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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

* * *

MEETING

* * *

THURSDAY,

OCTOBER 2, 2003

* * *

The Panel met at 9:00 a.m. in Salons A, B and C of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Warren Laskey, Acting Chairman, presiding.

PRESENT:

| | |
|--------------------------|-----------------|
| WARREN K. LASKEY, M.D. | Acting Chairman |
| SALIM AZIZ, M.D. | Member |
| THOMAS B. FERGUSON, M.D. | Consultant |

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PRESENT (Continued):

| | |
|----------------------------------|----------------------------|
| ALLEN A. HUGHES, Ph.D. | Consumer Representative |
| MITCHELL W. KRUCOFF, M.D. | Consultant |
| WILLIAM H. MAISEL, M.D., M.P.H., | Consultant |
| DOUGLASS A. MORRISON, M.D. | Consultant |
| MICHAEL C. MORTON | Industry Representative |
| GARY G. NICHOLAS, M.D. | Consultant |
| SHARON-LISE NORMAND, Ph.D. | Consultant |
| JOHN C. SOMBERG, M.D. | Consultant |
| CYNTHIA TRACY, M.D. | Member |
| CHRISTOPHER J. WHITE, M.D. | Consultant |
| GERETTA WOOD | Executive Secretary |

FDA REPRESENTATIVES:

BRAM ZUCKERMAN, M.D.

JOHN P. HOLDEN, Ph.D.

BARBARA KRASNICKA, Ph.D.

WOLF SAPIRSTEIN, M.D.

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SPONSOR REPRESENTATIVES:

CHRIS REISER, Ph.D

BRUCE GRAY, D.O.

JOHN LAIRD, M.D.

VENKATESH RAMAIAH, M.D.

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

(9:04 a.m.)

1
2
3 CHAIRMAN LASKEY: If we can all take our
4 seats, we'll get started.

5 Thank you.

6 Good morning. I'd like to call us to
7 order.

8 My name is Warren Laskey. I'd like to
9 call this meeting of the Circulatory System Device
10 Panel to order today.

11 The topic discussed will be the pre-
12 market application for Spectranetics CVX-300 Excimer
13 Laser System, P910001.

14 If Geretta could please read the
15 conflict of interest statement.

16 MS. WOOD: The following announcement
17 addresses conflict of interest issues associated
18 with this meeting and is made part of the record to
19 preclude even the appearance of an impropriety.

20 To determine if any conflict existed,
21 the agency reviewed the submitted agenda for this
22 meeting and all financial interests reported by the

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1 committee participant. The conflict of interest
2 statutes prohibit special government employees from
3 participating in matters that could affect their or
4 their employer's financial interests.

5 The agency has determined, however, that
6 the participation of certain members and
7 consultants, the need for whose services outweighs
8 the potential conflict of interest involved, is in
9 the best interest of the government. Therefore,
10 waivers have been granted for Drs. Mitchell Krucoff
11 and Christopher White for their interest in firms
12 that could be affected by the panel's
13 recommendations.

14 Dr. Krucoff's waiver involves consulting
15 on a competing technology firm's unrelated product
16 for which he receives an annual fee of less than
17 \$10,001.

18 Dr. White's waiver involves a grant to
19 his institution for the sponsor's product study in
20 which he had no involvement in data generation or
21 analysis and for which funding to the institution
22 was less than \$100,001 per year.

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1 The waivers allow these individuals to
2 participate fully in today's deliberations. Copies
3 of these waivers may be obtained from the agency's
4 Freedom of Information Office, Room 12A-15 of the
5 Parklawn Building.

6 We would like to note for the record
7 that the agency took into consideration other
8 matters regarding Drs. Krucoff and Cynthia Tracy.
9 These panelists reported past or current interests
10 involving firms at issue, but in matters that are
11 not related to today's agenda. The agency has
12 determined, therefore, that they may participate
13 fully in all discussion.

14 We would also like to note that Michael
15 Morton, the industry representative for the panel,
16 has reported interests in firms at issue.

17 In the event that the discussions
18 involve any other products or firms not already on
19 the agenda for which an FDA participant has a
20 financial interest, the participant should excuse
21 him or herself from such involvement, and the
22 exclusion will be noted for the record.

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1 With respect to all other participants,
2 we ask in the interest of fairness that all persons
3 making statements or presentations disclose any
4 current or previous financial involvement with any
5 firm whose products they may wish to comment upon.

6 CHAIRMAN LASKEY: Thank you.

7 If I can have the panel members
8 introduce themselves beginning with Mr. Morton.

9 MR. MORTON: My name is Michael Morton,
10 and I'm an employee of CarboMedics, and I'm the
11 industry representative.

12 DR. HUGHES: My name is Allen Hughes,
13 and I'm on the faculty at George Mason University,
14 and I'm the consumer representative.

15 DR. NICHOLAS: Gary Nicholas. I'm at
16 Lehigh Valley Hospital, the faculty of Penn State
17 University.

18 DR. TRACY: Cindy Tracy. I'm an
19 electrophysiologist at Georgetown University.

20 DR. MAISEL: William Maisel, a
21 cardiologist at Brigham & Women's Hospital in
22 Boston.

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1 DR. WHITE: Chris White. I'm an
2 interventional cardiologist from the Ochsner Clinic
3 Foundation.

4 DR. FERGUSON: Tom Ferguson,
5 cardiovascular surgeon, Washington University School
6 of Medicine, St. Louis.

7 MS. WOOD: Geretta Wood, Executive
8 Secretary.

9 CHAIRMAN LASKEY: Warren Laskey,
10 interventional cardiologist, National Naval Medical
11 Center.

12 DR. MORRISON: Doug Morrison,
13 interventional cardiologist, University of Arizona
14 in Tucson VA.

15 DR. SOMBERG: John Somberg, Rush
16 University.

17 DR. KRUCOFF: Mitch Krucoff. I'm an
18 interventional cardiologist at Duke University
19 Medical Center and the Durham VA and the Director of
20 devices trials at Duke Clinical Research Institute.

21 DR. AZIZ: Salim Aziz, adult cardiac
22 surgeon practicing in the D.C.-Maryland area, and a

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1 clinical associate professor at University of
2 Colorado.

3 DR. NORMAND: I'm Sharon-Lise Normand,
4 associate professor of biostatistics at Harvard
5 Medical School and Harvard School of Public Health.

6 DR. ZUCKERMAN: I am Bram Zuckerman,
7 Director, Division of Cardiovascular Devices at FDA.

8 CHAIRMAN LASKEY: Thank you, all.

9 If I can have Ms. Wood read the voting
10 status statement, please.

11 MS. WOOD: Pursuant to the authority
12 granted under the Medical Devices Advisory Committee
13 charter, dated October 27, 1990, and as amended
14 August the 18th, 1999, I appointed the following
15 individuals as voting members of the Circulatory
16 System Devices Panel for this meeting on October the
17 2nd, 2003:

18 Thomas Ferguson, M.D.

19 Sharon-Lise Normand, Ph.D.

20 Mitchell W. Krucoff, M.D.

21 William Maisel, M.D., M.P.H.

22 Douglass A. Morrison, M.D.

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1 Gary G. Nicholas, M.D.

2 John C. Somberg, M.D.

3 Christopher J. White, M.D.

4 For the record, these individuals are
5 special government employees and are consultants to
6 this panel under the Medical Devices Advisory
7 Committee. They have undergone the customary
8 conflict of interest review and have reviewed the
9 material to be considered at this meeting.

10 In addition, I appoint Warren K. Laskey,
11 M.D., to act as temporary chairperson for the
12 duration of this meeting.

13 And it's signed by David W. Feigal, Jr.,
14 M.D., M.P.H., Director, Center for Devices and
15 Radiological Health, on September 30th, 2003.

16 CHAIRMAN LASKEY: Thank you.

17 It is traditional at this point to have
18 the open public hearing portion of this morning's
19 meeting, and before I open the session up to the
20 public, I have a statement to read which is as
21 follows:

22 Both the Food and Drug Administration

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1 and the public believe in a transparent process for
2 information gathering and decision making. To
3 insure such transparency at the open public hearing
4 session of the Advisory Committee meeting, FDA
5 believes that it is important to understand the
6 context of an individual's presentation.

7 For this reason, FDA encourages you, the
8 open public hearing speaker, at the beginning of
9 your written or oral statement to advise the
10 committee of any financial relationship that you may
11 have with the sponsor, its product, and, if know,
12 its direct competitors.

13 For example, this financial information
14 may include the sponsor's payment of your travel,
15 lodging, or other expenses in connection with your
16 attendance at the meeting.

17 Likewise, FDA encourages you at the
18 beginning of your statement to advise the committee
19 if you do not have any such financial relationships.

20 If you choose not to address this issue
21 of financial relationships at the beginning of your
22 statement, it will not preclude you from speaking.

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1 That being said, is there anyone in the
2 audience who wishes to address the panel on today's
3 topic or any other topic?

4 (No response.)

5 CHAIRMAN LASKEY: Great. Than I'd like
6 to close this portion of the open public hearing and
7 move right into the sponsor's presentation.

8 DR. REISER: Good morning. My name is
9 Chris Reiser, and I'm the Vice President of
10 Technology and Clinical Research at Spectranetics.

11 I'd like to introduce the presenters
12 that will be assisting me this morning.

13 Immediately to my right is Dr. John
14 Laird from the Washington Hospital Center. Dr.
15 Laird was principal investigator for LACI and is a
16 member of the LACI Steering Committee.

17 Just to his left is Dr. Bruce Gray from
18 Greenville Memorial Hospital. Dr. Gray was also on
19 the LACI Steering Committee and a LACI investigator.

20 To his left is Dr. Venkatesh Ramaiah
21 from the Arizona Heart Hospital. Dr. Ramaiah is a
22 staff surgeon there and was the LACI PI at that

1 site.

2 We have prepared several presentations
3 for you this morning. The top four, the ones in
4 yellow, will be the ones that we'll give during our
5 hour's presentation this morning. We prepared
6 several others which are in white, which we'll hold
7 back in case there is a question from the panel and
8 the Chairman would so desire us to show that slides.

9 We reviewed today an application of
10 excimer laser atherectomy. Our device uses a xenon-
11 chloride excimer laser which emits pulses of
12 ultraviolet light at 308 nanometers. These pulses
13 are delivered via fiberoptic catheter which is
14 specifically designed to deliver this
15 intravascularly.

16 It was first approved, this technology,
17 by FDA in 1993 for use in coronary arteries. This
18 technology is similar, but slightly different from
19 LASIK, which you probably heard advertised on the
20 radio.

21 A quick comparison shows that LASIK uses
22 a slightly different ultraviolet wavelength at 193

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1 nanometers. One, ninety-three does not propagate
2 through fibers, and so in a LASIK machine the beam
3 basically propagates through free air inside a work
4 station, which is roughly the size of a small room.
5 One, ninety-three is good for working on corneas.

6 Three, oh, eight, by comparison, does
7 travel down fibers, and hence we can make catheters
8 which deliver 308 nanometers through arteries and
9 veins.

10 Both of these technologies use cool,
11 ultraviolet ablation, which basically shaves away
12 small layers of tissue either on the cornea or in
13 the arteries without burning or charring, like
14 previously used CW lasers.

15 This is a picture of the laser system
16 that was used in LASIK. The generation four CVX-300
17 Excimer Laser System was approved by FDA in 1993,
18 and we've been building and shipping the system for
19 about ten years.

20 The same system is used for all of our
21 applications, coronary atherectomy, and pacing lead
22 removal. That particular application uses a

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1 specialized catheter that still plugs into the same
2 laser.

3 And in Europe we've been shipping this
4 unit for peripheral atherectomy, but not in the
5 United States.

6 A few facts about this unit. It's about
7 the size of a console television set. It weighs 650
8 pounds, has four wheels, and it plugs into the wall
9 in a cath. lab.

10 Really what does the work is the excimer
11 laser catheter. All of our catheters look like this
12 picture here. At the proximal end is a black
13 connector that plugs into the laser. Connecting the
14 proximal end to the distal end are three meters of
15 fiberoptic cable. In this black connector the
16 fiberoptics shown here as a rectangular array of
17 about 250 fibers are arranged so that their shape is
18 the same shape as the beam in our laser, which
19 happens to be rectangular.

20 Those fibers go through the whole
21 catheter. The last 130 centimeters is the patient
22 contact end. Those fibers end in the distal tip.

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1 We put an optical polish on the tip, including the
2 fibers and the metal bands on the inside and the
3 outside of the fiber bundle.

4 These fibers deliver the ultraviolet
5 light directly to the tissue. That light goes into
6 the tissue and penetrates about 50 microns. Now,
7 human hair is about 60 microns. So the penetration
8 depth is about the depth of a human hair. That's
9 the tissue that's affected by the light. That's
10 where the light goes. It doesn't go to the side.
11 It doesn't penetrate deeply like a search light. It
12 basically shaves its way through the lesion that's
13 in contact with the tip.

14 All of our catheters, regardless of
15 whether they're coronary designed or peripheral
16 designed, have these same features and work the same
17 way.

18 How did we get interested in peripheral
19 angioplasty? Well, we looked at our seven
20 indications for the coronary arteries. We noticed
21 that the top three in yellow here are a reasonable
22 description of the disease that we expect to see in

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1 CLI patients, that is, long, diffuse lesions, total
2 occlusions, and moderately calcified lesions.

3 We did investigate our technology in the
4 legs under an FDA approved IDE early in the 1990s.
5 That data is not part of our PMA submission, and so
6 we won't be reviewing it today, but the point here
7 is that we had a reasonable expectation that our
8 technology would work well in the legs based on some
9 data obtained about ten years ago.

10 We also had experience in Europe since
11 we have commercialized this product there for the
12 past six years. FDA advised us that we should try a
13 pivotal trial and bring that data to the regulatory
14 authorities, and that was the purpose of LACI Phase
15 2.

16 At this point I'd like to invite Dr.
17 Laird to the podium to give us a review of the LACI
18 protocol and the LACI results.

19 DR. LAIRD: Well, thank you very much,
20 Chris.

21 It's a real privilege for me to be able
22 to present the LACI Phase 2 registry study to this

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1 distinguished panel.

2 I'd like to disclose up front that I do
3 not have any financial interest in Spectranetics
4 Corporation. I do not own any stock or stock
5 options, although I am paid as a consultant for my
6 time here today.

7 Just as a brief introduction, the
8 patients being treated in the LACI trial are
9 patients with critical limb ischemia, which is
10 basically end stage peripheral arterial occlusive
11 disease, which results in breakdown of the skin with
12 ulcers or gangrene or pain in the foot at rest.

13 In general, in the literature patients
14 with peripheral arterial disease are classified
15 either according to the Fontaine classification or
16 the Rutherford classification. In general, patients
17 with critical limb ischemia have either Fontaine III
18 or IV peripheral arterial disease, and those
19 patients with rest pain or tissue loss are
20 categorized as Category 4 or 6 on the Rutherford
21 classification.

22 Patients with a rest pain are Fontaine

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1 Class III or Rutherford Category 4. Patients with
2 tissue loss are Fontaine Class IV or Rutherford
3 Category 5 or 6.

4 The Rutherford classifications scheme
5 does also tend to try and further differentiate
6 patients to either having minor tissue loss, which
7 is Rutherford Category 5, or major tissue loss,
8 which is Rutherford 6, and in general, Rutherford
9 Category 6 patients are felt the most likely to
10 require amputation.

11 When these patients undergo study, in
12 general they have very diffuse, multi-level disease
13 with frequent calcification, and predominantly they
14 have occlusive disease in either most or all of the
15 tibial peroneal arteries. Only a minority of the
16 patients, in one study approximately 22 percent of
17 patients, present with lesion morphology that would
18 be felt to be suitable for balloon angioplasty.

19 And it wasn't the goal of the LACI to
20 try and test laser angioplasty for patients with
21 lesions that were otherwise suitable for balloon
22 angioplasty, nor was it a trial that was meant to

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1 compare laser angioplasty with the gold standard,
2 which is surgical revascularization for critical
3 limb ischemia.

4 What we were looking at was basically
5 the no option patient, the patient that had diffuse,
6 multi-segment, occlusive disease of the lower
7 extremities which was not favorable for balloon
8 angioplasty, and patients who were felt to be not
9 good surgical candidates.

10 The obvious criticism of this trial is
11 that it's not a randomized trial, and I would like
12 to kind of address this subject right up front. I
13 think it's important whenever you talk about a
14 randomized trial you have to have a reasonable or
15 specific therapy to test in the control group, a
16 therapy that's an accepted therapy for a particular
17 disease state.

18 When we talk about the alternative
19 therapies for patients with critical limb ischemia,
20 we could talk about balloon angioplasty medications,
21 primary amputation, or bypass surgery.

22 In our discussions with the FDA

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1 initially with regards to study design, up front we
2 decided that we were only going to treat patients
3 who were felt to be poor or non-surgical candidates.
4 So that sort of takes surgical bypass out of the
5 randomization scheme.

6 Also, I think the majority of us who
7 take care of patients with peripheral arterial
8 disease would not consider medical therapy or
9 primary amputation as an appropriate alternative
10 therapy for the majority of patients who present
11 with critical limb ischemia.

12 So that leaves us primarily with balloon
13 angioplasty, and the question is whether balloon
14 angioplasty would be an appropriate randomization
15 strategy for these patients.

16 If you look at the published literature
17 for balloon angioplasty for critical ischemia, it's
18 really all over the place. There's wide variability
19 in the published results for balloon angioplasty.
20 When the technique is used in very well selected
21 patients with discrete lesions in the femoral
22 popliteal or tibial vessels, the results can be

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1 quite good with limb salvage rates that have been
2 published in the 70 to 85 percent range.

3 However, when the technique has been
4 more broadly applied to diffuse disease or long
5 occlusions, the results are not nearly as good, and
6 if you look at the studies in general, there's a lot
7 of faults that could be found in these studies.
8 They are all retrospective, single center studies.
9 The follow-up intervals vary widely. The adjunctive
10 use of other treatments are often not completely
11 reported.

12 And if we look at the published
13 literature over the last 15 years, there have been
14 really no trials at all comparing balloon
15 angioplasty in any randomized format with other
16 therapies.

17 In the year 2000, in January in the
18 Journal of Vascular Surgery, the TASC document or
19 the TransAtlantic Inter-Society consensus document
20 for the treatment of peripheral arterial disease was
21 published, and this is a document which provides
22 very strong guidelines for those of us who treat

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1 patients with peripheral arterial disease.

2 And in the TASC document, they basically
3 stated that there's really only one lesion subset
4 that was recommended for balloon angioplasty for
5 patients with critical limb ischemia, and that was
6 the patient who presented with very discrete lesions
7 in the femoral popliteal segment or an
8 infrapopliteal segment.

9 For those patients who present with more
10 complex disease, such as the Type B patient with
11 multiple short stenoses, the Type C patient with
12 long stenoses or short occlusions, or the Type D
13 patient with long tibial occlusions or diffuse
14 disease, angioplasty was either not felt to be
15 recommended based on insufficient data or surgery
16 was the recommended therapy.

17 And we'll discuss this in greater detail
18 if we look at patients included in the LACI trial.
19 Eighty-eight percent of the patients or limbs in
20 this trial had TASC C or TASC D type disease, very
21 complex, diffuse disease with long occlusions. So
22 the type of patients that were felt not to be

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1 suitable for a balloon angioplasty.

2 And, again, if we try and present some
3 of the data from the literature with regards to
4 balloon angioplasty for critical limb ischemia,
5 looking at the last eight years or so, we see
6 several reasonable studies with reasonable follow-up
7 of at least six months in patients with critical
8 limb ischemia, and most of these modern studies
9 include use of balloon angioplasty, stents, a modern
10 anticoagulant and antiplatelet regimens, and in many
11 cases arterial closure devices.

12 This is just a sampling of the
13 literature, and if we would try and compare just in
14 general terms some of these publications with the
15 patient population treated in the LACI trial, in
16 general, these were less complex and less long
17 lesions, fewer lesions treated in patient, and
18 overall in terms of the important endpoints of death
19 and major amputation and re-intervention, I think
20 that the results from the LACI trial compare very
21 favorably with higher death rates and major
22 amputation rates seen in these three studies.

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1 And, again, the study from Danielsson
2 and Dorros published in 2001, again, less complex
3 lesion subsets, similar results with regards to
4 death or major amputation.

5 So to try and summarize the literature
6 for balloon angioplasty, all of the reports are
7 single center, retrospective case series, and we
8 know how that can sort of impact on the results of
9 the data that is presented.

10 Some of these articles report only on
11 initial successes. So those initial technical
12 failures were not included in the final outcomes
13 with regards to limb salvage and complications.

14 So why not randomize this patient
15 population to balloon angioplasty? Well, the
16 disease subsets that we're treating in this study,
17 diffuse disease, multi-segment disease, long
18 occlusions, were not recommended to be treated with
19 balloon angioplasty in the TASC document, and
20 there's really little evidence that angioplasty can
21 be successfully used to treat patients with diffuse
22 disease and critical limb ischemia who were felt to

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1 be surgical candidates.

2 And, clearly, there is no study that has
3 made balloon angioplasty the gold standard for the
4 treatment of patients with critical limb ischemia.

5 So we have basically a situation where
6 there's really no one therapy that's appropriate or
7 standard of care for patients with critical limb
8 ischemia who are not otherwise good surgical
9 candidates, and although certainly not optimal, it
10 is true that those of us who were investigators
11 involved in the design of this trial, we all felt
12 pretty strongly that we could not randomize patients
13 to balloon angioplasty, and that that trial design
14 was unworkable.

15 So we're left with either doing a self-
16 controlled study design or a historical control
17 study design. Well, the main goal of the control
18 group being that we want to demonstrate that we
19 somehow do not alter the natural history of these
20 patients in some negative way, either end up with
21 greater incidence of major amputation because of our
22 interventions or a higher mortality in those

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1 patients who are intervened on with the laser
2 system.

3 The ideal best case historical control
4 would be an exact match in patient characteristics,
5 a large enrolling study, full statistics with
6 excellent follow-up, and a treatment plan that
7 basically defines the standard of care in the
8 community, which in this case would likely be a
9 mixed set of modalities that might include
10 revascularization with surgery, medical therapy, or
11 other supportive care. And that document should
12 conform to the TASC definitions.

13 Luckily, right around the time that we
14 were trying to formulate the appropriate study
15 design for the LACI Phase 2 registry, a study was
16 published that we felt met fairly well our
17 requirements for a good historical control group,
18 and this was the ICAI study, which was an Italian,
19 multi-center, randomized study of Prostaglandin E-1
20 and critical limb ischemia patients.

21 Basically, they randomized over 15
22 patients to Prostaglandin E-1 versus standard

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1 treatment, which in this control group consisted of
2 bypass endarterectomy in approximately 43 percent of
3 patients and then medical therapy, in a few cases
4 balloon angioplasty. And this was felt to be
5 standard or best care possible in the community for
6 which these patients were treated.

7 This study was published in the Annals
8 of Internal Medicine in 1999 and did conform to the
9 TASC definitions in good clinical practice.

10 There are some important differences
11 between this control group and the LACI registry
12 group. The ICAI trial enrolled critical limb
13 ischemia patients regardless of their candidacy for
14 surgery, and ultimately 35 percent of these patients
15 received bypass surgery as their primary treatment
16 option.

17 As previously described, patients were
18 enrolled in the LACI trial only if they were felt to
19 be poor or nonsurgical candidates. So really the
20 ICAI treatment plan was not an alternative for these
21 LACI patients, nor was it a fall-back plan for these
22 LACI patients. The LACI population was really not

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1 eligible for the same treatments, and hence may not
2 have enjoyed the same outcomes as the ICAI patients.

3 The ICAI statistics do represent though
4 the benchmark, and if we believe that the ICAI
5 statistics reflect safe and effective therapy, then
6 a treatment plan with equal statistics must also be
7 safe and effective.

8 We did set, I think, a very high bar for
9 comparison. If you look at the data from the ICAI
10 trial, the mortality rates in this trial were lower
11 than or at expected levels compared to the published
12 literature for critical limb ischemia, and it was a
13 very low frequency of major amputation in this
14 group, lower than one would have expected based on
15 historical literature controls.

16 So we chose, I think, a very high bar to
17 compare against when looking at the data from the
18 LACI registry. The control statistics are
19 benchmarks, not a true measure of alternatives
20 available to the LACI population.

21 With that background, I'd like to
22 present the LACI trial and the results from this

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1 trial. I think it is worthy of mentioning that this
2 is the very first study of its kind, a prospective,
3 multi-center study evaluating a device for the
4 treatment of the endovascular treatment of patients
5 with critical limb ischemia.

6 As we previously mentioned, all of the
7 previous studies using angioplasty are
8 retrospective, single center experiences. We were
9 treating patients with critical limb ischemia,
10 Rutherford Category 4 to 6 who were felt to be poor
11 or nonsurgical candidates. We were treating lesions
12 in the SFA, popliteal, and/or infrapopliteal
13 arteries with adjunctive balloon angioplasty and
14 optional stenting.

15 The primary endpoint of the trial was
16 limb salvage at six months and basically freedom
17 from major amputation at or above the level of the
18 ankle.

19 The primary safety endpoint was death at
20 six months.

21 Patients were treated with a 2.2 or 2.5
22 millimeter Spectranetics peripheral laser catheter

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1 or any of the available coronary laser catheters.

2 They were poor surgical candidates
3 because of any of the following reasons: either
4 poor or absent vessel for an outflow anastomosis,
5 basically very diffuse and distal vascular disease,
6 so not good candidates for a distal bypass
7 operation, or the absence of any venous conduit for
8 bypass, or significant cardiac or medical co-
9 morbidity that would place them at high risk for
10 surgical mortality or complications, basically ASA
11 Class 4 or higher.

12 The enrollment period was from April of
13 2001 to April of 2002, and we ultimately enrolled
14 155 limbs and 145 patients.

15 These were the enrolling sites in the
16 trial. This was a multi-national, multi-center
17 study. There were three sites from Germany, two of
18 which contributed significantly to the enrollment in
19 this trial. Thirty-six percent of the site enrolled
20 68 percent of the patients in the study.

21 These are the patient descriptors. It
22 has been said that there were no demonstrable

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1 differences in terms of morbidity or preoperative
2 morbidity in the LACI trial, and one of the FDA
3 reviewers focused on the fact that there was a
4 higher incidence of smoking in the control group.

5 But I think if you look very carefully
6 at the patient demographics, there were very
7 significant differences in terms of patient
8 morbidities in the LACI group. Almost half of the
9 patients in the LACI trial were women, compared to
10 28 percent in the control group, and I think we're
11 all aware of the poor outcomes for women who have
12 critical limb ischemia and undergo revascularization
13 therapies.

14 There was a higher incidents of
15 myocardial infarction and stroke in the LACI
16 population, higher instance of hypertension,
17 hyperlipidemia, and obesity. And I'll focus here on
18 the fact that 66 percent of the patients in the LACI
19 group had diabetes compared to only 39 percent in
20 the control group.

21 I think we're all very aware of the
22 worst outcomes in patients with diabetes mellitus

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1 with regard to limb salvage and outcomes following
2 endovascular or surgical revascularization.

3 Twenty-seven percent of the LACI
4 patients and 30 percent of the control group had
5 ischemic rest pain at the time of presentation.
6 Seventy-two percent of the LACI patients and 70
7 percent of the control patients had tissue loss at
8 the time of the presentation.

9 It is worthy of mention that seven
10 percent of the patients in the LACI registry had
11 Rutherford Category 6 limb ischemia at the time of
12 presentation, basically major tissue loss at the
13 time of presentation.

14 We cannot from the ICAI study determine
15 how many of those patients had major tissue loss at
16 the time of presentation because they were
17 classified according to the Fontaine classification.

18 Of course, all of the patients had at
19 least one reason for being a poor candidate for
20 surgical revascularization in the LACI study by
21 definition. But actually one-third of the patients
22 had at least two reasons for not being a good

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1 surgical candidate, and six percent of these
2 patients had all three reasons for not being a good
3 surgical candidate for revascularization.

4 I'd like to present a couple of
5 representative case examples from the study. This
6 is a 61 year old Hispanic woman with diabetes for
7 greater than 20 years who had end stage renal
8 disease and had been on hemodialysis for one year.
9 This is really the most difficult of all patient
10 populations for us to treat, the longstanding
11 diabetic with renal failure on dialysis.

12 And she presented with multiple ischemic
13 ulcers on both feet to the Arizona Heart Institute,
14 where she underwent excimer laser assisted
15 angioplasty on the 14th of August 2001. This was
16 her two feet at the time of presentation. She had a
17 very large ulcer on the planer aspect of her right
18 foot, as well as a second ischemic ulcer on the
19 heel.

20 The left foot, again, had multiple
21 ischemic ulcers, including a very large ulcer on the
22 left heel.

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1 After a successful revascularization
2 procedure at three months, the ulcer on the right
3 heel had resolved completely. There was significant
4 improvement in the foot ulcer on the right and
5 significant improvement in the foot ulcers on the
6 left, and at six months complete healing of all of
7 the ulcers on both feet.

8 And I think this is a testimony
9 certainly to a very good revascularization, but also
10 to very good wound care.

11 This is a patient from our institution
12 who is a 45 year old female with longstanding
13 diabetes and morbid obesity. She weighed about 350
14 pounds, and my surgeons actually begged me to treat
15 this patient so that they wouldn't have to operate
16 on her. She had distal popliteal and tibial
17 occlusive disease with a painful ischemic second toe
18 on the left foot.

19 After a successful revascularization
20 procedure, she had near complete healing of the toe
21 at three months, complete healing of the toe at six
22 months to the point where she was now able to put

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1 toenail polish back on her toes.

2 As part of the LACI trial, we
3 photographed patients at baseline and follow-up and
4 performed digital morphometry to measure the area of
5 the ischemic ulcers, and we have really collected an
6 incredible library of photographs from before and
7 after treatment, and I think these photographs
8 really tell a very compelling story.

9 This is another example from the trial
10 of a patient with an ischemic ulcer in the lower
11 leg. This ulcer had been present for over six
12 months and was not healing nor responding to
13 standard therapy.

14 After a successful revascularization,
15 near complete healing at three months, complete
16 healing at six months.

17 This is another example of a very
18 challenging patient, a patient with a large ischemic
19 ulcer on the heel. After successful
20 revascularization, significant improvement at three
21 months and continued improvement at six months,
22 although this ulcer is not completely healed at six

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1 months. And this patient would be considered to
2 have persistent critical limb ischemia in the trial,
3 although clearly has had significant improvement
4 after revascularization therapy.

5 Not all patients can avoid minor
6 amputation. This was a patient with severe gangrene
7 of the second toe and a deep and severe ulcer on the
8 forefoot. After a successful revascularization
9 procedure, this patient underwent a transmetacarpel
10 amputation with successful healing of that surgical
11 incision at six months and avoidance of a higher
12 level of amputation, either below knee or above knee
13 amputation.

14 In the LACI study, just over 40 percent
15 of the lesions that were treated were in the
16 superficial femoral artery. Over half of the
17 lesions were either in the popliteal artery or in
18 the infrapopliteal vessels.

19 We treated a mean of 2.7 lesions per
20 patient. The mean length of each lesion was 6.1
21 sonometers. So we treated overall lesion length of
22 around 16.4 sonometers in each of the limbs of these

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1 patients. So these are very long, complex lesions.

2 The majority, over 70 percent of the
3 lesions treated or of the patients treated had a
4 combination of stenoses and occlusions.

5 As previously shown, 88 percent of the
6 lesions treated in the study would have been
7 classified as either TASC C or TASC D or subsets.

8 The lesions could be successfully
9 crossed with a guidewire in 92 percent of cases.
10 There were some cases where the lesion could not be
11 crossed by the guidewire, and the laser catheter was
12 used in step-by-step manner to facilitate crossing
13 of these refractory occlusions.

14 Adjunctive balloon angioplasty was
15 performed in 96 percent of cases and stent
16 implantation was performed in 45 percent of cases.

17 Procedure of success is defined as a
18 residual percent diameter stenosis, and less than 50
19 percent of all of the lesions treated in a given
20 limb was 85 percent. And straight line flow to the
21 foot was established in 89 percent of cases.

22 The median hospital stay was only one

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1 day. There were a few patients who had very long
2 hospital stays. So the overall mean hospital stay
3 in the study was three days.

4 Half of the improvement in luminal gain
5 that was seen following intervention was a result of
6 the excimer laser angioplasty. Final percent
7 diameter stenosis following all interventions ranged
8 from 16 to 24 percent. In general, in the
9 infrapopliteal arteries, the final percent diameter
10 stenosis was slightly higher.

11 Stenting was performed preferentially in
12 larger vessels.

13 Again, I'll show a few representative
14 angiograms from the study. This is the normal
15 infrapopliteal anatomy, anterior tibial artery,
16 tibial peroneal trunk, peroneal, and posterior
17 tibial artery.

18 This is a typical patient from the LACI
19 trial basically demonstrating occlusion of all of
20 the tibial peroneal arteries without any visible
21 distal vessels for bypass grafting, at least in this
22 image.

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1 This is after the laser catheter. A
2 channel is reestablished in the anterior tibial
3 artery. Adjunctive balloon dilatations were
4 performed in this vessel in multiple locations, with
5 an excellent angiographic result, with wide patency
6 now established in that anterior tibial artery.

7 Another LACI type case, again, very
8 diffuse disease below knee with occlusion of all
9 three of the tibial arteries, some faint
10 reconstitution of a diffusely diseased peroneal
11 artery distally. After laser assisted
12 recannulization and adjunctive balloon dilatation,
13 now straight line flow is established through this
14 patent peroneal vessel.

15 A little bit simpler anatomy, but again
16 difficult lesions to treat with just balloon
17 angioplasty alone. Occlusion of the popliteal
18 artery and sub total occlusion of the tibial
19 peroneal trunk, post laser and nice channel is
20 established in both of these lesions, and then
21 following adjunctive balloon dilatation without the
22 use of stents, an excellent angiographic result at

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1 the popliteal artery and in the tibial peroneal
2 trunk.

3 Again, another sort of representative
4 case to give you an idea of the severity of disease
5 treated in this trial for patients who have
6 significant orthopedic work done. Occlusion of the
7 distal popliteal artery with diffuse disease and
8 occlusion of all of the proximal tibial arteries
9 with faint reconstitution of the small peroneal
10 artery, again, the kind of case that would be
11 difficult for surgical revascularization.

12 After use of the laser catheter, a nice
13 channel is established with now patency into the
14 peroneal artery through this occluded popliteal
15 segment. Then after balloon angioplasty alone an
16 excellent angiographic result with good flow and
17 wide patency of the peroneal artery.

18 And I think this is an example of a case
19 where potentially with the use of laser
20 recannulization, we can now demonstrate actually a
21 very good distal target vessel which could
22 potentially be used for surgical revascularization

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1 in the future if the patient did not heal his
2 ischemic ulcers.

3 Many patients were treated in the trial
4 with long occlusions and the superficial femoral
5 artery. This is an example of a patient with total
6 occlusion almost over the entire length of the right
7 SFA, with reconstitution of the distal SFA adduct or
8 canal.

9 After passage of the laser catheter, we
10 see a nice channel now through the superficial
11 femoral artery with really a channel that is
12 actually larger than the diameter of the laser
13 catheter that was used, and I think this reflects
14 the ability of the laser to vaporize some of the
15 relatively acute or more chronic thrombus that's
16 present in some of these SFA occlusions.

17 After only adjunctive balloon
18 dilatation, no stents, an excellent angiographic
19 result is achieved.

20 As I previously mentioned in the control
21 group of the ICAI study, 35 percent of these
22 patients ultimately underwent bypass surgery or

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1 endarterectomy. Five percent received angioplasty,
2 and three percent underwent a thrombectomy
3 procedure.

4 Fifty-seven percent of these patients
5 underwent supportive care with analgesics,
6 vasoactive therapies, and antithrombotic therapies.
7 Some of them received hypobaric oxygen.

8 If we compare the groups with regards to
9 serious adverse events, there's overall no
10 difference between the two groups with regards to
11 SAEs, no difference in terms of mortality; no
12 difference in terms of major amputation or nonfatal
13 MI or stroke.

14 There is a higher re-intervention rate,
15 17 percent in the LACI group compared to four
16 percent in the control group, although it is
17 important that this four percent reflects the entire
18 group as a whole, and if you look at those patients,
19 the 43 percent of patients who underwent some
20 surgical or angioplasty treatment, they had a re-
21 intervention rate of 11 percent.

22 I think if you consider the lesions that

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1 were being treated, 2.7 lesions per patient with an
2 overall lesion length of 16 sonometers, a re-
3 intervention rate of 17 percent I don't think is
4 unacceptable. In fact, I think it's actually quite
5 good and would compare very favorably with any
6 historical angioplasty study.

7 I think if you think of some of the
8 alternative therapies, such as surgical bypass, this
9 also compares very favorably. Multiple series in
10 the literature, and some of these are included in
11 your packet, show that within six months of the
12 surgical bypass the re-intervention rate may be as
13 high as ten to 20 percent, and I see these patient
14 all the time who come in with intimal hyperplastic
15 lesions at the proximal or distal anastomoses,
16 retained valves in the graft, or actual acute graft
17 thrombosis.

18 Also, if you look at primary amputation
19 as a mode of therapy, 19 percent of patients who
20 undergo primary amputation for critical limb
21 ischemia will require some revision of that
22 amputation to a higher level within 30 days of that

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1 initial amputation.

2 In this LACI registry, the incidence of
3 acute limb ischemia or the need for bypass surgery
4 endarterectomy was strikingly low during the follow-
5 up time period.

6 With regards to the primary endpoint of
7 limb salvage, we can analyze the data in several
8 ways. If we analyze it on a per patient basis, we
9 enrolled 145 patients in this trial. Fifteen
10 patients died during the follow-up period.

11 It is important to note that only two of
12 those patients had a major amputation before they
13 died, and as we all know, a lot of these patients
14 end up dying because of the cardiovascular
15 complications of their severe and diffuse
16 atherosclerosis.

17 Eleven patients were lost to follow-up,
18 leaving us with 119 patients who reached their six-
19 month endpoint. Major amputation was required in
20 nine of the surviving patients, giving us 110
21 patients who survived with limb salvage.

22 If we look at the limb salvage rates on

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1 an intent to treat analysis, which is basically the
2 worst case scenario where we're considering all of
3 our deaths and all of our loss to follow-up patients
4 as a treatment failure and a limb loss, our limb
5 salvage rate is 76 percent, and that is a number
6 that you'll see presented by the FDA in their
7 discussions today.

8 But I think if we look at the more
9 meaningful statistic, which is basically what is our
10 limb salvage rate in our surviving patients, it is a
11 strikingly high 92 percent, which compares very
12 favorably with any study published in the
13 literature.

14 If we analyze the patients on the basis
15 of or the study on the patients that had limbs
16 treated, this would include 155 limbs, seven deaths,
17 11 lost to follow-up, nine major amputations.
18 Again, limb salvage on an intent to treat analysis,
19 76 percent; on a survival analysis, 93 percent.

20 Then when we compare the LACI group with
21 the control group with regards to our main endpoints
22 at six months, there was no difference with regards

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1 to death, no difference with regards to limb
2 salvage, no difference with regards to persistent
3 critical limb ischemia, and no difference with
4 regards to serious adverse events.

5 So at the very least, we did not alter
6 the natural history of these patients in a negative
7 way, increasing the mortality or the risk for major
8 amputation.

9 As mentioned, we performed digital
10 morphometry from the photographs that were performed
11 on these patients at baseline and during follow-up,
12 and we saw a decrease in the area of the ischemic
13 ulcers over the course of the study with 50 percent
14 completed healed at six months. Seventy-three
15 percent of these ulcers were healed or improved at
16 six months, and only 13 percent were noted to be
17 larger or had new ulcers at the follow-up time
18 period.

19 And if we look at overall functional
20 outcomes in this slide presented as the category at
21 baseline versus the category at six months, where
22 all of the patients are in green, reflect patients

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1 who are improved, and those in yellow reflect
2 patients who are in the stable condition, and those
3 in red reflect patients who have gotten worse during
4 the follow-up time period, we see a great majority
5 of patients who are improved and are in a non-
6 critical limb ischemia category at the six-month
7 follow-up period, and only a small percentage of
8 patients have had progression of their critical limb
9 ischemia and worsening of their ischemic ulceration.

10 There's only one major or only one
11 predictor of major amputation in the trial, and
12 that's not surprising a Category 6 Rutherford
13 classification or major tissue loss at the time of
14 presentation, and only one predictor of death. That
15 was advanced age at the time of presentation.

16 One of the confounding variables
17 obviously in this study is what was the impact of
18 stenting in the study, and we certainly would have
19 liked to have not had any stents implanted in the
20 study if at all possible. But in the modern era
21 it's just impossible to keep investigators from
22 placing stents for full vessels.

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1 It did appear that those vessels that
2 were stented had a higher procedural success
3 compared to non-stented vessels and a greater
4 incidence of straight line flow compared to non-
5 stented vessels. But there was no statistical
6 difference, statistically significant difference
7 with regards to limb salvage in those vessels that
8 were stented compared to those that were non-
9 stented.

10 And the same size is small enough that
11 it does make, you know, definitive analysis of this
12 data difficult.

13 So in conclusion, we were treating a
14 very complex patient population, patients with
15 multiple lesions, often long occlusions, diffuse
16 disease, who were felt to be poor surgical
17 candidates because of the diffuseness of their
18 disease, their significant co-morbidities, with the
19 lack of venous conduit for a bypass surgery. So we
20 were taking basically the worst of the worst,
21 patients with critical limb ischemia who had the
22 worst of all possible disease.

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1 Despite that, we had very high
2 procedural success rates with few in-hospital
3 serious adverse events and short hospital stays, and
4 an excellent limb salvage rate despite treating a
5 very high risk patient cohort.

6 The outcomes in this study met all of
7 the hypotheses in the protocol, and the statistics
8 met the benchmarks of safety and effectiveness.

9 So if we're going to try and define the
10 clinical benefit of this strategy of laser assisted
11 angioplasty, I think we can say that this strategy
12 did save limbs in the study with an efficacy
13 endpoint that equaled the controlled benchmark
14 without affecting the patient's chances of survival
15 or significantly increasing these patients' risk of
16 serious adverse events.

17 And as an endovascular approach to the
18 treatment of vascular surgery, it avoids the
19 perioperative risks and morbidity associated with
20 surgery. It shortens the initial hospital stay and
21 quickens the return to normal function, and it does
22 not jeopardize any further surgical options for

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1 these patients.

2 And as we demonstrated in that one case,
3 it may, in fact, create surgical options for these
4 patients by opening up occluded tibial arteries and
5 demonstrating an adequate distal vessel for possible
6 future surgical revascularization.

7 The results in the LACI Phase 2 trial
8 were achieved really with virtually no surgery.
9 Less than three percent of these patients went on to
10 have either bypass or endarterectomy during the six-
11 month follow-up time period.

12 As we've seen, the LACI strategy is
13 applicable to a wide range of vascular disease
14 states. We basically were taking on all comers with
15 the worst of all possible disease, with lesions that
16 would generally not have been considered amenable to
17 just balloon angioplasty alone.

18 And I think this is a strategy that is
19 useful for patients as a last ditch or last option
20 prior to major amputation.

21 The results were predictable with very
22 high procedural success, and I think remarkably low

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1 serious adverse events.

2 And with that I'll conclude my
3 presentation. Thank you for your attention.

4 CHAIRMAN LASKEY: Thank you. That was
5 excellent.

6 Although I'll remind the panel that
7 everyone will have their opportunity to provide
8 comments and insights later on, are there any panel
9 members who have any questions for the sponsor
10 and/or Dr. Laird at the moment?

11 Mitch, yeah.

12 DR. KRUCOFF: John, just one quick
13 question. You guys have a reasonable number of
14 patients who were sort of roll-in or learning curve.
15 Could you tell us a little bit about your experience
16 or share any data you have on what the learning
17 curve in applying this technology in these patients
18 looked like compared to the --

19 DR. LAIRD: That's a very good question.
20 I think it is important to recognize that around the
21 time of this study initiation there were not that
22 many operators in the United States who had

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1 experience with laser angioplasty in the periphery.
2 In fact, there were only a few places where this was
3 being done.

4 And as part of the both this trial and
5 another trial, there was a roll-in period where
6 patients were treated, some with LACI type anatomy,
7 some with less complex disease, and there was a LACI
8 Phase 1 trial which included roughly around 20, 25
9 patients who were treated with critical limb
10 ischemia with somewhat different enrollment
11 criteria. It did not include patients with critical
12 limb ischemia.

13 And overall -- I don't have the data,
14 and I can't present it to you -- but overall, the
15 results were favorable in that study. And I think a
16 lot of these very good results were achieved despite
17 the fact that there wasn't a long historical
18 experience with laser in the centers that were
19 included in the trials, reflecting, I think, a
20 relatively short learning curve for the use of this
21 device.

22 CHAIRMAN LASKEY: In that regard, you

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1 had the two German centers which were preponderant
2 in enrolling. Did they just have a longer track
3 record? Is that why? What was --

4 DR. LAIRD: Well, I think one of the
5 sort of pioneers in the use of excimer laser
6 angioplasty for peripheral arterial disease is
7 Giancarlo Biamino, and his site was one of the sites
8 that was included in this trial.

9 The referral mechanisms in Germany, I
10 think, are a little bit different. The patients,
11 you know, tend to get referred to the larger
12 centers, and so they really had a remarkable, you
13 know, referral base from around Germany where they
14 were getting patients from all over the country,
15 difficult patients with critical limb ischemia. So
16 they tended to have more patients than a lot of the
17 sites in the United States to be included in the
18 trial.

19 CHAIRMAN LASKEY: Yes, Dr. Somberg.

20 DR. SOMBERG: This type of therapy is
21 highly specialized and is not, as you point out, an
22 alternative in terms of something that could be just

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1 whipped in as an alternative to. So what would
2 happen either prior in your center or concomitantly
3 in other centers to these type of patients? You
4 didn't really draw that out.

5 You said they were not candidates for
6 balloon angioplasty. At this point would they have
7 all gone to amputation?

8 DR. LAIRD: I think a significant
9 percentage of them would have gone to amputation.
10 It's possible that some of these patients may have
11 been referred for surgery and undergone a distal
12 bypass with synthetic graft, and I think we're all,
13 I think, aware of the generally poor results when
14 synthetic grafts are used for long bypasses in the
15 popliteal arteries.

16 Some of these patients may have
17 undergone balloon angioplasty, but I think our
18 expectation from the literature trying to treat
19 patients such as this with balloon angioplasty, the
20 results would not have been very good, and some of
21 them would have undergone the other sort of
22 modalities that are tried, such hyperbaric oxygen,

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1 some of the newer drugs for ischemic ulcers, things
2 like that.

3 CHAIRMAN LASKEY: Dr. Aziz.

4 DR. AZIZ: John, I see that in your
5 presentation there were no perforations. I think
6 there were zero. Are you aware of in any other
7 centers, maybe even outside this trial, there was a
8 perforation of the vessel?

9 DR. LAIRD: I thought actually there
10 were a couple of perforations in the study. I don't
11 know if I have reflected on the slide, but there
12 were no serious adverse outcomes related to
13 perforation.

14 In a related experience, we've done the
15 PELA trial for long occlusions. We did see
16 perforations in roughly eight percent of cases, none
17 of which really had any significant sequelae because
18 we're often in the middle of a long occlusion when
19 this occurs. So the patients don't bleed, and it's
20 a self-sealing perforation.

21 I think it's worthy of mention that the
22 incidence of distal embolization in this trial, I

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1 think, was also remarkably low. It's three percent,
2 and when you're talking about treating long
3 occlusions with a total lesion length of 16
4 sonometers in these limbs, that rate of embolization
5 is very, very good.

6 CHAIRMAN LASKEY: Yes, sir. Dr.
7 Nicholas.

8 DR. NICHOLAS: A question regarding the
9 definition of "inadequate venous conduit." Were
10 these patients looked at with duplex for upper
11 extremity, lesser saphenous, contralateral vein?

12 DR. LAIRD: We really don't have the
13 full data on that as to whether upper extremities
14 were looked at in terms of inadequate upper
15 extremity conduit. I think that sort of practice is
16 very much, you know, center dependent. I think
17 there are centers who specialize in using veins from
18 the upper extremity and can do good work with that,
19 but not all centers.

20 And so it was pretty much left up to the
21 individual sites to make the determination of
22 whether, quote, unquote, adequate venous conduit was

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1 present.

2 All of these patients had no saphenous
3 vein for bypass.

4 DR. NICHOLAS: While I'm asking, one
5 other question. In ASA Class 4 patients, how many
6 had that as the sole exclusion? Because we do a
7 fair number of those.

8 DR. LAIRD: Forty-six percent of
9 patients were in ASA Class 4 or greater. Now, some
10 of those patients may also have had another reason,
11 either lack of vein or poor distal targets, too. I
12 don't know that we know for sure just the pure ASA-
13 4.

14 Chris?

15 But at least 46 percent of them had that
16 as one of their criteria for being in the trial.

17 CHAIRMAN LASKEY: Well, I'll be the bad
18 guy here. You glossed over the statistics, although
19 I'm sure that will get dredged up again this
20 afternoon. Could you just tell us why a delta of
21 ten was felt to make everybody happy with this?

22 DR. LAIRD: I think I'm going to punt

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1 that one to Chris.

2 DR. REISER: When we designed the trial,
3 it was anticipated that the basic population would
4 exhibit significantly more co-morbidities than the
5 ICAI control population. As Dr. Laird presented, we
6 believe that turns out to be true. That was the
7 rationale that the Steering Committee gave me for
8 the delta of ten.

9 As Dr. Laird points out though, we
10 didn't see in the LACI results that the results were
11 inferior to the control population. So we didn't
12 invoke the delta of ten when we inferred that the
13 results were equivalent.

14 CHAIRMAN LASKEY: Let's make it short
15 because you'll have another opportunity.

16 DR. NORMAND: Okay. I'll just ask a
17 very straightforward question, I think.

18 Had the two populations been randomized
19 or really comparable, what would the delta have
20 been?

21 DR. REISER: I don't think we ever had
22 that conversation.

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1 DR. NORMAND: Well, I'm just asking now.
2 I'm trying to understand the choice of a delta, and
3 part of helping me understanding the choice of that
4 delta, I guess I would wonder had I -- I don't want
5 to say "done it right" -- but had I been able to
6 randomize or had really truly comparable patients, I
7 guess that's the way I would think of the delta.

8 And if you haven't thought about that,
9 that's okay, but in terms of me trying to understand
10 that, that would be a useful number.

11 CHAIRMAN LASKEY: I'm sorry. Are you
12 thinking about a response or just --

13 DR. REISER: No, we haven't had that
14 conversation. So I really don't have a good
15 response for that.

16 CHAIRMAN LASKEY: Okay. Dr. Ferguson.

17 DR. FERGUSON: I was going to ask this
18 later, but it seems appropriate now.

19 It was a very nice presentation. I'm
20 curious as to why you were not able to get the raw
21 data from the Italian study because there's several
22 points that come up during the course of what I've

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1 read and what you've said that would make it at
2 least better had you known what the raw data were,
3 and just curiosity.

4 DR. REISER: Frankly, it's fairly rare
5 in my experience that a study coordinator actually
6 gives away the raw data. It has been my experience
7 that you can buy an analysis of data. It depends on
8 how much you would like to pay, but I as a sponsor
9 have never received raw data from any other sponsor
10 coordinator.

11 DR. FERGUSON: I thought we were all
12 scientists. I don't understand that.

13 DR. LAIRD: Well, that was an industry
14 sponsored trial, and they may not have been so
15 forthcoming for that reason.

16 DR. FERGUSON: I would just comment. I
17 think you're limited to have to go to a journal to
18 gather your data.

19 DR. LAIRD: Agreed.

20 CHAIRMAN LASKEY: Great. We are moving
21 right along nicely. If it's okay with the
22 transcriptionist, can we just move to the next

1 portion without the break? We'll take the break
2 after the FDA presentation. Is that okay?

3 Great. Thank you. Thank you,
4 gentlemen.

5 And I'd like to invite the FDA.

6 (Pause in proceedings.)

7 CHAIRMAN LASKEY: We could have taken a
8 bathroom break at this point, eh?

9 Your clock.

10 (Laughter.)

11 DR. HOLDEN: I'm not sure where we got
12 this computer, but it's a great ad for Windows XP, I
13 suppose, that probably loads faster.

14 CHAIRMAN LASKEY: I've been suggesting
15 McIntosh for years up here, but I don't --

16 (Laughter.)

17 DR. HOLDEN: Finally. Good morning.
18 This presentation will include a brief summary of
19 FDA's review of the preclinical, clinical, and
20 statistical data for Spectranetics' PMA supplement
21 application.

22 Well, good. Apparently we have to

1 reboot this and go through this procedure again.

2 Maybe a --

3 CHAIRMAN LASKEY: I'm reluctant. If we
4 do a break, we may lose some. We're three minutes
5 on a reboot, right? It shouldn't be --

6 DR. HOLDEN: I suppose. I didn't --

7 CHAIRMAN LASKEY: Well, if nature calls,
8 nature calls. Let's see if we can keep right on
9 schedule or before schedule.

10 DR. HOLDEN: One suggestion. Perhaps
11 while this is happening we could begin the
12 presentation if you all have handouts of our slides
13 while this is happening.

14 CHAIRMAN LASKEY: That's fine up here.

15 DR. HOLDEN: Mine in particular are all
16 -- let me get a copy. So while this is happening,
17 I'll speak to slide one, meaning top right.

18 Again, the presentation will include a
19 summary of our reviews of the data for
20 Spectranetics' PMA supplement application for its
21 excimer laser system to treat critical limb
22 ischemia.

1 On the next slide my name is Dr. John
2 Holden. I'm an engineer and a review scientist in
3 the Division of Cardiovascular Devices, and I'll
4 begin with just an introduction and a very brief
5 description of the preclinical evaluation.

6 And as an overview, I'll describe the
7 FDA review team, a brief history of the clinical
8 trial, and the PMA supplement application, and then
9 FDA comments on the various evaluations, in
10 particular, the clinical and statistical reviews,
11 and we'll conclude with just a few key points from
12 the clinical and statistical summaries.

13 The next slide in the lower left shows
14 the FDA review team for this PMA supplement. Dr.
15 Sapirstein will provide FDA's clinical comments, and
16 Dr. Krasnicka will give the FDA's statistical
17 summary.

18 And you should note that there were
19 quite a number of other FDA reviewers who were
20 involved in the review of the IDE application and of
21 earlier supplements to this PMA application.

22 The currently proposed indications for

1 use are as follows, as shown on the slide in the
2 lower right: for facilitating limb salvage in
3 patients with critical limb ischemia associated with
4 Rutherford Categories 4, 5, and 6 who have
5 angiographically evident culprit stenoses and/or
6 occlusions in the SFA, popliteal and/or
7 infrapopliteal arteries, who are poor surgical
8 candidates and who are acceptable candidates for
9 revascularization.

10 The next slide at the top of the second
11 page of our presentation. The device, again, is the
12 CVX-300 Excimer Laser System, plus 15 models of
13 Spectranetics' excimer laser atherectomy catheters.
14 Three types of these ELA catheters have been
15 evaluated in the LACI trial, over the wire, graft
16 exchange, and eccentric models.

17 All of these models, as the sponsor
18 described, include a proximal end that couples
19 exclusively with this CVX-300 Excimer Laser, and
20 then that system is controlled by software that
21 instructs the laser to deliver the correct energy
22 for each particular catheter model.

1 Ten of the catheter models have been
2 previously approved for use in coronary arteries.
3 Five of them are new catheter models that are
4 specific to this use in peripheral arteries to treat
5 critical limb ischemia.

6 And if I might take just a break to
7 catch up.

8 Okay. The applicant refers to its IDE
9 study as the LACI trial. It was conditionally
10 approved; Phase 1 was conditionally approved in
11 December in 1998 as a feasibility study with 25
12 patients, and that study was completed using the
13 device to treat 25 limbs from 23 patients.

14 An expansion of the study was
15 conditionally approved in January 2001. This
16 pivotal trial was proposed by Spectranetics who was
17 a single arm registry to treat 167 patients. Thirty
18 of these were reserved for training, although not
19 all of those were used.

20 As described by the sponsor, the trial
21 used as an historical control the control group from
22 a publication by the ICAI group in Italy. That

1 publication is listed in the middle of this slide.

2 The primary effectiveness endpoint was
3 freedom from amputation at or above the ankle at six
4 months, and the primary safety endpoint was death
5 within six months of the laser procedure.

6 FDA's conditional approval letter for
7 the pivotal trial included several comments and
8 recommendations to the sponsor as noted here on this
9 slide. The trial began that a risk-benefit analysis
10 would be needed for the PMA application and should
11 include an analysis of all device and procedure
12 related adverse events.

13 We suggested that this analysis also
14 quantify the purported benefits of the device, for
15 example, reducing stent use and/or the creation of
16 surgical options.

17 And we indicated that it would be
18 necessary to show that stenting, which was to be
19 discouraged in the trial, did not confound the
20 analysis of the study endpoints.

21 In February of 2002, three models of the
22 Extreme II catheters were added to the trial. Also,

1 the lacing parameters for these catheters were
2 changed from a cycle of five seconds on, ten seconds
3 off to ten seconds on, five seconds off.

4 The laser catheter usage in the trial is
5 indicated on this slide. There were a total of 203
6 laser catheters used. Note that four of the
7 catheter models were used only once in the trial.

8 This led to a PMA supplement application
9 that was submitted in January of this year with the
10 clinical data from the LACI II study. Since that
11 time we've had a highly interactive review process,
12 including a face-to-face meeting with the sponsor to
13 discuss FDA's questions related to the risk
14 analysis, the safety and effectiveness results, and
15 certain aspects of the clinical protocol, the device
16 software, and the instructions for use.

17 And this interaction has led to today's
18 consideration for the Advisory Panel's comments and
19 recommendations.

20 The peripheral catheters underwent a
21 variety of preclinical testing, including tissue
22 ablation and tip integrity testing, artery model and

1 collateral tissue testing, some software validation,
2 biocompatibility, and qualification of the
3 sterilization process.

4 And at this time there are no additional
5 questions from the FDA about this preclinical
6 testing. So at this time I'd like to introduce Dr.
7 Wolf Sapirstein, who will provide FDA's clinical
8 review summary.

9 DR. SAPIRSTEIN: Good morning. In the
10 spirit of full disclosure or possible conflict, I
11 must say that I am a cardiovascular surgeon by
12 background, but I count many interventional
13 radiologists and cardiologists amongst my friends.

14 (Laughter.)

15 PARTICIPANT: Is that a waiver?

16 (Laughter.)

17 DR. SAPIRSTEIN: Okay. The sponsor has
18 described in very great detail the laser trial that
19 was undertaken to assess the use of laser energy for
20 ablation of vascular obstructions in patients
21 suffering from critical limb ischemia in end stage
22 arteriosclerotic disease. The patients were felt to

1 be poor candidates for surgical revascularization.
2 As such, they presented a desperate situation such
3 that primary amputation can be a management option.

4 The LACI study single arm design with a
5 historical control was thought to be ethically
6 necessary where a randomized controlled trial was
7 ruled out for lack of clinical equipoise.

8 This has resulted in an outcome open to
9 conflicting interpretation which does not, however,
10 detract from the excellent conduct and monitoring of
11 the study by the sponsor and the investigators.

12 Critical limb ischemia was determined by
13 patients enrolled in the study in Rutherford Classes
14 4, 5, and 6, which were comparable to the Fontaine
15 Stages III and IV used in the ICAI study. Raw data
16 from the non-treatment control arm of ICAI that was
17 selected for the historical control of LACI is not
18 accessible. This is a common problem when using
19 historical controls generally, but is particularly
20 troublesome in denying robust comparison of many
21 important secondary endpoints for evaluating
22 treatment of critical limb ischemia.

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1 The sponsor justifies this design
2 because LACI patients are perceived as not suitable
3 candidates for surgical intervention. However, an
4 extensive literature review suggests that these
5 patients can be very effectively managed with a
6 variety of alternative treatments. This is
7 especially evident for patients available to an
8 endovascular procedure, particularly when an
9 infragenicular vessel is present, which is a LACI
10 entrance criterion.

11 And international consortium of experts
12 in management of peripheral arterial disease, the
13 TASC group, has published evidence based
14 recommendations for a study on management of this
15 condition. Critical issues are listed for
16 situations where such evidence is as yet not
17 defined.

18 This is the case, for example, for the
19 treatment of lesions described as Type B and C.
20 TASC recommendations has become an accepted standard
21 for treatment of peripheral vascular disease and
22 study of peripheral arterial disease to which both

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1 ICA and the LACI study groups have attempted to
2 conform.

3 The LACI study enrolled patients with
4 critical limb ischemia who were considered
5 unsuitable for surgical revascularization defined by
6 at least one of three entrance criteria: operative
7 risk for surgical survival of at least American
8 Society of Anesthesiology physical Class 4 or
9 higher; absence of a suitable autogenous vein
10 conduit; or by the extent of disease.

11 In fact, only 46 percent of patients
12 fell into the ASA Class 4. Only 32 percent had no
13 suitable autogenous vein conduit, and many of these
14 criteria existed in the same patient.

15 Forty-one percent of lesions were in the
16 superficial femoral artery, and 27 percent in the
17 popliteal artery or the peroneal tibial trunk. The
18 mean number of lesions per limb was 2.7, and the
19 mean length, six centimeters.

20 Many of these lesions are often TASC
21 Class B and C for which the role of endovascular
22 treatment has not been established, as listed in

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1 TASC critical issue number 14.

2 The LACI exclusion requirement of a
3 patient infragenicular artery is a factor favorable
4 for PTA where bypass is not an option.

5 The surgical risk status is claimed
6 indicative of co-morbidities placing LACI patients
7 in a higher risk category for a poor outcome.
8 Therefore, demonstration of equivalence to the
9 selected control, many of whom underwent a surgical
10 procedure, is a conservative estimate of
11 effectiveness that can be disputed.

12 The ASA classification classifies the
13 patient's general clinical status by probability for
14 postoperative survival, which may be unrelated to
15 the surgical intervention. Although linked to co-
16 morbidities, it does not necessarily impact on the
17 risks for treatment of a regional condition, such as
18 critical limb ischemia or under benefits derived
19 from such treatment.

20 Univariate analysis of LACI outcomes
21 identified that the only statistically valid
22 predictors of outcomes were age for mortality and

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1 gangrenous changes for amputations, both of which
2 occurred as similar baseline incidences in LACI and
3 the ICAI control. A smoking history was more
4 prevalent in the ICAI control, while other risk
5 factors occurred more frequently in LACI.

6 However, many of these risk factors were
7 moot considering the patient's ischemic level of
8 Class 4, 5, and 6.

9 Delivery of the laser energy is
10 controlled over a guidewire. The guidewire
11 successfully navigated the culprit lesions in 85
12 percent of cases, and the step-by-step laser
13 procedure was necessary in only 13 cases.

14 Procedural success defined as equal or
15 less than 50 percent residual stenosis was achieved
16 in 91 percent of cases, but required adjunctive PTA.
17 It is, therefore, conceivable that PTA alone may
18 have been affected and the laser angioplasty
19 superfluous.

20 Use of stents in 70 percent -- I'm sorry
21 -- in 70 cases, 46 percent of the LACI patients, the
22 majority placed in the superficial femoral artery

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1 further clouds the issue. Although similar levels
2 of salvage was achieved in stented and non-stented
3 limbs, stents may have significantly impacted the
4 short-term, six-month limb survival.

5 Block randomization insured that cases
6 were withdrawn equally from both arms. The race for
7 the outcomes have been calculated for patients not
8 lost to follow-up. Re-intervention was required to
9 maintain limb perfusion, was significantly higher in
10 LACI. The rehospitalization necessary can only
11 adversely impact on the already constrained quality
12 of life.

13 During the six months of follow-up,
14 persistence of critical limb ischemia categories
15 occurred in 30 percent of patients.

16 The sponsor claims that the review of
17 literature base for alternative treatments supports
18 both the LACI study design and the clinical
19 advantage of laser arthroplasty in these patients.

20 These are extrapolations from
21 heterogeneous studies and patient populations.
22 Disease conditions were also heterogeneous, and

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1 studies varied considerably with follow-up
2 evaluations that ranged from 30 days to five years.

3 Furthermore, these reports cover two or
4 three decades, and many antedate the more recent
5 significant advances in both the technology and
6 clinical management of peripheral arterial disease.

7 The benefit of limb salvage is not in
8 controversy. However, a documented need for
9 amputation, end stage critical limb ischemia, to
10 manage local and/or systemic effects of ischemia is
11 recognized in the TASC recommendations, and it's
12 critical issue number 45.

13 Medication absent an alternative is a
14 procedure essentially of desperation as studied in
15 the ICA trial. Newer drugs can provide short-term
16 palliation and perhaps adjunctive benefit to
17 borderline revascularization procedures.

18 Bypass surgery remains the gold standard
19 for critical limb ischemia. Considerable success
20 has been documented for periods extending to five
21 years for aggressive revascularization, including a
22 pedal bypass. Modifications in surgical approach

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1 and advances in use of alternative conduits,
2 together with newer radiological active drugs may
3 have permitted improvement in tissue perfusion over
4 the short term to allow healing and then salvage
5 even in the absence of a suitable autogenous vein.

6 Improvement in endovascular
7 interventions also fueled by technology have
8 generally excellent results in critical limb
9 ischemia for even the periphery located disease.

10 In summary, therefore, why the LACI
11 study single hypothesis of survival with limb
12 salvage in critical limb ischemia at six months has
13 been met, any benefit claimed for this modality is
14 diminished by the re-intervention rate and the
15 persistence of critical limb ischemia as
16 symptomatology.

17 The value added to a management strategy
18 employing only percutaneous angioplasty and not
19 utilizing laser therapy remains uncertain.

20 Thank you.

21 I would now like to introduce Dr. --
22 pardon me.

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1 DR. KRASNICKA: Good morning. My name
2 is Barbara Krasnicka. I am an FDA statistician.

3 In my presentation, I will focus mainly
4 on the problems connected with the study design and
5 statistical analysis.

6 As Dr. Sapirstein already mentioned in
7 his presentation, the objective of this clinical
8 study was to determine safety and effectiveness of
9 the use of excimer laser for ablation of vascular
10 obstructions.

11 The primary effectiveness endpoint was
12 the percentage of live patients without major
13 amputation at six months. The primary safety
14 endpoint was any death occurrence during six months
15 of the follow-up period.

16 I will discuss only some issues
17 connected with the statistical analysis for the
18 primary effectiveness endpoint and for one of the
19 secondary endpoints, namely, the survival time to
20 six months of the follow-up.

21 Note, again, that this study was
22 designed as a non-randomized clinical trial with one

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1 prospective treatment group called LACI and an
2 historical control group based on a single published
3 paper in 1999.

4 Please note there is no data available
5 at the individual patient level for the control
6 group. Only summary statistics, such as estimated
7 proportions, means, standard deviations, and figures
8 were accessible from the paper.

9 Now let me summarize again some general
10 information about the study. The prospective LACI
11 trial was carried out at 14 sites, 11 located in the
12 U.S. and three in Germany. Altogether, 145 patients
13 with 155 treated limbs were enrolled in the
14 treatment group.

15 However, during the six months of the
16 study, 11 patients dropped out of the study.

17 The historical control study was carried
18 out at 56 sites in Italy. Six hundred seventy-three
19 patients enrolled in this study were considered in
20 the analysis. Only seven patients were lost to
21 follow-up in the control group.

22 Essentially, the sponsor's objective was

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1 to show that the results in the treatment group were
2 at least as good as for the control one. FDA agreed
3 to accept the equivalence design based on the
4 assumption that the control patients would be less
5 sick than the LACI patients.

6 The results of the statistical analysis
7 on the primary effectiveness endpoint are as
8 follows. The percentage of alive patients without
9 amputation for the LACI group was 75.9 percent, and
10 for the control group was 73.4 percent. The 95
11 percent two-sided confidence interval of the
12 difference of limb salvage rates for the two intent
13 to treat populations was roughly minus 510. This
14 means there was no statistical difference between
15 the two groups.

16 Let me now pose a question. Should we
17 accept the point estimates and confidence interval
18 without any restrictions?

19 The study was not randomized.
20 Therefore, the real treatment effect is uncertain.
21 The LACI and control groups are not comparable.
22 Patients' smoking history and previous major

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1 amputations were statistically more prevalent in the
2 control group than in the LACI group.

3 However, more diabetes, prior stroke and
4 obesity were noted in the LACI group of patients.
5 Additionally, the LACI and control studies were
6 carried out in different countries and hospitals,
7 with likely differences with respect to
8 manufacturers connected with the patients.

9 All of the above-mentioned factors may
10 impose a bias on the results.

11 Now the question is whether we could
12 overcome the bias problem. Information on the
13 historical control study was based on a single
14 published paper without any possibility to use the
15 individual patient's information. Therefore, the
16 visible differences at baseline between these two
17 groups of patients could not be taken into account
18 in the statistical analysis.

19 It is worth to mention that small
20 differences in important covariates, like previous
21 major amputations could reasonably explain the
22 differences in outcomes in treated and control

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1 groups.

2 Also, a formal sensitivity analysis for
3 hidden bias due to the non-randomized study is
4 impossible to perform because of the lack of the raw
5 data of the patient level.

6 Additionally, in the LACI group, the
7 laser treatment was not the only single procedure
8 applied. All patients received also balloon
9 angioplasty and 45 percent of them received stents.

10 In the control group, the treatment was
11 conventional medications for blockage of arteries.
12 Only sometimes the treatment included a bypass
13 surgery and/or other procedures at the time of
14 enrollment.

15 Due to the concomitant procedures that
16 were not included in the control group treatment, it
17 is very difficult to evaluate the effectiveness of
18 the use of the laser device alone. For this reason,
19 the statistical analysis given by the sponsor does
20 not uniquely prove the advantage of the laser
21 therapy.

22 One of the secondary endpoints of the

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1 study was survival time during a six-month follow-up
2 period. The average survivor functions for the LACI
3 and control groups were approximated using Kaplan-
4 Meier estimated. Results are shown in the figure
5 prepared by the sponsor.

6 The upper curve corresponds to the LACI
7 group and the lower one to the control group. The
8 visual impression is that the LACI patients could
9 survive longer than the patients from the control
10 group, but based on the Wilcoxon test, the
11 difference between these two groups is not
12 significant at the .05 level, P equals .17.

13 Now the question is how perfect this
14 survivor analysis is. It is very well known that
15 heterogeneity between patients may have considerable
16 impact on the estimation of the difference between
17 the two treatment groups. In the LACI group, the
18 range of patients' age was 41 to 91. Evidently even
19 the LACI group of patients is not a really
20 homogeneous one.

21 It is worth nothing that the stratified
22 comparison of survivor times with or without

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1 adjustment for important covariates could solve the
2 problem of biases in survivor analysis. However, it
3 is impossible to apply such methodology without
4 having access to zero data at the patient level.

5 As I already mentioned before, the
6 laser treatment was injunctive with PTA. Because
7 of all the above problems, the survivor analysis is
8 also questionable.

9 Thank you very much.

10 And now Dr. Sapirstein will present the
11 clinical and statistical summary.

12 DR. SAPIRSTEIN: Thank you, Dr.
13 Krasnicka.

14 Well, in conclusion, the sponsor has
15 demonstrated equivalence to the selected control for
16 the endpoints of survival with salvage of the limb.
17 The data does not, however, support an assumption
18 that LACI registered patients were at greater risk
19 than the control on which the hypothesis was based.

20 The non-randomized study design dictates
21 caution in analyzing the data. The extent to which
22 non-assessed covariates influence effectiveness of

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1 the laser treatment is difficult to determine. Re-
2 intervention rate impacts negatively on the risks
3 and the benefits of the laser intervention.

4 Thank you very much.

5 CHAIRMAN LASKEY: And thank you.

6 Questions from the panel members for the
7 FDA presenters? Yes, Sharon.

8 DR. NORMAND: I have a question about I
9 think it's slide 29, and this is where the FDA
10 apparently agreed to accept an equivalence design
11 where, in fact, the patients were different. And
12 perhaps you could elaborate, someone could elaborate
13 on the reasoning for doing that, on the one hand,
14 and, on the other hand, it seems that you're
15 criticizing the sponsor or there are questions
16 raised about the sponsor on the second half for the
17 effectiveness endpoint, saying that, in fact, the
18 patients are different.

19 So I guess if someone could help me
20 understand maybe the decision to accept a design in
21 which the patient populations are different.

22 DR. SAPIRSTEIN: We discussed this with

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1 the sponsor. They felt that they could not develop
2 a control other than this historical control, except
3 that they were accepting of the fact that these
4 patients were permitted to enter the study with
5 multiple interventions. They felt that this was a
6 more rigorous control of their study, which they
7 felt they could justify with a, I think, ten percent
8 delta.

9 CHAIRMAN LASKEY: This may be something
10 at Dr. Zuckerman's level, but traditionally I think
11 of pivotal trials as randomized. Could you give us
12 some insight or guidance into non-randomized pivotal
13 trials? What is an acceptable study design at this
14 level that is acceptable to the agency?

15 DR. ZUCKERMAN: Okay. Let's take a step
16 back. There's nothing in our regulations that says
17 that the pivotal study design for a PMA device or
18 PMA supplement needs to be a randomized controlled
19 clinical trial. Certainly from a clinical trial
20 design, an agency perspective we would prefer this
21 study design for the obvious reasons. The obvious
22 reasons are at the end of the day, it's frequently

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1 the easiest way to analyze in a fair manner any
2 differences between control and experimental
3 therapy.

4 Now, as Dr. Sapirstein has recollected,
5 the sponsor and their investigators believed at the
6 time of design of this trial that a randomized
7 controlled clinical trial for this patient
8 population would not be a doable one. As such, they
9 attempted to develop a control group that they
10 thought could provide a fair comparison with their
11 experimental therapy.

12 As pointed out by multiple FDA comments,
13 when one goes to non-randomized designs, frequently
14 the number of questions regarding a fair comparison
15 of control in experimental groups seems to increase,
16 and that's one of the things that the panel will
17 deal with.

18 The other thing to note is, again, going
19 back to Dr. Holden's initial comments, although the
20 agency can give conditional approval for a pivotal
21 trial design, and in this situation that's what
22 happened, the usual FDA letters always have a final

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1 paragraph that explains that while the trial can go
2 forward, this is not a total FDA endorsement, and
3 several caveats were mentioned by Dr. Laird in his
4 initial presentation.

5 CHAIRMAN LASKEY: Dr. Somberg.

6 DR. SOMBERG: What I would appreciate
7 from the FDA, whoever wants to take this, is some
8 further clarification. I understand that the
9 equivalency hypothesis was accepted with a caveat,
10 as I stated by Dr. Zuckerman, but was that for
11 safety or was that for efficacy?

12 Because I'm confused in that there was a
13 selection of a control group for a pharmacologic
14 study where essentially there was current practice
15 indications for whatever was done. So you were
16 trying to be current with a trying to be current
17 practice in this control group, whatever that might
18 be -- and that's, of course, varied in the study,
19 and it's current practice in Italy in the early '90s
20 one would have to say as opposed to the United
21 States approximately ten years later.

22 So is that an efficacy acceptance of

1 equivalence or was it a safety acceptance, the
2 latter, I think, being more logical?

3 DR. SAPIRSTEIN: It was an acceptance of
4 an effectiveness equivalence, feeling that that was
5 the basis for the study design, the belief that
6 these patients were in a desperate situation of
7 inevitable limb loss. So it basically was an
8 effectiveness measured by limb salvage.

9 DR. ZUCKERMAN: Does that answer your
10 question, Dr. Somberg?

11 DR. SOMBERG: Well, if it was a
12 superiority to that group, the answer is no. If
13 that was a superiority to that group, I would
14 understand that, to the control group, but if it was
15 equivalent to the control group, I don't see how
16 that could prove effectiveness.

17 You know, the internal parsimony in that
18 study is that Prostaglandin E-1 was superior to
19 standard of care therapy. I think what the sponsors
20 were trying to do was show that laser angioplasty
21 systems was superior, but if it was equal to the
22 standard of care, how does that prove that something

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1 was done that was effective in the FDA statement of
2 effectiveness, you know, by the Federal Register?

3 DR. ZUCKERMAN: I think what you have to
4 accept -- and, again, this is for panel discussion -
5 - is that there was an implicit belief that the
6 control arm from ICAI would be a less sick control
7 arm, and therefore, if there was shown in the sicker
8 experimental group equivalence to that less sick
9 control arm, these were acceptable results.

10 CHAIRMAN LASKEY: Dr. Krucoff first.

11 DR. KRUCOFF: I think what Bram just
12 said is key to trying to figure out where we are.
13 The hypothesis here of equivalence literally, as I
14 understand it, and I had to go through this pack
15 twice because I didn't get it the first time around,
16 is that essentially doing something in a higher risk
17 group would be equivalent to doing nothing in a
18 lower risk group. And at least statistically you're
19 going to have to help because I don't know how to do
20 that.

21 But I think that's the issue that seems
22 to be on the table in this data set, and it really

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1 gets back to the question of how do you deal with
2 equivalence in different patient populations, but I
3 guess we'll have time to go back through some of
4 that.

5 I just wondered from a statistical point
6 of view is there a way of doing this. I mean, are
7 you actually -- can you share with us a statistical
8 approach that defines equivalence in a higher versus
9 a lower risk patient population where you're
10 intervening in one and not in the other?

11 Oh, we're going to a higher authority.

12 (Laughter.)

13 DR. GERRY GRAY: I'm Gerry Gray, the
14 team leader for Cardiovascular and Ophthalmic
15 Statistics.

16 And the answer to that is, of course, --
17 well, the answer to that is really no. I don't
18 think that it's meaningful to show that equivalence
19 when the patient populations are that much
20 different. It's kind of hard to -- I'm not sure how
21 you would actually interpret the results of that
22 even if you were successful in showing equivalence.

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1 DR. KRUCOFF: Okay. Then just a brief
2 follow-up to you or Bram or whoever, Gerry. So my
3 sense of the process is the sponsors go to their
4 investigators, their steering committee. They get
5 their wisdom, and they come back and say this is the
6 only way you can do a trial ethically or whatever in
7 this patient population.

8 And you guys send a letter that says,
9 "We will conditionally let this go ahead. However,
10 here, in fact," as John Holden showed with us and is
11 in the pack, "here are some things that we suggest
12 that you also do," like the risk-benefit analysis,
13 et cetera.

14 But then the sponsor actually going
15 ahead with the trial, I mean, is there any further
16 dialogue after that letter or they just go ahead and
17 then here we are today?

18 DR. ZUCKERMAN: I think there is always
19 dialogue with the sponsor. At least I seem to find
20 that to be the case, but you know, in the end the
21 sponsor was prepared to take a certain risk with
22 this trial design. It's a difficult situation for

1 evaluation, and that's why, you know, the eventual
2 trial results are here at this panel deliberation.

3 The agency is looking for outside expert
4 advice.

5 CHAIRMAN LASKEY: All right. Dr.
6 Morrison.

7 DR. MORRISON: Well, I'd like to take a
8 risk and add one more level of complexity. I've
9 heard non-random, non-comparable, equivalence versus
10 superiority. My question at the end of the day is:
11 why is the control group medical therapy as opposed
12 to angioplasty, particularly given that 83 percent
13 of these patients had wire crossing and 98 percent
14 of them received balloon angioplasty and 45 percent
15 received stents?

16 It seems to me there are three different
17 levels of difficulty here. One is noncomparable
18 groups. The other is why is the addition of laser
19 not better, but secondly, why compare it to medical
20 therapy as opposed to angioplasty?

21 And that's addressed to anyone.

22 CHAIRMAN LASKEY: Well, we're supposed

1 to confine our questions to the FDA at the moment.
2 I think Spectranetics is twisting in the wind here,
3 but we should confine this to the FDA.

4 DR. MORRISON: Did the FDA agree to that
5 as part of the agreement in the first place, that
6 this particular study would be the control group, or
7 was it just an agreement that in principle some
8 control group?

9 DR. ZUCKERMAN: When designing a study
10 with a sponsor, there are always multiple factors
11 that are considered both at the FDA and sponsor, and
12 certainly the agency did provide caveats in its
13 interaction with the sponsor, but this is the design
14 that we have at the end of the day.

15 DR. SAPIRSTEIN: And to add to that, PTA
16 was an adjunctive intervention in this condition.
17 So we felt that it was an adequate control to have
18 this historical control where a multitude of
19 interventions were permitted at the initiation of
20 the ICAI control included PTA and surgical
21 intervention. So we thought it was an adequately
22 robust control.

1 CHAIRMAN LASKEY: I guess for those
2 interventional people on the panel here, if you get
3 a wire across something, you can follow it with
4 anything, and I guess we're just sitting here
5 wondering, as did everyone else, why not a balloon.

6 We've heard the track record with
7 balloons for long lesions, but these are expert
8 investigators and best hands, best case scenarios.
9 So it's a very uncomfortable feeling at the moment.
10 Really if you get your wire down there, anything
11 goes after that.

12 DR. WHITE: Well, I just was going to
13 add actually the same comment, and that is that I
14 think in some ways the FDA shares responsibility for
15 not providing a little better guidance here for this
16 trial. I disagree with the interpretation of the
17 sponsor's reading of the literature. I've found
18 several prospective trials, one of which they've
19 cited themselves, a Soder paper. I think it's
20 number 18 in their reference list in Package 3,
21 which were prospective PTA trials in chronic limb
22 ischemia patients that did quite well.

1 And I know that the standard practice in
2 my laboratory, and I'm sure some of the sponsor's
3 investigators' laboratories are that we treat every
4 day patients with this type of disease without
5 lasers. The real question that we'd like to be
6 answered today is what the laser adds to other
7 interventional therapy, and I'm afraid we're not
8 going to be able to come to that conclusion, and I
9 think the FDA let the sponsor down by not insisting
10 that that happened.

11 Dr. Sapirstein says that ICA was used
12 because of the interventions, but you know, Wolf,
13 there was only four percent angioplasty done in that
14 series. Only a very small, small number of patients
15 in the ICAI trial actually got an intervention. It
16 was not part of their treatment.

17 DR. SAPIRSTEIN: Well, we thought that
18 the control was sufficiently robust. Somewhere
19 around 40 or 50 percent of the control arm had an
20 active intervention, either by bypass or an
21 angioplasty or thrombolytic agent. So I think that
22 a control to PTA per se might have been even -- and

1 many of these patients were considered unsuitable
2 for PTA, but as we pointed out in our review, we
3 didn't feel that any -- we thought it was
4 questionable whether any added value was provided by
5 the laser to PTA.

6 CHAIRMAN LASKEY: Okay. I think we beat
7 that one.

8 Well, congratulations to all for keeping
9 us way ahead of schedule. My suggestion is if the
10 lunchroom is ready for us that we break for lunch.
11 It's a tad early, but I hesitate to start the open
12 committee discussion at this point. Okay?

13 It is ten after 11. Can we regroup at
14 12:15 and resume? That way we pretty well will get
15 everybody to the airport on time. So let's adjourn
16 for the moment and regroup at 12:15.

17 Thank you very much.

18 (Whereupon, at 11:11 a.m., the meeting
19 was recessed for lunch, to reconvene at 12:15 p.m.,
20 the same day.)
21
22

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

(12:23 p.m.)

CHAIRMAN LASKEY: All right. Thank you for returning on time. We have a quorum here.

So we will lead off with Dr. Nicholas who is the lead reviewer for this PMA, and then we'll just go around the table from there.

Dr. Nicholas.

DR. NICHOLAS: Thank you.

Some of what I say, I think, unfortunately will be a bit redundant, but I feel I've got to sort of put it all in one place.

By way of summary, the investigators presented the study using excimer laser as a catheter based treatment for lower extremity peripheral vascular ischemia. The device has been previously approved with smaller catheters, and the investigators have utilized several new, larger catheters previously unapproved for the peripheral vascular interventions.

An initial feasibility study was conducted on 23 patients, 25 limbs. The pivotal

1 study identified laser angioplasty for critical limb
2 ischemia, known by the acronym LACI, was then
3 conducted, 15 sites, 12 in the United States, three
4 in Germany. There were 145 patients enrolled.
5 Fifty-eight of these patients were from centers
6 outside of the United States, and 69 patients were
7 enrolled from three sites, two of which were in
8 Germany and one in the United States.

9 Preclinical studies, as you heard, of
10 biocompatibility have all been taken care of and
11 tested.

12 The results of the registry, patients
13 who entered the LACI protocol were compared to a
14 historic group published in the Annals of Internal
15 Medicine in 1999. This was a study from 56
16 departments within the Italian National Health
17 Service. In that study, patients were randomized
18 into two groups, one receiving Prostaglandin E-1 and
19 the control group received standard medical care at
20 the same institutions.

21 The current LACI study utilized this
22 control group from that protocol to compare their