Dr. Blanco.
24 DR. BLANCO: Thank you, Mr. Pollard. All
25 right. At this point, the next issue in the agenda is

1 to have the public -- open public hearing
2 presentation. We do not have anyone signed up at the
3 current time.
4 Is there anyone in the audience that would
5 like to be heard from the public or make a statement
6 at this time on the issues before this Panel? Seeing
7 no raised hands, I will presume that we don't have any
8 public statements at this time. And we will proceed
9 with other items in the agenda.
10 The first item -- the first -- the next
11 item is the presentation from CryoGen. And I believe
12 that Ms. Cheryl Shea of CryoGen will be the first
13 speaker. No, sorry -- okay. Mr. Dave Murray,
14 President and CEO of CryoGen. Please remember to
15 state your name for the record, and any relationship
16 with the -- well, you are the Company.
17 MR. MURRAY: There we go. Pardon our
18 technical interruption here. But I think we're wired
19 and ready to go. Good morning, Mr. Chairman,
20 distinguished Panel. I'm Dave Murray. I'm the
21 President and CEO of CryoGen.
22 I know that I speak for all 45 CryoGen
23 employees when I say I'm excited to be here. After
24 more than four years of product development, and a
25 randomized clinical study, we are happy to be before

1 this group, seeking PMA approval for our First Option
2 cryoablation therapy system, for the specific
3 indication of endometrial ablation to treat abnormal
4 uterine bleeding.
5 Approximately 180,000 women in the U.S.
6 undergo a hysterectomy each year to treat AUB. And
7 approximately 30,000 have roller ball ablations. Many
8 more are believed to either rely on hormone therapy,
9 even when it might not be working too well.
10 Or, to just suffer in silence because
11 they're unwilling to consider what they believe to be
12 a severe surgical solution. Well, more than four
13 years ago, our founder, Dr. John Dobec, developed the
14 concept of a closed cycle cryosurgical system.
15 His initial interest was in cardiac
16 ablation to treat arrhythmias. But the work of
17 physicians, who attempted cryoablation of the
18 endometrium in the early '70s, called his attention to
19 the potential for a simple, non-threatening technique,
20 to treat abnormal uterine bleeding.
21 And approximately five years later, we are
22 here to present data, which demonstrates that the
23 device is safe and effective for that indication. The
24 Company has completed a randomized clinical study.
25 And we're here today to assist the Panel in its

1 deliberation in support of the PMA.

2 As you will see from the data presented,
3 the First Option system is safe and effective for
4 endometrial ablation for the treatment of AUB. In
5 addition to the safety and effectiveness data, we will
6 share data showing that cryoablation with the First
7 Option system requires less anesthesia than the
8 rollerball control, and that the quality of life of
9 the patients treated in the study, demonstrated
10 significant improvement.

11 As you all know from the Panel package,
12 the First Option system is currently being marketed
13 under an existing 510(k). It's a bit unusual for us
14 to have commercial experience at a Panel meeting.
15 However, we may refer to information from our
16 commercial experience during your deliberation if it's
17 helpful.

18 I have with me several physicians and
19 employees of the Company to assist in the presentation
20 and to answer questions you might have. Dr. Martha
21 Heppard will present the results of our clinical
22 study. She is a Board certified OB/GYN, and the
23 Director of the Inverness Women's Health Center in
24 Inglewood, Colorado.

25 Dr. Heppard is a graduate of Harvard

1 University, and received her medical degree from the
2 University of Southern California. She completed her
3 internship and residency at the University of
4 California, Irvine. She had the distinction of being
5 the one to treat the first patient in our study. Dr.
6 Heppard.
7 Dr. Antoni Duleba. Dr. Duleba was a
8 Clinical Investigator, and is an Associate Professor
9 of Obstetrics and Gynecology at Yale University. Dr.
10 Duleba and his associates at Yale began cryoablation
11 of the endometrium prior to the First Option
12 development, using a larger cryosurgical system
13 developed for liver tumor ablation and prostate
14 ablation.
15 His experience has been important to the
16 success of our study. Dr. Duane Townsend. Dr.
17 Townsend is a Clinical Investigator and is in private
18 practice in Salt Lake City, Utah. Dr. Townsend is one
19 of the fathers of rollerball endometrial ablation, and
20 a very early adopter of cryosurgery in gynecology.
21 Dr. Townsend was the most prolific of the
22 investigators, treating 60 patients in the study.
23 Also, participating in the presentation are Cheryl
24 Shea, the Vice President of Regulatory Affairs in
25 Quality Assurance, and Gene Reu, Vice President of R

1 and B and Operations.

2 This slide is the agenda for today's
3 meeting. We'll start with a video, which will give
4 you a little bit of background of the procedure and
5 the device. We will then -- Mr. Reu will then
6 overview the technology and the clinical device
7 assessment, a little bit about the background of the
8 development.

9 Cheryl Shea will go through a regulatory
10 overview in the -- in the status of our quality
11 system. And then we'll do a -- and we'll do a pre-
12 clinical data overview and Dr. Heppard will review the
13 multi-center study design and the clinical data
14 results.

15 So with that, can I ask that we roll the
16 video. I want everyone to note that this is not --
17 I'm sorry. This is not intended to be a complete,
18 training video, and will not be distributed as a
19 training video, but it uses excerpts from our training
20 video.

21 It was prepared specifically for this
22 meeting. Sorry, I should have mentioned that before
23 you see it.

24 (Video shown.)

25 MR. MURRAY: To follow the video -- I'm

1 sorry -- now, to follow the video, I want to introduce
2 Gene Reu, again, our Vice President of R and D and
3 Operations, who will talk more about the First Option
4 product and about the development.
5 MR. REU: Good morning. Many of the key
6 features in the First Option system have been
7 illustrated in the video you just saw. A few key
8 points that are important to understanding the
9 operation, the system deserves some additional
10 comment.
11 The First Option system employs three
12 principles to achieve the typical operating
13 performance. First, the Joule-Thomson principle of
14 creating a cooling effect by expansion of compressed
15 gasses through a restrictive orifice.
16 The second, the idea of using a mixture of
17 refrigerant gasses to reduce the pressure required to
18 create that cooling effect. And third, is the use of
19 a cascade system, or two closed refrigerant circuits,
20 with a secondary circuit serving to pre-cool the gas
21 of the primary circuit.
22 Together, the Joule-Thomsonprinciple, the
23 mixed gasses and the cascade system, increase the
24 cooling power of the system, and reduce the typical
25 operating temperature and pressure associated with

1 typical cryosystems.

2 The disposable control unit employs

3 features to enhance the safety of the device. First,

4 is a reused prevention mechanism, which renders a

5 truly single use.

6 Next, key specifications include the tip

7 diameter, the catheter diameter, and the shaft tip

8 length of 4.7, 5.5, and 35 millimeters, respectively.

9 This minimizes the need for cervical dilatation, and

10 accommodates the typical uterine cavity.

11 Finally, the operating temperature at the

12 tip end tissue is between minus 90 and minus 100C,

13 which enhances penetration depth. This might be a

14 little hard to see. I apologize for that.

15 This is a schematic of the First Option

16 system. The components within this box here are

17 within the console. Those within this box here are

18 located within the cryoprobe of the system. And those

19 here are within the flexline that connects the console

20 to the cryoprobe.

21 The yellow loop represents the pre-cool

22 circuit, which is made up of a compressor similar to

23 that found in a commercial air conditioner or

24 refrigerator. And a pre-cool heat exchanger, where

25 the temperature of the refrigerant used there is used

to reduce the temperature of the primary or gas mix refrigerant within the probe through the cascade effect.

The gas mix circuit is in blue, and it utilizes a unique oil-free gas bearing compressor, that circulates the gas mix refrigerant through the pre-cool and recuperative heat exchangers. And finally, into the probe tip, where the cryosurgical effect is created.

The tip houses a capillary tube that has an inside diameter of about ten thousandths of an inch, where the Joule-Thomson effect is created. The gas mix changes temperature as it travels through the system. In the flexline, it's approximately 30 degrees C, or just above ambient temperature.

At the exit of the pre-cool heat exchanger, it's approximately minus 40 degrees C. At the exit of the recuperative heat exchanger, it's approximately minus 70 degrees C. And then finally, at the cryoprobe tip, the temperature drops to minus 120 degrees C.

The most significant challenge to closed cycle cryosystems is contamination. Minute amounts of moisture or volatiles, such as those emitted from plastic materials in the system, or small particles,

1 can be released into the gas stream.

2 And they can be carried to the point in

3 the system where they might be condensed, or literally

4 frozen out of the gas stream. That point is often

5 right here at the capillary tube, the very small

6 diameter, where these contaminants can cause plugging

7 of the system.

8 For reference, ten thousandths of an inch

9 is about the diameter of a couple of human hairs.

10 This and other challenges occurred with the device

11 used in the clinical study, and I'd like to provide a

12 brief overview of the steps we took to resolve the

13 issues.

14 We undertook this product development with

15 design control in mind. We followed FDA's design

16 control regulation in doing so. This included the

17 parameters of defining inputs to the design, verifying

18 outputs of the design, with considerable design

19 verification testing prior to initiating the clinical

20 study.

21 Then, clinical validation of the design

22 and implementation of user feedback was implemented,

23 too, as issues arose during the study that required

24 design improvements. As part of our design control

25 process, we needed to learn as much as possible about

1 device performance during clinical use.

2 And this feedback was solicited through

3 our Clinical Device Assessment system, or we call it,

4 CDA system. What FDA will present will be -- they

5 call it -- they didn't call it -- we previously

6 referred to it as the CDER system.

7 So I apologize now for any discrepancy or

8 confusion that may have created. With this system,

9 all observations and performance feedback received

10 during the clinical study, was documented and

11 investigated for corrective action.

12 One hundred and eighty nine patients were

13 enrolled in the cryo arm of our study. And a total of

14 59 CDAs were filed. Of the 59, 54 were acute

15 treatment successes, meaning the patients received

16 their therapy as scheduled.

17 Five were acute treatment failures, and

18 the patients were either crossed over to Rollerball or

19 were rescheduled. The CDAs we received during this

20 study can be grouped into the following four

21 categories. Three were related to non-performance --

22 non-performance related user feedback.

23 An example of. this is where the -- a

24 request was made to increase the length of the power

25 cord. Seven were related to user error. An example

1 of this is the physician forgot to perform the pre-
2 cool test, which is required prior to the ablation.
3 This test -- this resulted in a longer
4 time to receive -- to achieve the desired temperature.
5 And this was resolved with our automated pre-cool
6 software.
7 Nine of these were related to the
8 disposable control unit. Of these, four were
9 functional, and were able to be used for the
10 procedure, while five required replacement of the
11 disposable to successfully complete the procedure.
12 An example of a functional unit,
13 generating a CDA in this case, is a CU attachment
14 problem due to excess thermal conductive medium being
15 applied by the user. The user was previously required
16 to apply a thermal conductive medium, and this was
17 used to assure a good thermal contact between the
18 disposable and the cryoprobe.
19 The user could have resolved this during
20 the procedure by wiping the excess medium and then
21 continuing the treatment. This has been resolved with
22 pre-applied medium now that is incorporated into our
23 manufacturing process.
24 All five of these CDAs for the disposable,
25 which required replacement, had root causes, which

1 have been resolved and validated. No control unit
2 related CDA resulted in acute treatment failure.
3 There were 40 console-related issues. of
4 these, 35 were functional systems, and allowed
5 successful patient treatment, while five failed and
6 prevented treatment. Subsequently, all five of those
7 issues have been resolved and validated.
8 Again, good design control requires us to
9 determine the root cause for each issue reported. Of
10 the four categories I just described, 18 different
11 root causes were identified. All root causes have
12 been addressed, with 16 having been resolved and
13 validated, and two with validation under way.
14 It's important to note that the five acute
15 treatment failures that are included in the 16 issues
16 that have been resolved. FDA reviewed and was
17 satisfied with the design control validation results
18 for all 16 of those root causes in their pre-PMA
19 quality system inspection completed in August of 2000.
20 Verificationandvalidationactivities are
21 under way for the remaining two root causes. And as
22 mentioned earlier, one of these is gas-mixed circuit
23 obstruction, which is related to small amounts of
24 particulate water or contaminants in the system.
25 We have significantly reduced the

1 contaminant sources in our system from over 500
2 micrograms, when we originally tested, to less than
3 ten. To the point where they are nearly undetectable
4 by today's analytic methods.
5 Also, we have modifiedourproduct release
6 criteria to include a high/low test, which detects
7 these small amounts of contaminants. This test
8 challenges the system beyond conditions that can be
9 expected in a clinical setting.
10 As well, system automation software has
11 been implemented for self-recognition and a system
12 lock out if unsatisfactory performance-is detected .
13 prior to the ablation. Also, the system provides an
14 early warning method to alert the user of the need for
15. service.
16 Much like, you might get an indicator
17 light on your automobile, indicating an oil change is
18 required. The majority of the modifications, required
19 to achieve the contaminant reduction described, were
20 validated through our first round of reliability
21 testing and resultant system service intervals, in
22 excess of one year of use.
23 Currently, we are going through a second
24 round of testing to validate additional modifications,
25 expected to lengthen the service interval even

1 further. The remaining CU attachment issue is related
2 to variable thermalconductedmedia application, which
3 created a user inconvenience in achieving an
4 unacceptable -- or, excuse me -- acceptable connection
5 to the handle.
6 Recently, we validated a method to
7 dispense of fixed volume of thermal conducted media
8 that successfully controls the application during our
9 manufacturing process.
10 In summary, the device issues seen during
11 the clinical study had minimal impact of the patient -
12 - on patient treatment. Through a -- though
13 reliability improvements were made, performance
14 specifications of our system remain unchanged.
15 Our design validation was comprehensive,
16 and supported by FDA review in August of 2000. The
17 successful resolution of the 16 root causes
18 demonstrates this. Our method of design validation
19 includes in vitro testing that is more rigorous than
20 that experienced in clinical use.
21 And finally, we feel that the device
22 reliability issues have been addressed and support
23 product approval.
24 Cheryl Shea, our VP of Regulatory,
25 Quality, and Clinical Affairs will now discuss our

1 pre-clinical results, and provide a review of our
2 Regulatory and Quality System status. Thank you.
3 MS. SHEA: Thanks, Gene. Good morning,
4 Mr. Chairman and distinguished Panel. My name is
5 Cheryl Shea. I'm the Vice President of Regulatory
6 Quality and Clinical for CryoGen. I've been involved
7 with this project for almost four years now.
8 From the pre-hysterectomy study through
9 the IDE submission, and now the PMA process, I'm going
10 to provide a brief overview of the regulatory and
11 quality system status for CryoGen. Then move on to
12 summarize our pre-clinical work, that supported our
13 IBE and the multi-center study.
14 Cryosurgical devices, which ablate tissue
15 using liquid nitrogen, are Class II. The early
16 cryodevices are pre-amendment, in that they were on
17 the market prior to the Medical Device Amendments of
18 1976.
19 In fact, some of the earliest cryodevices
20 entered the market as early as the 1950s. Based on
21 the predicates, CryoGen obtained a 510(k) for general
22 ablation, including entry uterine ablation, in October
23 of 1997. We have been marketing our device, the First
24 Option Uterine Cryoablation Therapy System, since May
25 of 1999.

1 We have submitted this PMA to expand our
2 labeling to include the specific indication of
3 endometrial ablation. CryoGen has developed a quality
4 system which meets the requirements of both the U.S.
5 Quality System regulation and the EN/IISO 9001 Quality
6 System requirements.
7 As Gene mentioned, our pre-PMA Quality
8 System audit was conducted by FDA in August of last
9 year. There were no observations noted during the
10 audit. Our device is also marked for CE -- or CE
11 marked for European distribution.
12 We are not selling in Europe at this time.
13 However, we are planning to launch First Option in the
14 European community in the second quarter of this year.
15 Initial bench testing was conducted in
16 gelatin media to establish the performance parameters
17 for the First Option device. Subsequent verification
18 was done in beef liver, warmed to 37 degrees, with
19 ten-minute freezes. Amulti-probe thermal array, with
20 ten millimeter spacing between each probe, was
21 utilized to confirm the isothermal gradients within
22 the frozen tissue.
23 The ten-minute.freezes andwarmbeef liver
24 produced a similar sized ice front, or cryozone, to
25 that observed earlier in the gelatin media. Next, an

1 in vivo study was completed in an anesthetized goat,
2 that involved two five-minute freezes with five
3 minutes of thawing between each cycle.
4 The resulting cryozone was also comparable
5 to the earlier bench testing completed in gelatin and
6 beef liver. Additional bench testing was then
7 performed in eight freshly harvested human uteri.
8 The testing was designed to characterize
9 the cryozone, including temperature gradients within
10 the cryozone and growth over time. To confirm safety,
11 we also investigated the depth of penetration of the
12 cryozone through the uterine wall, as well as the
13 serosal temperature measurements.
14 In addition, we did some early work in
15 technique development. All testing was completed
16 under ultrasound guidance. Free cycles completed
17 included one and two single and double mid-line
18 freezes in six of the uteri. And two single freezes
19 to each cornu and three uteri.
20 The average freeze time was five and
21 three-quarters minutes for freeze one, and sixminutes
22 for freeze two. As seen in the earlier pre-clinical
23 work, the cold front, or cryozone, rose evenly over
24 time, advancing through the tissue by freezing
25 intracellular tissue, or intracellular fluid, without

causing uterine distention.

2 There was no evidence of freezing through
3 to the serosal surface. The leading edge of the ice
4 front is non-destructive at minus 2 degrees C. And
5 the zone for tissue necrosis, which is recorded in the
6 literature, to be between minus 15 and minus 20
7 degrees C, lies three to five millimeters behind the
8 leading edge of the cryozone.

9 A pre-hysterectomy safety study in ten
10 women was completed then at two clinical sites to
11 support our IDE. Treatment was also completed under
12 ultrasound guidance, and thermal couples were placed
13 on the serosal surface of the uterus during the open
14 hysterectomy cases to confirm safety.

15. The depth of ablation as measured with
16 tetrazolium staging was nine to 12 millimeters. This
17 was confirmed with electron microscopy. One of the
18 patents received a five-minute first freeze, followed
19 by a six-minute second freeze.

20 Two of the patients received a six-minute
21 first freeze, followed by a six-minute second freeze.
22 The remaining seven patients received a four-minute
23 first freeze, followed by a six-minute second freeze.

24 It was found in this pre-hysterectomy
25 study that the four-minute first freeze facilitated

1 repositioning of the probe the opposite cornu of the
2 uterus for the second freeze. In addition, based on
3 what we saw in our acute histology, a four-minute
4 first freeze, followed by a six-minute second freeze,
5 appeared to be adequate to affect the desired depth of
6 tissue necrosis in the average sized uterus.
7 Based on the results seen in our pre-
8 hysterectomy safety study, the decision was made to
9 perform a two-minute freeze protocol, a two-freeze
10 protocol, and a multi-center study. The first, a
11 four-minute freeze angled to one cornu, followed by a
12 six-minute freeze to the opposite cornu.
13 The IDE was filed, and approval was
14 granted by FDA to begin on multi-center study. We
15 designed our multi-center study to support the
16 following proposed indication for use. The first
17 option, Uterine Cryoablation Therapy System, is a
18 cryosurgical systemintendedto ablate the endometrial
19 lining of the uterus in pre-menopausal women, with
20 abnormal uterine bleeding, due to benign causes, for
21 whom child bearing is complete.
22 I would now like to introduce Dr. Martha
23 Heppard. She will be providing a summary of the
24 multi-center clinical data. Dr. Heppard.
25 DR. HEPPARD: Thank you, Cheryl. Good

1 morning Mr. Chairman and distinguished Panel. My name
2 is Dr. Martha Heppard, and I'm one of the Clinical
3 Investigators for First Option. And I've served as an
4 Advisor to the Company. I have no financial equity in
5 the Company, but the Company did pay my expenses to
6 come for the meeting today.
7 The multi-center clinical study was
8 designed to evaluate the effectiveness and safety of
9 the First Option system for the treatment of abnormal
10 uterine bleeding, or AUB. The objective of the study
11 was to demonstrate the safety and effectiveness of the
12 First Option device.
13 Menstrual bleeding was documented using
14 the Pictorial Blood Assessment Chart, or PBAC. The
15 diaries were kept and maintained by the patients. The
16 primary end point was clinical success as defined by
17 a PBAC score less than or equal to 75 at 12 months.
18 Effectiveness also consideredtheneed for
19 repeat ablation, or hysterectomy, either of which
20 would classify the patient as a clinical failure. The
21 secondary end point for the study was quality of life
22 parameters.
23 These were measured by the SF-36 and the
24 Dartmouth COOP tools. Device safety was established
25 by analysis of the incidents and severity of adverse

1 events reported during this study, anticipated as well
2 as unanticipated.
3 The study was designed in accordance with
4 the FDA guidance document for thermal autoablative
5 devices for endometrial ablation. The design included
6 a two to one randomization, using the Rollerball
7 endometrial ablation, or REA, as the control.
8 There were a total of ten sites and 275
9 patients treated to allow for those lost to follow up.
10 All patients received pre-operative Lupron,
11 approximately 28 days prior to treatment. This pre-
12 treatment was given because many of our investigators
13 routinely use it to thin the endometrial lining.
14 Patient follow up assessments were done at
15 weeks -- week two, as well as months three, six, and
16 12. Patients reported menstrual bleeding using their
17 PDAC diaries. The quality of life assessments were
18 done and completed at months six and 12,
19 postoperatively, using the validated assessment tools.
20 The inclusion criteria for the study were
21 defined in accordance with the FDA guidance document,
22 and are consistent with those in other studies for
23 endometrial ablation. I think there's suddenly -- I
24 must have pushed something there. Here we go. That
25 looks about right.

1 Sorry guys. Similar computer, but
2 different from mine. We're almost there. There we
3 go. Okay. All patients were required to meet the
4 inclusion and exclusion criteria.
5 The examples include PBAC score of greater
6 than or equal to 150, for a minimum of one menstrual
7 cycle, uterine sound, less than or equal to ten
8 centimeters, and that the patient no longer wishes to
9 bear children.
10 The exclusion criteria are also definedin
11 the FDA guidance document, and include examples such
12 as women who have had a prior ablation, uterine
13 reconstructive surgery, as well as women who have had
14 a positive endometrialbiopsy within six months of the
15 procedure.
16 The study was conducted at ten sites
17 within the United States. The sites are a mix of both
18 teaching centers, such as Mass General and Denver
19 Health, as well as private practice physicians, such
20 as Dr. Paul Inman.
21 There are 11 investigators listed on this
22 and the prior slide. And two of the investigators,
23 Dr. Walsh, as well as Dr. Isaacson, both fell under
24 the Harvard IRB. They were, therefore, considered a
25 single site.

1 Safety -- excuse me -- efficacy assessment
2 was based on success or failure at 12 months post-
3 operatively. A conservative definition of success was
4 used. To be a success, all of the following must be
5 true: A woman's PBAC score must be 75 or less, and
6 she has not had a need for a repeat ablation or
7 hysterectomy. She must be an acute success, and did
8 not have a perforation, and she must have come to her
9 post-operative visits with her menstrual diaries.
10 Safety assessment was based on serious
11 adverse events and study related adverse events. The
12 study was designed to demonstrate the equivalence with
13 respect to success at 12 months. Our formal test of
14 hypothesis was conducted using Blackwelder's method.
15. A 95 percent confidence interval for the
16 difference in success was also calculated.
17 Statistical evaluations also included demographic
18 comparisons, descriptive statistics to evaluate the
19 secondary outcomes.
20 To determine that cryo and REA are
21 equivalent, we must reject the null hypothesis in
22 favor of the alternative hypothesis. By rejecting the
23 null hypothesis, we can conclude that cryo and REA are
24 similar with respect to the 12 month success.
25 Inotherwords, the difference in clinical

1 success is less than 20 percent. Two hundred and
2 seventy-five patients were randomized. After the
3 randomization that lead to 189 patients in the cryo
4 group and 86 in the REA.
5 You'll note that three of the cryo
6 patients were then crossed over to REA due to device
7 issues. This left 186 in the cryo treated group. At
8 the -- excuse me -- at the time that the PMA was
9 filed, we had 12 month data on 158 of the cryo, right
10 down in there, and 75 of the REA.
11 I would like to begin the discussion of
12 results with demographics. Only one variable was
13 found to be statistically significant. The median
14 pre-operative PBAC score for the cryo group was 100
15 points higher than for the REA.
16 To the extent that pre-operative bleeding
17 is at all associated with post-operative bleeding, a
18 bias against the cryo group may have been present.
19 This shows that the randomization was successful in
20 producing similar treatment groups.
21 NOW I would like to discuss some of the
22 results. The primary outcome of the study was looking
23 at success. This slide graphically illustrates the
24 success at 12 months for both groups based on the
25 conservative definition of success.

1 These rates are not statistically
2 significant. This is the cryo, and then this is for
3 REA. The cryo success rate at 12 months is 74.1, as
4 compared with the REA of 81.3. Using Blackwelder's
5 method, the P value is 0.012.
6 Therefore, we reject the null hypothesis,
7 and conclude that cryo is statistically equivalent to
8 REA with respect to the 12 month success. You'll note
9 that the 95 percent confidence interval for the
10 difference in success is 3.8 percent up to 18.4
11 percent.
12 This slide does have a lot of numbers, but
13 that's down there. This interval is consistent with
14 Blackwelder's method. This -- excuse me -- this slide
15 graphically displays the results by age. There were
16 no statistically significant differences noted.
17 This slide shows failures for both groups
18 by type of failure. The first three rows demonstrate
19 that according to -- excuse me -- the first three rows
20 represent the failures according to the original
21 failure definition.
22 The last three highlighted rows represent
23 the additional failures that were included with the
24 conservative definition. When looking at these
25 numbers, please bear in mind that there was a two to

one randomization.

This chart summarizes the patient accountability at the time the data summary amendment was filed in November of 2000. Thirty-seven cryo and ten REA patients did not complete their 12 month follow up.

Of these patients, eight cryo and four REA were lost to follow up. And 18 cryo and three REA still had 12 month visits pending. As of today, all patients enrolled in the study have been accounted for.

The definition we use for acute treatment success is that the patient was treated as scheduled with the First Option device. 96.8 percent of our cryotherapy patients were acute treatment successes, and six patients, or 3.2 percent, were classified as acute treatment failures.

Five of these six were acute treatment failures because of equipment related issues. One was due to a perforation during sounding prior to the procedure.

As you would expect with any surgical procedure, success rates do vary from site to site. It appears that two study sites did have lower success rates than the others.

1 However, you can also see that this
2 appears to be true for REA. I would like you to note
3 that the two sites that were the lowest success rates
4 for cryo, are among the three sites with the lowest
5 rates for REA.
6 Secondary assessment included evaluation
7 of the quality of life. This slide shows quality of
8 life outcome data for cryo patients, both pre-
9 operatively and at 12 months. You can see that the
10 patients do report a significant improvement in these
11 three areas.
12 So in mood, in PMS, and severe cramping,
13 so this is pre-op, and then post-op. There we go.
14 And this was not expected. We did not expect to find
15 this. Many other studies are beginning to show this,
16 too. And we actually defined it very similarly for
17 the REA.
18 Ninety-four percent of the cryo patients
19 report that they are satisfied to extremely satisfied
20 with the procedure at 12 months, and that 98 percent
21 would recommend it to a friend. This shows high
22 patient satisfaction with the procedure.
23 There were no -- excuse me -- I'll get to
24 that in a moment. This slide illustrates the same
25 quality of life for the REA, that they also had a very

1 high amount that were satisfied to extremely
2 satisfied, and would recommend it to a friend.
3 There were no unanticipated adverse
4 events, serious or otherwise, reported during the
5 study for either group.
6 This slide demonstrates the anticipated
7 serious adverse events. There were six serious
a adverse events reported the day of surgery. One
9 perforation was reported in each group. They cryo
10 perforation occurred during sounding, prior to the
11 treatment, and the treatment was thus not rendered at
12 that time.
13 The REA perforation occurred during the
14 ablation process. In addition, the REA group reported
15. one instance of hyponatremia, and one instance of
16 fluid overload with hyponatremia. Both were resolved
17 with the administration of LASIX.
18 One cryo patient had a slow recovery from
19 spinal anesthesia. She was discharged the following
20 morning without any sequelae. In the first 14 days
21 following treatment, only one serious adverse event
22 was reported.
23 This was a UTI in the REA group, which was
24 treated with antibiotics. One month later, she
25 presented as a late adverse event, and was diagnosed

1 with a hematoma, which was successfully evacuated.

2 Late serious adverse events are defined as

3 those reported more than 14 days following treatment.

4 The late serious adverse events, three for each group,

5 are as follows: Two cryo patients were hospitalized

6 with reports of severe abdominal cramping. The first

7 patient was diagnosed with a cyst on the left ovary,

a as well as fluid within the uterus on an ultrasound,

9 and she had a DNC, and her pain resolved.

10 The second patient was one with a

11 diagnosis of gastroenteritis, and was discharged home

12 two days after IV fluid hydration and antibiotic .

13 treatment. The third cryo patient was hospitalized

14 for severe vaginal bleeding, and she received a

15 hysterectomy, and was discontinued from the study.

16 Actually, we'll stay on that for just a

17 moment. We're now going to be on the bottom half of

18 it right here. The late adverse events for REA

19 included one late serious adverse event.

20 One of the patients described previously

21 -- the one with the bladder infection, who was treated

22 with antibiotics -- when she came in, subsequently,

23 about a little over a month later, she did have not

24 only a bladder infection that was still persistent,

25 but also had a hematoma that needed evacuation.

1 So she was classified as a serious adverse
2 event. There was a second patient who was
3 hospitalized for a herniated disk, and had subsequent
4 surgery to repair this. The third patient with a
5 serious adverse event for REA was diagnosed with a
6 probable hematometra, which was resolved with a DNC.
7 For consistency of reporting, adverse
a events were classified into organ systems using the
9 WHO/ART coding scheme. For statistical tabulations of
10 the following events, when it was appropriate, these
11 were combined: Abdominal pain and cramping, bleeding,
12 hot flashes, nausea, urogenital abnormalities, vaginal
13 discharge.
14 Adverse event rates in 95 percent
15 confidence intervals, for rate differences, were
16 calculated for in-hospital events as well as early
17 events. Rates were compared using the Fisher's Exact
18 test. Overall, the rates of adverse events were
19 comparable.
20 We have included anesthesia requirements
21 in the safety discussion, as we believe that the
22 reduction in the need for general anesthesia does
23 enhance the safety profile of our device. During the
24 study, anesthesia was left to the discretion of the
25 physician as well as the anesthesiologist.

1 Only 46 percent of the cryo patients
2 received general anesthesia, as compared to 92 percent
3 in the REA group. The difference between groups is
4 statistically significant. Two of the investigators
5 did perform cryotherapy in the office.
6 It should be noted that the numbers don't
7 add to 100 percent as other anesthetic alternatives
a were also used, such as pericervical block without
9 conscious sedation.
10 To summarize, the study hypothesis was
11 met. And a high degree of patient satisfaction was
12 achieved. No unanticipated adverse events were
3.3 observed. And the study confirmed presumed safety
14 benefits, including less general anesthesia, and no
15 need for fluid distention of the uterus.
16 In conclusion, the clinical study has
17 demonstrated that CryoGen First Option Uterine
18 Cryoablation Therapy System is safe and effective for
19 the treatment of abnormal uterine bleeding. Thank
20 you.
21 At this point, I will turn the podium back
22 to Dave Murray for his closing comments.
23 MR. MURRAY: Thank you, Dr. Heppard. To
24 close, I'd like to thank all of you on the Panel for
25 your efforts in reviewing the Panel package and your

1 attention to the presentation.

2' I know that each of you spent significant

3 time reviewing this information on behalf of the FDA,

4 but also, on our behalf. As I stated in the beginning

5 of our presentation, we have presented data that

6 demonstrates the safety and effectiveness of the First

7 Option System.

a The data generated during our clinical

9 study met the hypothesis put forth in the IDE, and

10 demonstrated effectiveness. There were no serious

11 adverse events which would raise safety concerns.

12 System reliability issues have been, and were,

13 addressed.

14 And patients reported significant

15 improvement in their quality of life and overall

16 satisfaction with the procedure. The First Option

17 Cryoablation Therapy System is safe and effective for

18 endometrial ablation for the treatment of AUB.

19 Women's lives will be improved when this

20 device is marketed for this indication. We look

21 forward to answering your questions following the

22 FDA's presentation. And again, thank you all for your

23 attention.

24 DR. BLANCO: Thank you for the

2 5 presentation of all the presenters. Before we go on

1 to the FDA presentation, we have a small break
2 scheduled. But we're doing well on time if there's
3 any of the -- do any of the members of the Panel have
4 any questions of fact for any of the presenters at
5 this point?
6 Doesn't look like it. Oh, Mike.
7 DR. DIAMOND: I had a couple of questions
a -- actually two different lines. The uterine cavity
9 -- enrollment criteria stated the uterine cavity had
10 to be less than ten -- ten centimeters in diameter --
11 in length.
12 The cryotip probe was 35 millimeters.
13 what portion of the cavity, therefore, was treated
14 with the probe during the freezing, as you saw by the
15 length of -- by visualization during the ultrasound
16 procedure?
17 MR. MURRAY: Are we talking about real
18 time?
19 DR. DIAMOND: Or any other way that you
20 have assessed that, ten centimeters versus three. and
21 a half centimeters.
22 DR. BLANCO: If you're going to speak, you
23 need to identify yourself and come to the mike,
24 please.
25 MR. MURRAY: Just for clarification, there

1 were a couple ways this information could have been
2 gained. One is in the pre-clinical work that was
3 done, where we actually had the benefit of harvesting
4 a specimen and doing a work up.
5 The other thing is -- the other answer,
6 potentially, is a real time observation under
7 ultrasound. Which are you interested in?
8 DR. DIAMOND: I would actually be
9 interested in either one. Basically, the question is
10 whether the uterine cavity that could be up to ten
11 centimeters -- or that's going to be cervix, and not
12 uterine endometrium -- but a tip length of only 35
13 millimeters -- how much of that length of the cavity
14 is truly going to be treated?
15' DR. BLANCO: I think, Mike, if I can
16 rephrase your question. Do you have any data showing
17 the extent of the length of the freeze ball, either
18 through the ultrasound or through the in vitro, or in
19 vivo, extra patient experiments that you perform?
20 DR. DIAMOND: And what other bit of
21 information you may have which may relate to that is,
22 you say that the tip reaches a temperature of about
23 minus 90 to minus 100. But it is that the very tip of
24 the tip, or when you say the tip in that context, are
25 you talking about the 35 millimeters?

1 MR. MURRAY: Dave Murray, again. The
2 active tip is three and a half centimeters, or 35
3 millimeters long. That's the temperature of that
4 entire tip of the probe, about minus 90 to minus 100
5 end tissue.
6 What was the other -- I'm sorry --
7 DR. DIAMOND: The other question is length
8 of the ball. Do you have any data to demonstrate the
9 length or diameter of the freeze ball?
10 MR. MURRAY: We do have, in our back up
11 slide, some -- I don't know if we have ice ball
12 dimension in there, but --
13 DR. HEPPARD: I'm Dr. Martha Heppard. And
14 at this moment, may I answer the portion of the
15 question about the depth? If a uterus has sounded to
16 10 centimeters, that is the length from the external
17 os of the cervix to the interior of the uterine cavity
18 at the fundus.
19 A cervix could be, for example,
20 approximately four centimeters in length. So that
21 would leave six centimeters for the uterine cavity.
22 When the cryoprobe is placed, the probe is placed up
23 to the fundus, and then tilted towards one of the
24 sides, and then I withdraw the tip just about a half
25 centimeter.

1 So that I am trying to place it so that
2 it's not right into the cornu, which is a thinner
3 portion of the uterus. But also, so that it will
4 achieve effective destruction of that half of the
5 uterine lining.
6 And based on studies that probably Cheryl
7 can go into, with the rate of ice ball formation, and
a the sort of, ice front, we are -- 1 am very
9 comfortable with having read the literature.
10 And now, with having gone through the
11 clinical study, that we are destroying the effective
12 amount of uterine lining tissue in that half of the
13 uterus. There is a potential that perhaps, if they
14 have a very long uterine cavity itself, that perhaps
15 the very lower region near the isthmus might not be
16 destroyed.
17 But we have not run into that as being the
18 area that has not been destroyed. So in some follow
19 up questions, we can address those concerns, but we
20 have found high success with this method of doing the
21 ablation.
22 DR. DIAMOND: Is there a correlation
23 between length of the uterine cavity and success?
24 MR. MURRAY: That's a statistical
25 question. I don't believe we -- I'm Dave Murray

1 again. I might want to refer to our statisticians.
2 To the best of my knowledge -- we'll need to verify
3 this -- that there is not.
4 By the way, we can refer to Mr. Reu. He
5 has the actual ice ball dimensions at four and six
6 minutes in just a moment.
7 DR. STEN-NIS: Hello. My name is Dr. Eric
8 Polk Stennis. I am a Statistical Consultant hired by
9 the sponsor. I have no financial interest in the
10 Company besides our fee for service arrangement.
11 What I can tell you as far as our
12 statistical analysis was concerned, there is no
13 relationship between uterine sound measurements and
14 clinical success.
15 DR. BLANCO: Thank you. Someone was going
16 to address the issue of the size of the ice ball.
17 MR. REU: Hi. I'm Gene Reu. If you turn
18 to your packet on page 26, there's some information on
19 typical ice print diameters. The ice front length was
20 not recorded as part of this study originally.
21 But as you can see from the bottom graph
22 on page 26, you'll see that at the end of first freeze
23 at six minutes, the typical ice front diameter was
24 about 24 to 34 millimeters. In our experience,
25 subsequent to that, a typical ice front length will be

1 in the neighborhood of about six centimeters at the
2 end of a six-minute freeze.
3 DR. BLANCO: Thank you. I think Diony was
4 -- go ahead.
5 MS. YOUNG: Diony Young. It's my
6 understanding that the control unit is disposable.
7 And I just wondered why -- why the whole control unit
8 -- looking at your slide, and sort of, looking -- I
9 don't know whether you've got a -- you actually
10 brought a control unit with you that we could have a
11 look at.
12 No? Okay. But the cryoprobe seems to be
13 the only item that is actually inside the woman's
14 body. Is that correct?
15 DR. BLANCO: I'm sorry. Could someone
16 from the Company go to the mike? Thank you.
17 MR. MURRAY: I'm Dave Murray, again. It's
18 just the part of the shaft of the probe and the tip of
19 the probe that's inside the uterine cavity, yes.
20 MS. YOUNG: Therefore, why is it necessary
21 to make the whole control unit disposable? It would
22 seem that would be a rather, sort of, expensive item
23 to dispose of.
24 MR. MURRAY: The intent is to create a
25 sterile field at the point, to be able to take a probe

1 that's cleaned, and then put a sterile disposable over
2 it. There's also an accordion drape, as was
3 demonstrated in the video that goes down over the
4 cord, so that the physician is generally gloved.
5 We want the device to stay reasonably
6 clean, and not be contaminated with blood or other
7 body fluids, so that you don't get patient to patient
8 transfer.
9 DR. BLANCO: Dr. Shirk.
10 DR. SHIRK: I guess the question is along
11 the lines of Dr. Diamond. This is Dr. Shirk. My
12 question is along the lines of Dr. Diamond, and that's
13 basically with the freeze process itself.
14 You've described the first and second
15' freeze. I guess, dealing with a cryo unit, as far as
16 treatment of cervical problems, the -- you're using a
17 freeze thaw freeze technique, which infers that you're
18 using the same kind of technique when you talk about
19 a second -- second freeze.
2 0 In this whole process, basically, you're
21 obviously a first freeze on each segment of the -- the
22 uterus itself, okay? So that basically, my questions
23 would be A, number one, why the difference in time
24 frame in the two freezes, since you're obviously, you
25 know, each unit is getting only -- each segment of the

1 uterus is getting frozen once.

2 Also, you're creating a Y by the freeze

3 balls, leaving a segment in the center that obviously

4 is not always going to be covered by the freeze balls.

5 And would it not be better to have a technique where

6 the procedure allowed for a third freeze, you know,

7 that basically concentrates on the center portion, and

8 that you ended up with three four-minute freezes,

9 rather than three-minute freezes?

10 And obviously, looking at your data, as

11 far as variances, this obviously happens in a

12 significant number of times with your review people

13 that were doing the procedures, so -- your

14 investigator. so I guess that's -- that's -- my

15 question would be why call this a second freeze, when

16 obviously, these are just each first freezes to the

17 specific units of the uterus?

18 MR. MURRAY: Dave Murray, again. Dr.

19 Shirk, I think the best answer we have is that when we

20 did our pre-hysterectomy work, we demonstrated there,

21 through testing of those specimens, that we were able

22 to get adequate coverage of the entire uterine cavity,

23 using a four-minute and six-minute freeze.

24 To the issue of one versus two freezes,

25 for tissue destruction, again, I guess it's a

1 semantics thing. But we did one freeze, truly, on
2 each side of the uterus. So it's not a double freeze
3 in the same place.
4 However, again, the pre-hysterectomy work
5 was what was utilized to determine whether we were
6 getting adequate destruction, and we believe we
7 demonstrated that with our pre-hysterectomy work and
8 with the subsequent electron microscopy that was done
9 to verify the staining.
10 Does that --
11 DR. SHIRK: I guess my point is, it's
12 going to be confusing to the general gynecologist
13 who's used to two freeze technique on the cervix, and
14 he's going to assume that, basically you're using two
15 freeze type of thing.
16 And I think it would be better in your
17 literature, to not refer'to it as a second freeze, but
18 to change the terminology so that it's -- the user
19 understands that, you know, there's only one freeze to
20 each segment of the uterus, rather than two freezes.
21 MR. MURRAY: Certainly. We can clarify
22 that in our literature and in any videos and
23 information that we use for training.
24 DR. BLANCO: Thank you. Dr. Janik.
25 DR. JANIK: I just had one clarification

1 question. In your evolution of technique with the
2 pre-hysterectomy specimens, you started out with a
3 direct technique, and then you went to lateral
4 placement in the cornu.
5 Were your serosalcervix studies done when
6 you were doing lateral placement to the cornu, or was
7 that before your evaluation?
8 MS. SHEA: Cheryl Shea, CryoGen.
9 Actually, in the pre-hysterectomy study, we were not
10 doing mid-line freezes. We were doing the angle
11 freezes. What we were looking at is the difference in
12 time.
13 As I said, one patient received a five-
14 minute first freeze, and then a six-minute second
15 freeze. Two received a six and six, also angled to
16 the cornu. And then the remaining seven received a
17 four and six.
18 DR. JANIK: Thank you.
19 DR. BLANCO: Thank you.
20 DR. NEUMAN: Yes. Mike Neuman on the
21 Panel. I have two questions for clarification. First
22 of all, I'd like to know whether the effect of
23 profusion of the tissue had any effect in the size of
24 the ball recorded. I wonder if you could comment on
25 that, comparing, for example, the goat liver with the

1 beef liver.

2 My second question is, perhaps, a little

3 esoteric, but let me just put it on the record anyway.

4 The Panel is smiling. I guess I have a record of

5 doing that sort of thing.

6 But if we can change our hats for a bit,

7 and think of the other side of cryobiology, where

a people are concerned with the cryo preservation of

9 tissue, one of the factors that is very important in

10 that work is the rate of freezing, and there is some

11 controversy as to whether the rate of reheating

12 affects tissue damage.

13 I wonder if the Company could comment on

14 rates in both of these cases, especially in the

15 reheating, because it appears that the reheating is

16 done only for the purpose of releasing the probe so it

17 can be placed in the second position.

18 MR. MURRAY: Dave Murray, again. I don't

19 think we have specific data that would show

20 differences in ice ball size due to profusion. We

21 didn't have any kind of specific profusion data

22 tracked on the clinical patients.

23 And the work that we did in the various

24 animals -- we did have some live animal work, as you

25 know, in the liver. And we had other work that was

1 done in a synthetic medium that followed all of that,
2 this gelatin type.
3 We tried to simulate the heat load of the
4 body when we did do gelatin studies, using a water
5 bath. So the issue of rate of thawing, we do not
6 attempt to actively thaw the ice, as you mentioned, or
7 the frozen tissue.
a We simply heat the tip so that it can be
9 removed and placed to the other side of the uterine
10 cavity. However, I guess all I can say about the
11 effectiveness of the technique, is that the study
12 demonstrated in the clinical setting, that using a .
13 four-minute and a six-minute freeze angled at each of
14 the two cornu, that we were able to achieve the
15 results demonstrated, and produce data sufficient to
16 meet our hypothesis.
17 We can't really comment on other
18 techniques and whether they would be better or worse
19 yet, although those are interesting to us.
20 DR. NEUMAN: Could I -- I just asked for
21 a clarification. Was there any difference in the size
22 of the ice balls in the liver work when you used a
23 live perfused liver compared to the beef liver?
24 MR. MURRAY: I'm being told no, there was
25 not.

1 DR. NEUMAN: Thank you.

2 DR. BLANCO: All right. Let's try to keep
3 it short so we can move on. Go ahead, Dr. Diamond.

4 DR. DIAMOND: The other question that I
5 had was actually related to conduct of the study
6 itself. If I brought my wife in because she was
7 having dysfunctional bleeding, and she was going to
a see one of the physicians today, how is the actual
9 enrollment process take place?

10 When was the patient considered a
11 valuable? When was a patient actually randomized for
12 entry to the study relative to when the study was
13 conducted?

14 MS. SHEA: Hello. Cheryl Shea, CryoGen.
15 These studies are very difficult to enroll because of
16 the inclusion/exclusion criteria. We probably
17 screened a thousand women that fell out during the
18 process to get to the patients that were actually
19 treated in the study.

20 They were not randomized until they
21 completed their inclusion/exclusion criteria.
22 However, there was one patient that was randomized,
23 that fell out before treatment because she did not
24 meet an inclusion criteria. I think it was a lab work
25 issue.

1 It came in later, that after she had been
2 randomized, but typically, the patients were not
3 randomized until they fulfilled their enrollment
4 criteria for the inclusion/exclusion.
5 DR. DIAMOND: That actually -- I think --
6 make sure I heard you right, because I think that's a
7 key issue in view of the fact that the major end point
a that you're looking at -- and unfortunately, just by
9 the randomization, you ended up with huge differences
10 initially with the original blood scores.
11 But you're saying, once the patients are
12 randomized, only one patient fell out and did not
13 undergo treatment, is that correct? Or, were there
14 others -- I mean, because it sounds like there could
15 have been weeks between the two, because the surgeons
16 -- some of them did them in different places, from the
17 time of actual randomization until they actually
18 underwent the procedure?
19 MS. SHEA: There were four that fell out.
20 Three changed their mind, and then one did not.meet
21 the inclusion/exclusion criteria.
22 DR. DIAMOND: And the choice of whether it
23 was going to be randomized, to which the physicians
24 were not aware of that until they opened the envelope?
25 MS. SHEA: No, it was -- it was totally

1 blinded.

2 DR. DIAMOND: Okay.

3 DR. BLANCO: All right. It's time to take

4 a break. Let's meet back and start promptly at 11:00.

5 (Whereupon, the foregoing matter went off

6 the record at 10: 51 a.m. and went back on

7 the record at 11:07 a.m.)

a DR. HARVEY: I just want to make a quick

9 announcement for the Panel in terms of lunch. You

10 have a flyer in front of you that is for a luncheon

11 buffet. You don't' have to order the buffet, but in

12 terms of getting us in and out of lunch promptly, you

13 may want to consider that.

14 And when you go into the restaurant, tell

15 them you're with the FDA Panel because they'll seat

16 you in a special area.

17 DR. BLANCO: All right. Let's go ahead

18 and get started. And now we're going to hear

19 presentations from the FDA, and I believe that the

20 first presenter will speak to us on pre-clinical

21 aspects.

22 Veronica Price, Biomedical Engineer

23 Reviewer for the Obstetrics and Gynecology Devices

24 Branch.

25 MS. PRICE: Thank you, Dr. Blanco. Good

1 morning ladies andgentlemen and distinguishedmembers
2 of the Panel. I'm Veronica Price, and I have been the
3 lead Reviewer of the CryoGen First Option Cryoablation
4 Therapy System for endometrial ablation since the pre-
5 IDE stage.
6 The review team for this -- okay --
7 DR. BLANCO: I'm sorry, Ms. Price, for a
a minute. That cell phone going off reminded me again.
9 Please, we have a policy that if you're in here,
10 you're not supposed to have a cell phone or have it
11 turned off. So I've heard about four or five of them.
12 So if you could please, turn them off. Thank you. Go
13 ahead.
14 MS. PRICE: Okay. The review team for
15 this PMA is listed in this slide. In addition to my
16 presentation this morning, you will hear from the
17 Statistician, Richard Kotz, and the Medical Officer,
18 Dr. Diane Mitchell.
19 Although not presenting today, Jim Seiler
20 had reviewed the software for the system. Dr.
21 Mridulike Virmani has reviewed the bio-compatibility
22 test information. Sharon Murrain Ellerbe has reviewed
23 the manufacturing, and Barbara Crow1 has been
24 responsible for the bio-research and monitoring.
25 During my presentation this morning, I

1 will provide you with information on the
2 administrative handling of the PMA, an overview of the
3 First Option System, a summary review of the clinical
4 device experience, which will include a discussion of
5 the device failures, the sponsor's analysis of these
6 failures, and the corrective actions implemented by
7 the sponsor to mitigate these failures.
a Finally, I will summarize where our review
9 of these issues stands at this point.
10 The majority of information contained in
11 a conventional PMA has already been reviewed using the
12 modular approach. This is an administrative
13 procedure, whereby the sponsor and the FDA agree to an
14 outline of information that can be reviewed by FDA
15 prior to submission of the PMA.
16 The sponsor then submits subsections,
17 modules, of the PMA for review. CryoGen opted to
18 submit the majority of their information regarding the
19 First Option device under modules, while their multi-
20 center trial was being conducted.
21 FDA has reviewed modules containing
22 general information, the device description,
23 manufacturing information and product development
24 testing.
25 The product development testing consisted

1 of the hazard analysis and software information, the
2 bench testing, by compatibility test information,
3 sterilization, shelf life, packaging, and shipping
4 testing, information from extirpated uteri, and the
5 pre-hysterectomy safety study.
6 FDA has worked interactively with the
7 sponsor during the review of these individual modules,
a and each of them have been accepted and closed. I
9 will reiterate here that these modules were reviewed
10 and closed prior to the submission of the PMA, which
11 consists of the results of this multi-center trial.
12 CryoGen has already provided a detailed
13 description of the First Option System, so I'll just
14 briefly review the system components for you.
15 The First Option Cryoablation Therapy
16 System consists of a console, cryoprobe, and
17 disposable control unit. The console serves primarily
18 to house the compressors that are used to pressurize
19 and circulate the refrigerant to the cryoprobe in a
20 closed loop system.
21 The front of the console has an LCD that
22 conveys information on the tip temperature, freeze
23 heat cycle, and cycle time, Attached to the console,
24 via a flexible hose, is the cryoprobe The cryoprobe
25 has an insulated shaft with a metal tip.

1 As explained by Mr. Reu, pressurized
2 gasses expanded through a small orifice to produce
3 rapid cooling according to the Joule-Thomson
4 principle. The specifications are shown.
5 The disposable control unit is a sterile
6 single use component, that covers the cryoprobe.
7 Buttons for initiating the freeze and thaw cycles are
a located on the control unit. It contains the heater
9 that is used for the thaw cycle, and two
10 thermacouples.
11 These thermacouples monitor the tip
12 temperature and the temperature along the shaft. The
13 tip temperature is displayed on the console, while the
14 shaft temperature is used as a safety mechanism to
15 monitor the insulation along the shaft.
16 The control unit has an injection port for
17 saline. The cold tip has a length of 35 millimeters,
18 and the diameter of 4.7 millimeters.
19 I would like to highlight some of the key
20 performance specifications of this system, regarding
21 temperature, time, and pressure. The system is
22 designed such that during a freeze cycle, a
23 temperature of negative 80 degrees C will be achieved
24 within five minutes.
25 While in the thaw mode, a temperature of

1 plus 20 degrees automatically shuts off the heater.
2 Each freeze cycle can be carried out for a maximum of
3 ten minutes. Throughout the ten minutes, audible
4 beeps are triggered every two minutes. Finally, the
5 system operates at a pressure of 400 PSI.
6 The use of the First Option system is
7 accompanied by ultrasound. Ultrasound guidance
a ensures that the procedure is not blind.
9 When used in conjunction with the First
10 Option system, ultrasound is used to verify that the
11 cryoprobe is placed within the uterine cavity to
12 confirm the desired position of the cryoprobe for each
13 of the freeze cycle, and ensure that the cryoprobe is
14 not positioned within the prior ice ball, and aid the
15 user in spatially orienting the leading edge of the
16 ice ball or ice front within the serosa.
17 The user is able to observe the
18 progression of the ice ball because the leading edge
19 is hyperechoic. The leading edge is minus two degrees
20 C and non-destructive.
21 Since the temperature is necessary to
22 destroy tissue that is minus 15 to minus 20 degrees C
23 have been shown to lag behind this ice front by three
24 to five millimeters, the user is able to terminate the
25 freeze cycle based on the position of the leading

edge, and thereby ensure an added level of safety for
2 this procedure.

3 As described in the approved clinical
4 protocol, treatment is carried out when the cryoprobe
5 has been placed in one cornu, and a freeze cycle has
6 been initiated. The first freeze is carried out for
7 four minutes, or until ultrasound indicates the ice
a front is within one millimeter of the serosal surface
9 of the uterus.

10 A thaw is then initiated. The probe is
11 pulled back and repositioned in the opposite cornu.
12 The second freeze is carried out for six minutes, or
13 again, until ultrasound indicates the ice front is
14 within one millimeter of the serosal surface of the
15 uterus.

16 Let me highlight at this point, that
17 during the freeze cycles, while the user is monitoring
18 the progression of the ice front via ultrasound, the
19 console displays the time of the freeze cycle, and
20 provides an audible beep at two-minute intervals.

21 We'd be interested in hearing the Panel's
22 opinion on the acceptability of this particular design
23 feature of the First Option system. The following --
24 this slide represents the clinical device experience
25 during the multi-center trial.

1 attachment/detachment problems between the disposable
2 control unit and the cryoprobe, erroneous error
3 messages, the system becoming stuck in a stand-by
4 mode, an inability to activate the heater, and a
failed self-test.

6 As mentioned in CryoGen's presentation,
7 they developed a reporting system, a clinical device
a assessment CDA, to catch the user's experience with
9 the device during the multi-center clinical trial.
10 The sponsor has done a nice job in explaining how they
11 handled the feedback perceived from the users-during
12 this trial.

13 In 59 of the 189 First Option cases, a
14 report was written. The sponsor has broken them down
15 into different categories, as shown here. There were
16 three categorized as user feedback that the -- Mr. Reu
17 went over with you.

18 There were seven user errors, and I will
19 go into them further in the next slide. The sponsor
20 has indicated 13 user resolvable device reports. This
21 category includes those instances in which the device
22 malfunctioned, did not keep the user from successfully
23 completing the procedure.

24 Finally, there were 36 non-resolvable
25 device reports, five attributed to the disposable

1 control unit and 31 to the console. This means that
2 in five cases, the disposable control unit had to be
3 replaced to complete the procedure.
4 And in 31 cases, the console malfunctioned
5 leading to a system failure, such as the target tip
6 temperature not being reached. Five of these are the
7 acute treatment failures.
a There were six CDAs classified as user
9 error. Some examples of user error related to the
10 application of the thermal conductive medium, or TCM,
11 that was placed inside the disposable control unit by
12 the user at the time of the procedure.
13 The commercial units now have pre-greased
14 control units supplied to the user. Another user
15 error had to do with the freeze technique, in which it
16 was noted that the user initiated the second freeze in
17 the same ice ball.
18 The sponsor has modified their labeling
19 and training to help address this issue. We would be
20 interested in the Panel's input on the labeling and
21 training with respect to this issue.
22 There were cases in which the user did not
23 perform a pre-cool. The software has been modified on
24 the commercial model, such that a pre-cool is required
25 before the first freeze cycle can be initiated.

1 Finally, there were 20 cases in whichmore
2 than one disposable was used. In some cases, three
3 and four disposable control units were used. Although
4 additional clarification on these cases still needs to
5 be provided, the sponsor has indicated that some of
6 these cases were due to contamination of the
7 disposable or dropping.
8 In analyzing the investigative reports,
9 the sponsor examined and tested the consoles and
10 control units to determine the root causes for the
11 observations. The sponsor has categorized these root
12 causes into the following device components: Console,
13 control unit, cryoprobe, and electrical software.
14 As can be seen in the next few slides,
15 there are a variety of reasons for the observed device
16 malfunctions. This slide lists those related to the
17 console. These are the causes attributed to the
18 control unit. And finally, a listing of those
19 attributed to the cryoprobe and the electrical and
20 software.
21 For each root cause identified, the
22 sponsor worked to determine a corrective action. The
23 validated corrective actions have been implemented in
24 the commercial model. They include software
25 modifications that added an automated pre-cool cycle,

1 and additional performance criteria that is assessed
2 by the software.
3 Designand specification changes have been
4 made to the commercial model. As described earlier,
5 the thermal conductive medium is now pre-applied. In
6 addition, the cryoprobe was changed from a two-piece
7 to a one-piece design.
a The sponsor has modified their quality
9 assurance procedures to include additional or improved
10 testing. For example, there is now 100 percent
11 electrical test of the flex circuit.
12 There has been additional training for the
13 assembler, to ensure that the device is manufactured
14 to specifications. And finally, the sponsor has made
15 changes to the device labeling.
16 So when examining the experience of the
17 beta consoles and the earlier version of the
18 disposable control unit, it is important to do so in
19 the context of this high malfunction rate. The
20 sponsor has systematically worked to determine device
21 improvements for the commercial model that is made in-
22 house by CryoGen to minimize its malfunction rate.
23 The sponsor seeks approval of this
24 commercial model under this PMA, in spite of the fact
25 that it has not been studied in a clinical setting.

1 They have provided bench testing on the commercial
2 system under one of their modules.
3 The bench testing module was accepted and
4 closed. However, I would like to point out that this
5 review was conducted before the results of the
6 clinical study were known. The sponsor has indicated
7 that they have some market experience with this model
8 under their cleared 510(k).
9 One of the ongoing issues with this PMA
10 has to do with the validation of these changes. The
11 issue of whether the previously reviewed bench testing
12 is sufficient to warrant approval of this model is the
13 subject of one of the discussion questions. We are
14 very interested in the Panel's input on this issue.
15 As indicated in the presentation, CryoGen
16 continues to work to minimize the incidents of GMC
17 obstruction, disposable control unit attachment
18 difficulties, and to further reduce user errors.
19 In summary, we know that there was a high
20 rate of device problems noted during the clinical
21 trial, and this leads us to examine two things. What
22 impact did this have on the results of the multi-
23 center trial, and what is our confidence level in the
24 reliability of the commercial model?
25 When assessing the safety and

1 effectiveness of the First Option system and the
2 procedure used in the clinical trial, it is important
3 to remember that 11.6 percent of the First Option
4 cases were treated -- were not treated with the
5 prescribed four-minute, six-minute freeze cycle
6 because of a device malfunction.
7 In many of these cases, the freeze
8 temperature did not reach the expected value, and so
9 the user altered the treatment time to compensate.
10 The effect of longer treatment times are additional
11 freeze cycles, with temperatures warmer than the minus
12 80 degrees C on studies, success is unknown.
13 The device malfunctions did not, however,
14 effect the safety of the procedure. As pointed out
15 earlier in my presentation, the use of ultrasound
16 provides an added safety factor, since the user can --
17 which allows the user to monitor the progression of
18 the ice front.
19 With respect to device reliability, we do
20 not have the benefit of controlled clinical feedback
21 on the new model, because it was not introduced during
22 the clinical study. The sponsor has done a thorough
23 evaluation of the malfunctions, and has developed and
24 applied corrective actions tomitigate these failures.
25 But the commercial model has not been

clinically validated.' Bench testing did not always adequately simulate the clinical usage of the -- of a device. We look forward to the Panel's discussion with regards to this issue.

I would now like to introduce our Statistician, Richard Kotz, who will provide you with a summary review of the statistics provided in the PMA.

MR. KOTZ: Thank you, Veronica. I am Richard Kotz, and I am the Statistical Reviewer of CryoGen's pivotal -- pivotal trial for their First Option endometrial ablation device.

My talk will include discussions of their study designs, study hypothesis, sample size, and study results. I will also discuss a randomization issue, and then summarize my discussion.

The sponsor's randomized control study was designed in accordance with FDA's guidance document. CryoGen's device, the First Option endometrial ablation device, or what I have abbreviated as CR in my slides, as compared to the control, Rollerball, abbreviated as REA.

The subjects are randomized at each site, with two patients receiving cryo to each subject receiving Rollerball. The randomization is also

1 stratified at each site into patients under and over
2 40 years of age.
3 The study ended up employing ten sites,
4 with 17 to 60 subjects per site. A patient -- for
5 this study, a patient's success, as was earlier
6 explained, was defined as a 12 month pictorial blood
7 loss assessment chart score, or PBAC score, of less
8 than 75.
9 It should be noted that to be included in
10 the study, a baseline of -- the patient had to have a
11 baseline score of greater than 150. And in fact, some
12 patients had baseline scores well above 2,000.
13 The study hypothesis was at the success
14 rate for the First Option, or cryodevice, was equal to
15 that for the control, Rollerballversus an alternative
16 hypothesis that they were not equal.
17 A two-sided test of proportions, with a
18 five percent significance level and 80 percent power,
19 was used to calculate the sample size. The acceptable
20 clinical difference was set at 25 -- 20 percent. This
21 large clinical difference was previously discussed
22 with, and accepted, by the Panel.
23 The expected Rollerball success rate of 85
24 percent was based on previously published studies.
25 Given these rates, the sample size was calculated as

1 discussed in the next slide. As you may recall, the
2 randomization scheme was to enroll two cryo patients
3 at each site for each Rollerball patient enrolled.
4 Given the rates and statistical test
5 presented in the previous slide, the necessary study
6 sample size was calculated to be 222. This translated
7 into 148 patients receiving cryo, and 74 receiving
8 Rollerball.
9 It was expected that the loss to follow
10 rate might be as high as 15 percent. Therefore, the
11 total approved study sample size was 260 patients.
12 The total number of patients actually treated was 275,
13 of which 189 were treated with cryo, and 86 received
14 the control treatment, Rollerball.
15 Of these 275 patients, 21 still had 12
16 month evaluations pending as of the latest analyses.
17 This includes 18 cryo and three Rollerball patients.
18 And these patients' results were not used in the
19 analysis of the results.
20 The observed intent to treat success rates
21 were 68 percent for the First Option, and 73 percent
22 -- or 73.5 percent for the Rollerball patients. Note
23 that the intent to treat analysis includes as
24 failures, the 13 cryo and eight Rollerball patients
25 who were lost to follow up, or who had no 12 month

1 diaries available.

2 But as I said, it did not include the 21
3 patients whose 12 month evaluations were still
4 pending. The sponsor earlier presented an analysis
5 for all evaluable patients. The results for this
6 analysis gave a success rate of 74 percent for cryo
7 and 81 percent for Rollerball.

8 Note that this analysis doesn't use the
9 data from either the lost to follow up patients or
10 those patients who had -- the 21 patients who had not
11 reached the 12 month evaluation.

12 Recall that the acceptable clinical
13 difference was set at 20 percent for the purpose of
14 evaluating device effectiveness. Therefore, the
15 device was deemed effective if we are 95 percent
16 confident that the difference in success rates between
17 the two devices does not exceed 20 percent.

18 Or, in other words, it is desired that the
19 upper bound of the two-sided 95 percent confidence
20 interval, on the difference of the Rollerball success
21 rate minus the observed cryo success rate view, less
22 than 20 percent.

23 Since the upper bound on the 95 percent
24 confidence interval for the evaluable patients was
25 18.4 percent, and the intent to treat was 16.9

1 percent, both of which are less than 20 percent, the
2 device has met the pre-specified statistical criteria
3 for effectiveness.
4 Just a short note that, though the sponsor
5 used the Blackwelder approach to analyze the data,
6 this approach is technically acceptable, but the
7 sample size was not calculated based on this method.
8 However, the sponsor met the primary study objective
9 by both test methods.
10 When the evaluable results are stratified
11 by age, we find that the patients over 40 appear to do
12 a little better than those under 40. As you see, the
13 cryo success rate and REA success rates are 72 and 76
14 percent, respectively, for the under 40 category, and
15 75 and 84 percent for the over -- over 40 category.
16 If a straight subgroup analysis is done,
17 no significant differences are detected. But the
18 study was not intended to detect these differences;
19 The success rates across sites were
20 significantly different. In particular, two sites, as
21 was already mentioned, Alabama and Boston, had very
22 poor results. Note that the Boston site is a
23 combination of Brigham and Women and Mass General
24 Hospitals.
25 Alabama had success rates of 43 percent

1 and 25 percent for cryo and Rollerball, respectively.
2 But an additional eight cryo patients and one
3 Rollerball patient still have 12 month evaluations
4 pending.-
5 The Boston site had cryo and Rollerball
6 success rates of 85 percent -- excuse me, of 25
7 percent and 71 percent, respectively. And at this
8 site, an additional four cryo and one Rollerball
9 patient still have 12 month evaluations pending.
10 In fact, note that these two sites have
11 two thirds of the patients with results still pending.
12 Actually, the results are in, but they were pending at
13 the time of these analyses.
14 Possible explanations offered by the
15 sponsor for these poor success rates were that the
16 Alabama investigator treated all -- all subjects in
17 his office, and the Boston sites, I believe, did not
18 use an ultrasound technician for the procedure.
19 If you'll recall, the protocol called for
20 a two to one randomization scheme for each site. The
21 sponsor had reported that each site was given 30
22 envelopes with 15 for each -- for patients under, and
23 15 for patients over 40 years of age.
24 In each of these strata, ten envelopes
25 specified that the patients received cryo, and five

1 envelopes specified that the patients received the
2 controlled Rollerball. However, I did note that 13 of
3 the last 14 patients enrolled at the Alabama site,
4 were randomized to cryo. And eleven patients in a row
5 were randomized to the cryo at the Denver site.
6 The sponsor stated that these were both
7 chance occurrences.
8 DR. BLANCO: You just said it backwards
9 from what you have on the slides.
10 MR. KOTZ: Oh, let's see. Actually, I
11 think I blew -- I blew -- I think the -- that's right
12 It's 13 of the last 14 Alabama patients, I believe, in
13 the -- and then the Denver site had the 11 patients in
14 a row.
15 DR. BLANCO: So it's reverse from what you
16 have on the slide?
17 MR. KOTZ: I'm quite certain it's reverse.
18 If it's otherwise, I'll let you know. I just have it
19 wrong.
20 DR. BLANCO: Thank you.
21 MR. KOTZ: Sure. In summary, the sponsor
22 did meet the objective of their primary end point.
23 That is, the upper bound of the two sided confidence,
24 95 percent confidence interval, of the differences --
25 control minus First Option did not exceed 20 percent,

1 for either the intent to treat or evaluable analyses.

2 Secondary analyses did not detect any

3 statistical differences between patients under and

4 over 40 years of age. But you should remember the

5 study was not all designed or powered to -- or powered

6 to test this.

7 We also found that two sites had

8 significantly worse success rates, Alabama and the

9 Boston sites. And we also discussed randomization

10 anomalies at the Alabama and Denver sites.

11 Our next speaker will be Dr. Diane

12 Mitchell. She's the Clinical Reviewer for this

13 device.

14 DR. MITCHELL: Good morning. Thank you,

15 Richard, for your presentation of the statistical

16 issues. I'm now going to review the clinical issues

17 with -- that the FDA has been looking has been looking

18 at with regard to the First Option Uterine

19 Cryoablation Therapy System.

20 This is an outline of my presentation.

21 And my asterisk up there is to remind me to say that

22 the previous presenters to include the sponsors as

23 well as Richard and Veronica, I think, have done a

24 very adequate job of presenting the protocol as well

25 as, in general, the results of the study.

1 And so, that's why I'm just going to
2 highlight or focus on these certain review issues.
3 For safety, I'll be discussing the adverse events,
4 thermal safety, and effectiveness of the device, as
5 well as ultrasound use.
6 For effectiveness, I'll review again, the
7 success rates and talk a little bit about
8 understanding the study results. As far as the
9 labeling goes, we'll review a little bit about the
10 contraindications, possible use of antibiotics, other
11 labeling issues, and finally, physician training.
12 During the summary, I'll also talk a
13 little bit more about what else the FDA needs to do to
14 complete the review process. As we recall, the
15. pivotal study was a two to one randomization. CR up
16 there represents cryotherapy, or the active treatment
17 group.
18 REA is Rollerball endometrial ablation,
19 which is the control group. As I stated, the first
20 thing I'd like to review is the adverse events. This
21 sponsor presented the adverse events in three
22 different time categories. Peri-operative was the
23 time that the patient was in the hospital until she
24 was discharged.
25 And that's this first group here. Again,

1 there were two perforations that occurred. For pain
2 and cramping identified during this time, there were
3 42 women in the CryoGen group, and 14 in the
4 Rollerball.
5 Complicated anesthetic recovery, severe
6 vaginal bleeding, one each in the treatment group,
7 spotting, fluid overload, and hyponatremia in the
8 Rollerball group, as well as lacerations of the cervix
9 and vagina.
10 The pain and cramping issue, there is a
11 discrepancy we see there, 42 and 14 are not really two
12 to one. And we're in the process of continuing to
13 look at that with the sponsor.
14 Oh, I just want to mention one thing
15 before I go on. I'm not looking at just the serious
16 adverse events, as the sponsor did in their
17 presentation. I looked at all the different adverse
18 events, to include the serious and the non-serious.
19 And what I have done is highlighted the
20 ones that I think are of interest -- have been of
21 interest at the FDA.
22 The next grouping was adverse events in
23 the first 14 days. As you can see, abdominal pain, 12
24 and eight, infection, not -- certainly not high.
25 Bleeding, one in the control group, and there were six

1 women who experienced vaginal discharge in the CryoGen
2 group.
3 Not surprising, given that it's
4 cryotherapy, and based on what we know about cervical
5 treatment with cryoablation. With regard to the third
6 grouping, which was greater than two weeks out, there
7 were 26 and 21 patients who had pain. Seventeen
8 patients in the cryo group who had bleeding, two in
9 the control group.
10 Again, we're looking at this with the
11 sponsor. It turns out that there's some -- the
12 adverse events were not always reported the same way .
13 within each site. And it turns out that 12 of those
14 were reported from two different sites, and those --
15 and actually, some of those were women who ultimately
16 went on to retreatment, who were considered failures.
17 So we're looking with more detail at the
18 adverse events to help better understand that. And
19 then, as you can see, one patient in the control group
20 had -- had a hematoma.
21 And Dr. Heppard has gone over what's the
22 asterisk, which is that three of the patients did
23 require DNC. One in the pain group from cryo, one in
24 the pain group from REA, and the lady with the
25 hematoma.

1 In the cryo group, the woman who received
2 the DNC was ultimately considered -- was ultimately
3 lost to follow up. In the control group, one of the
4 women was lost -- was considered a failure. And one
5 of the women at 12 months was considered a success.
6 Okay. The next thing I want to talk about
7 is the thermal safety and effectiveness. And we -- as
8 you will recall, the protocol during the pivotal
9 study, and what's planned for marketing the device, is
10 four minutes in one cornu, followed by six minutes in
11 the second cornu.
12 with regard to thermal safety, I just want
13 to review a little bit about what we know about the
14 thermal safety of the device. Again, the pre-
15 hysterectomy study, there were serosal surfaces --
16 there were serosal surface temperatures measured in
17 two patients.
18 Just of note, in both patients, they were
19 unable to measure the anterior serosal surface during
20 these pre-hysterectomy studies. It had to do with the
21 technicality of placing the thermometer.
22 The woman who underwent the four-minute
23 first freeze had a 356 gram uterus. The woman who
24 underwent the six-minute first freeze had a 140 gram
25 uterus. In both cases, there was no decrease in

1 serosal temperature during -- when the temperatures
2 were measured.
3 And in addition, for thermal safety, there
4 was no evaluation done in‘the pre-hysterectomy studies
5 of additional freezes, meaning more than two. What we
6 have learned about thermal safety with regard to the
7 protocol is that during the pivotal study, 12 patients
8 did have freezes that were longer than first freezes
9 that were longer than four minutes.
10 Six patients had additional freezes, just
11 one additional freeze, a third freeze. I do want to
12 point out, as Veronica did, that these patients
13 predominantly -- not all of them -- but the majority
14 of these women had this deviation from the protocol
15 because of the fact that there was a device
16 malfunction.
17 Andpresumably, the investigator felt that
18 extending the freeze time, or the number of freezes,
19 would make a difference. And that's the third arrow
20 there.
21 With regard to thermal effectiveness
22 during the pre-pivotal studies, both extirpated uteri
23 and pre-hysterectomy, as the sponsor explained, they
24 did look at the depth of necrosis to get an
25 understanding of how much freezing was required to

1 adequately necrose the tissue.

2 Again, in the pivotal study, there were
3 longer freezes and additional freezes done, but most
4 of the time, secondary to device malfunction.
5 Veronica did a very nice job of explaining the device
6 design, and I want to review these key features.

7 The device does beep every two minutes
8 while you are freezing, but it does not automatically
9 shut off until after a freeze has been going on for
10 ten minutes. And the console, at this point, does
11 allow the practitioner to decide to freeze -- use more
12 than two freezes on an individual patient.

13 The ultrasound use, again, Veronica I
14 think has done a very nice job of describing the
15 ultrasound use. It is to monitor the ice front, which
16 is safety feature, as well as to detect perforation,
17 which is another safety feature.

18 The label will indeed include the use of
19 ultrasound as a part of the procedure. And the other
20 things that we found out, that they found out from the
21 study, is that at least when you look at that one
22 slide that Richard referred to, it looks like you do
23 need a second separate pair of hands to be holding the
24 ultrasound while you're performing the procedure. And
25 clearly, you need to be experienced at looking -- in

1 looking at ultrasound to perform this procedure.

2 Okay. Our success rates, the

3 effectiveness, when the FDA is using an intent to

4 treat analysis to understand the effectiveness, and

5 with that you can see that success at 12 months for

6 cryotherapy is 68 percent. And for REA, it's 73

7 percent.

8 Again, the acute failures, there were six.

9 We include the one perforation for cryotherapy, and

10 one for REA, which was a secondary to a perforation.

11 Again, pending evaluations at 12 months, 18 women in

12 the cryotherapy group, and three in the control group.

13 Okay. So we've had some discussion as to

14 the results -- as to the study results and the

15 effectiveness rates. And I just want to point out

16 that one of the things that maybe contributing to the

17 effectiveness rates as they currently are, are the

18 number of device malfunctions.

19 We're also looking at -- there were those

20 couple of outlier sites. There were some other

21 issues, such as mentioned during the question and

22 answer session, about the uterine size and the ice

23 ball length.

24 At this point, I think it's fair to say

25 that we cannot assume that changing the length of

1 freeze time, or the number of freezes, will improve
2 effectiveness rates. And the sponsor is stating that
3 we're going to have a four-minute and a six-minute
4 freeze for this particular -- in the labeling for this
5 particular device.
6 A little comment about the cold tip length
7 being 35 millimeters. I want to look at it in the
8 opposite way from during the Panel discussion, and ask
9 if there should be a lower limit on uterine size.
10 As we know, if you assume that the cold
11 tip length -- well, we know that the cold tip length
12 is the amount -- is where the freezing is going on.
13 So if you have a seven sonometer uterus, and you
14 assume that the cervical length is four sonometers,
15 and the cold tip length is 3.5, if you go much lower
16 than seven sonometers, I think you do run the risk of
17 freezing the endocervical canal.
18 And during the discussion of
19 contraindications, I think we want to consider
20 possibility a lower limit on uterine size. So now
21 I've sort of slipped into the labeling part of my
22 discussion without announcing it, but here we are.
23 With regard to antibiotics, I just want to
24 mention when we're looking at labeling, that
25 antibiotic prophylaxis maybe warranted, a discussion

1 of that in the labeling. It turns out that about half
2 the patients in each group received prophylaxis,
3 specifically 65 percent in the treatment group, and 51
4 percent in the control group.
5 And there was a fairly low rate of
6 infection in the first two weeks. There were only
7 five patients in each group who developed an
8 infection.
9 Other labeling issues that I think are
10 worth considering as we look at the labeling for this
11 device, in the Panel package that you have, there is
12 a discussion -- or a description of the anesthesia
13 that's required as minimal anesthesia.
14 In the discussion here today, during the
15 Panel meeting, it was described as requiring less
16 general anesthesia. I think it's going to be helpful
17 for us to consider how, if at all, we want to discuss
18 anesthesia in the labeling.
19 Just to review -- and again, in your Panel
20 package on page 52, there's a nice table of the types
21 of anesthesia required for this device. But the local
22 anesthetic, which is a paracervical block, there were
23 ten percent of the patients received that. Thirty-
24 eight percent of the patients had local with conscious
25 sedation.

1 And just of note, when we're looking at
2 this, the adverse event rates, we're still looking at
3 that 42 versus 14 for the pain and cramping adverse
4 event rates in the patients through discharge.
5 The last thing about anesthesia is there
6 was not a discussion here, but there is a discussion
7 in your Panel package about the freezing being --
8 giving off a natural anesthetic effect. And at this
9 point, we have no data on the actual freezing being a
10 natural anesthetic.
11 Another comment that's made in your Panel
12 package regards cervical dilation. And I just want to
13 point out that only 21 out of 189 patients did not
14 require cervical dilation during the -- during the
15 pivotal study.
16 With regard to training, we only have
17 preliminary information on training, essentially
18 what's in your Panel pack is our training information
19 currently. And I would like, during the Panel
20 discussion, I would hope that we would get some sorts
21 of suggestion as to what sort of training -- what sort
22 of information should be provided in the training
23 information that the sponsor is going to present.
24 And some examples I might give is the
25 discussion about how the -- how the physician needs to

1 be knowledgeable in ultrasound, as well as uterine
2 anatomy. Possibly some counseling suggestions. And
3 then we heard Dr. Heppard talk about how she withdraws
4 her tip a little bit.
5 You know, if there have been any little
6 suggestions like that learned throughout the pivotal
7 study, that might be helpful to add. Okay. Next
8 we're going to go to ongoing review issues.
9 And I'd just like to point out that these
10 are things that we are still working with with the
11 sponsor, as well as waiting for. Again, we're in
12 discussion still about the adverse events.
13 We need to receive more information about
14 the labeling and training, the malfunctions analysis
15 is still ongoing, the BIMO inspections, which are
16 where the -- where we have somebody from the FDA go
17 out and evaluate the clinical study sites. And then,
18 we still like to look at the information from the
19 patients who have not yet completed follow up.
20 In summary, I've given you an idea as to
21 what we're looking at with regard to safety,
22 effectiveness, labeling and training, as well as an
23 additional review that's currently ongoing. And thank
24 you very much.
25 DR. BLANCO: Thank you. We have a couple

1 of minutes before we're going to break for lunch if
2 any of the Panel members would like to ask the FDA any
3 questions of facts or clarifications of the data they
4 presented. Diony.
5 MS. YOUNG: Thank you. Diony Young. I'd
6 like to know if the adverse events were
7 disproportionately from the two sites that had the
8 lowest success rates.
9 DR. MITCHELL: That's actually a very good
10 question. And off hand, I don't know the answer to
11 it.
12 DR. BLANCO: Could we ask the Company if
13 they would please take a look at the data and see if
14 they can answer that question after lunch.
15 DR. D'AGOSTINO: I have a couple of
16 questions about the format of the statistical test.
17 The power calculations is really done for just a test
18 of the null hypothesis of equality against inequality.
19 And then the actual statistical test was non-
20 inferiority test.
21 When you do a non-inferiority test, or you
22 are calling it equivalency -- when you do a non-
23 inferiority test, you come up with a margin of how
24 close you want the new product to be to the standard
25 product. And 20 percent was suggested. And that to

1 me seems like a very large margin -- evidently the
2 Panel has considered it before.
3 But I'd like some -- you know, some talk
4 on it. But more importantly, is that when you're
5 doing these tests, you also like to see that the
6 control is doing reasonably well. In the power
7 calculations, the control was thought to be 85
8 percent.
9 If you look at your intent to treat
10 analysis, your intent to treat analysis, the control
11 comes out to be 73 percent. In the evaluable, it's 81
12 percent. And where I'm heading is that, the sloppier
13 the study, the control rate can drop down quite
14 dramatically.
15 Do we have any discussion, or is there a
16 discussion on what we -- in terms of interpreting
17 this, what kind of rate we would expect from the
18 control, and need, in order to interpret this data?
19 Because again, the worse the study is, the control
20 group rate could drop down to 50 percent or something
21 like that.
22 And then you're saying the new treatment
23 could be 30 percent, and you're saying they're
24 equivalent.
25 DR. BLANCO: Let me address this. First

1 of all, it's a great -- 1 think we need to bring that
2 up in the discussion session after lunch. But I guess
3 your question, in fact, is whether the Company has an
4 explanation for why the control arm did not come up to
5 the 85 percent number that was expected.
6 DR. D'AGOSTINO: I'm really asking the
7 FDA, but you're right. How do I interpret these
8 results? They're giving us the statement of the
9 numbers without leaving it for us to judge in terms of
10 this study's success. And should we be looking beyond
11 these numbers? And then we can ask the Company later
12 on why they didn't get the 85 percent.
13 But they did in terms of the evaluable
14 patients.
15 MR. KOTZ: Right. We have seen several
16 other studies. And the evaluable ranges from 80 to 85
17 percent effectiveness, generally. These studies were
18 designed many years ago. But since that time,
19 generally, the evaluables in the other studies have
20 ranged -- evaluable effectiveness rate for the
21 controls have ranged from 80 to 85 percent.
22 DR. BLANCO: I'm sorry. For the record,
23 can you identify yourself?
24 MR. KOTZ: Oh, Richard Kotz, FDA,
25 Statistical Reviewer. So these rates were not

1 unreasonable for the control, when including the
2 intent to treat. Possibly a little lower than what
3 we've seen otherwise, but not --
4 DR. D'AGOSTINO: The intent to treat is 73
5 percent.
6 MR. KOTZ: Right. And I don't remember
7 the other numbers. So it was lower, but it wasn't --
8 you know, that much lower than the other cases. As
9 far as the -- 1 did not calculate the post hoc power
10 of the study, which is what I think you might be
11 getting at in this case.
12 But as we had designed the study, they
13 still met the effectiveness criteria. Your concern is
14 is that the control is a lot lower than the study was
15 powered for. The study was powered for an 85 percent
16 control.
17 DR. D'AGOSTINO: My concern is when I'm
18 looking at non-inferiority, I want to see the margin
19 of difference. But I also want to see something in
20 the control. You know, is the study sensitive? Have
21 I actually achieved absolute rates from the control
22 that make me think that the control -- that the study
23 is worth something, and worthwhile interpreting.
24 I mean, if the control was ten percent, I
25 would think the study is terrible.

1 DR. BLANCO: All right. So question is --
2 the clarification you'd like to see, whether there was
3 anything going on in the control group that might
4 explain why they did not achieve their 85 percent
5 assumption.
6 And then from that probably needs to,
7 maybe, might want to see if the Company can address
8 that when we meet back. And then from Dr. Kotz,
9 whether the difference might -- the difference between
10 the expected analysis and what was found, would alter
11 the statistical analysis results in the range or the
12 margin. Correct?
13 DR. D'AGOSTINO: Can I ask one other
14 question?
15 DR. BLANCO: Yes, let's finish with this
16 one. So would you please try to address that so we
17 can hear back before we start our deliberations?
18 MR. KOTZ: Okay, but one quick note was
19 that the study was based -- the study was powered or
20 sized on the evaluable patients. And the evaluable
21 rates were not -- were not really below what's
22 expected, which is in the 80 to 85 percent range for
23 the control.
24 DR. D'AGOSTINO: In terms of the
25 randomization, you raise the question about the