

1 along then. If there are no other questions from the
2 panel, I would like to finish with Mr. Worrell.

3 MR. WORRELL: I do have a couple of points
4 of clarification that we did find data on for you.
5 There is a question about diabetic patients; and 5 of
6 27 diabetic patients had infection, and the analysis
7 revealed that was not significant.

8 DR. KOLTUN: There were 27 diabetics, is
9 that what that means?

10 MR. WORRELL: Correct.

11 DR. KOLTUN: And five had an infection.

12 MR. WORRELL: And give had an infection.

13 DR. KOLTUN: What was the number that we
14 got that was 0.0001 for diabetics with regards to risk
15 of failure?

16 DR. TALAMINI: That was risk of revision,
17 things correlating with revision.

18 DR. KOLTUN: Okay.

19 MR. WORRELL: And also regarding
20 microorganisms. We did some cultures when the
21 infection control specialist looked at the study, and
22 culturing patients who presented with infection was

1 not part of the protocol. So the organisms that you
2 did see on the slide were from patients in the study.

3 I would also like to address the infection
4 control specialist we had come in. The preliminary
5 results were of concern to the investigators, and the
6 infection rate did seem to be high.

7 Initially the antibiotics were prescribed
8 by colorectal surgeons at their individual sites. We
9 had an infection control specialist analyze results
10 from the study and present those results to the
11 investigators.

12 And I would like Dr. Wong to speak a
13 little bit about how the investigators received those
14 results.

15 DR. WONG: Well, Walter is perfectly
16 right. These were all done by colorectal surgeons,
17 and everybody was on antibiotics. There was no
18 question at all, and it was that everyone used their
19 own antibiotic selection.

20 So these patients did in fact all get
21 antibiotics, and as the study progressed, it was
22 evidence that our infection rate was higher than where

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1 we really wanted to see it.

2 And at that point in time, we asked the
3 infectious disease specialist, actually in St. Paul
4 where we were working, to review the data, in terms of
5 the organisms, and look at the entire spectrum of
6 things, and then to give us his recommendation as to
7 antibiotic regimen that we could adhere to that might
8 be more specific to the type of organisms and
9 infection that were seen.

10 And in the data that was shown there, even
11 though the numbers are still relatively small, with
12 only 16 in the right-hand column. And it does show a
13 fairly significant incidence.

14 So, even just clinically, even though we
15 haven't -- that is not large enough to make a
16 decisional statement, there has been improvement in
17 the infection rates when that particular regimen is
18 used.

19 Since then, because all the investigators
20 were very, very concerned about the infection, the
21 majority of the investigators had it here to those
22 regimens. Some hospitals are very rigid in terms of

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1 what antibiotics they can have, and some formulators
2 in various hospitals don't actually have it.

3 So we have run into problems in the study,
4 and not all hospitals saying that, yes, you can have
5 this particular antibiotic. But, in general, when you
6 have gone back to them, and to the infectious disease
7 specialist, they have okayed it.

8 DR. KOLTUN: So what is the protocol now
9 to you understanding?

10 DR. WONG: The protocol is as what Sue had
11 put up on the slide, one pre-operative dose. The
12 recommendation is for one pre-operative dose, and he
13 presented data on other devices where post-operative
14 doses make no difference whatsoever. There was the
15 recommendation for one pre-op dose.

16 And I know that there are some
17 investigators who have not felt comfortable with that,
18 and gave post-operatives doses. I have gone with a
19 one plus pre-operative dose.

20 DR. KOLTUN: And of the most recent 16
21 implants, you could not follow them long enough to --

22 DR. WONG: Yes, that's correct.

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1 DR. TALAMINI: I have just one last
2 question for Dr. Worrell or Mr. Worrell. Many of --
3 well, I guess the question boils down to this. There
4 is plenty of European and now the United States
5 experience, and I am just wondering why the company
6 has not exhaustively studied some subset of them,
7 particularly since the results seem perhaps a bit
8 better?

9 MR. WORRELL: Some data is included in the
10 controlled clinical trial from Europe, and we can say
11 that those results have been studied exhaustively.

12 DR. TALAMINI: From the 1988 study, or --

13 MR. WORRELL: From this study, from the
14 second pivotal study. They do make up less than 10
15 percent of the patient population, however. So it is
16 a small sample.

17 There was also a question regarding
18 revision due to patient dissatisfaction. Four
19 patients stated dissatisfaction as a reason for
20 revision, and that is 3.6 percent of implanted
21 patients. It may, as Dr. Congilosi suggested, have
22 accompanied another reason for revision, such as

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1 recurrent fecal incontinence.

2 So in conclusion, no gold standard
3 currently exists for the treatment of severe fecal
4 incontinence. In fact, no other device other than the
5 Acticon exists today for these patients.

6 The device addresses the unmet medical
7 need of controlling severe fecal incontinence for
8 patients who have failed other therapies, and whose
9 only remaining option is permanent stoma.

10 The key benefits of treatment with the
11 device include, number one, improved fecal continence.
12 A majority of patients achieved clinical success.
13 Many of these patients were fully continent, or had
14 dramatic improvement in continence status.

15 The results from statistical analysis of
16 the primary effectiveness indicated that significant
17 sustained improvements in continence were attributable
18 to the device.

19 And, number two, significant improvements
20 in the patient's quality of life. Results from the
21 study indicated that the average patient's quality of
22 life was significantly improved after treatment with

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1 the device.

2 Significant improvement was indicated in
3 the total HSQ score, and on 6 of the 8 HSQ domains.
4 Improvement also was indicated on the remaining two
5 HSQ domains, although it was not significant.

6 Just as important, no declines in quality
7 of life were indicated by analysis after follow-ups.
8 The fecal incontinence quality of life instrument also
9 measured improvements on the effect of fecal
10 incontinence on patients' quality of life after being
11 treated with the device.

12 And, number three, the device is same for
13 use in selected patients. The device uses technology
14 and operating principles proven in thousands of
15 patients over two decades of clinical use with the AMS
16 800 urinary sphincter.

17 And the device itself has established its
18 own acceptable safety profile over several years of
19 clinical use. Morbidity is moderate to high, and to
20 reemphasize, we were following an IDE approved
21 controlled protocol.

22 And anyone who has been involved in

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1 research with the agency knows that those protocols
2 are very prescriptive in the types of adverse events
3 that are collected.

4 Sometimes we had to convince investigators
5 to report all adverse events. We feel that we have
6 collected all adverse events that were reported during
7 the study.

8 Remember that 80 percent of the adverse
9 events reported in the study were mild to moderate,
10 which means that they resolved on their own, or with
11 minimal interventions.

12 Study results indicate that adverse events
13 are manageable and resolve without long term sequelae.
14 If necessary, the device can be removed and a patient
15 may proceed to permanent stoma.

16 The Acticon Neosphincter is a safe and
17 effective treatment option for patients with end-stage
18 fecal incontinence who have failed, or who are not
19 candidates for other forms of restorative therapy.

20 The risks from use of the device are
21 outweighed by the benefits of significantly improved
22 fecal continence and greatly enhanced quality of life.

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1 We ask the panel for your recommendation to approve
2 this device and to offer patients this opportunity for
3 restored continence and for improvements in the
4 quality of life.

5 Thank you very much for your attention,
6 and as a reminder, Dr. Wong does need to leave this
7 afternoon. So if there are any more questions to Dr.
8 Wong or to Dr. Congilosi, we invite them at this time.

9 CHAIRMAN KALLOO: Thank you. Are there
10 any questions from the panel to the sponsors?

11 DR. STEINBACH: Mr. Worrell, why are you
12 not satisfied with the humanitarian device exemption?

13 MR. WORRELL: Satisfied in what regard?

14 DR. STEINBACH: This can already be
15 marketed under a humanitarian device exception, and
16 you are seeking a general marketing. Why? I mean,
17 you can already sell it.

18 MR. WORRELL: Well, that is a good
19 question. The device is approved and it is legally
20 marketed at the moment. I think there are two reasons
21 that we are looking for this.

22 Number 1 is that HDE is a temporary

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1 marketing status. It can be revoked. There are
2 certain criteria that need to be fulfilled, but the
3 PMA would provide permanent marketing status for the
4 Acticon.

5 There is also another obstacle that we
6 have run into, and that is really in terms of allowing
7 access for patients to the device. As long as you
8 have an HDE approval, the device must be reviewed by
9 IRBs per regulation.

10 When an IRB grants their approval, and
11 every IRB who has reviewed the device has granted
12 approval for use at their institution, it also can
13 carry the label of an investigational device.

14 Insurance carriers have denied patients
15 the Acticon because of this IRB approval and
16 investigational status. We do try and work with
17 insurance carriers and explain that we have an FDA
18 approval, but that it has not always allowed the
19 patient to get reimbursement and to gain access to the
20 device.

21 CHAIRMAN KALLOO: Any other questions?

22 MR. BANIK: Were there any device design

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1 changes made to the device during the protocol?

2 MR. WORRELL: During the protocol? Yes.
3 We made a change to the cuff. We have a picture and
4 let me see if I can show you. We have increased the
5 size of the cuff adapter it is called. Let me show it
6 to you quickly.

7 And you can get some feel for it right
8 here. This has been increased in order to prevent the
9 cuff from unbuckling in vivo. It creates a greater
10 unbuckling force to help prevent that phenomenon.

11 MR. BANIK: Could those changes affect the
12 outcome of the study?

13 MR. WORRELL: The new cuff adapter has not
14 been used in a study yet, and so a change has been
15 made, but it has not been implemented.

16 CHAIRMAN KALLOO: Any other questions? If
17 not, I am proposing that we take a short break of 10
18 minutes. My goal is for us to lunch at 12:35. So,
19 please if you could come back in 10 minutes while the
20 FDA sets up for their presentation. Thank you.

21 (Whereupon, at 11:43 a.m., the meeting was
22 recessed, and resumed at 11:55 a.m.)

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1 CHAIRMAN KALLOO: Welcome back. Next will
2 be the FDA presentation of the open public hearing.
3 Again, I would like to remind the panel that you may
4 ask for clarification of any points included in the
5 FDA's presentation, but discussions should not go
6 beyond clarification.

7 The first speaker for the FDA is Ron
8 Yustein.

9 DR. YUSTEIN: Good morning, Mr. Chairman
10 and panel members. My name is Ron Yustein, and I am
11 a gastroenterologist in the Office of Device
12 Evaluation here at the Food and Drug Administration.
13 Kathy Olvey and I today will be presenting the FDA's
14 review of the Acticon Neosphincter.

15 Quite a few of the slides that I have
16 actually repeat some of the information already given
17 by the sponsors, and so I may go fairly quickly
18 through some of those and feel free to slow me down at
19 any point if you want any clarification.

20 I also just wanted to quickly run through
21 the FDA review team, including myself, Carolyn
22 Neuland, who is our branch chief in the GI Devices

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1 Branch, and Kathy Olvey, who will talk in a couple of
2 minutes, who did the pre-clinical review; and Elias
3 Mallis, the engineering review; T.C. Lu, the
4 statistical review, and Jack McCracken, patient
5 labeling review; and Sharon Murrain-Ellerbe, consumer
6 safety office; and Marian Linde-Serge, from the
7 bioresearch monitoring, and Dr. Jeffrey Cooper, who is
8 our Executive Secretary, who has done a yeoman's job
9 in getting this ready for today.

10 To start with, the Acticon Neosphincter,
11 as per the PMA submission, the indication for us, the
12 Acticon Neosphincter is indicated for the treatment of
13 severe fecal incontinence in post-pubescent males and
14 females who have failed or are not candidates for less
15 invasive forms of restorative therapy.

16 In this clinical protocol, severe
17 incontinence was defined as the involuntary loss of
18 liquid or solid stool on a weekly or more frequent
19 basis.

20 The Acticon Neosphincter received
21 humanitarian use device designation in December of
22 1998, and just for a quick definition, an HUD is

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1 defined as a device which is intended to benefit
2 patients in the treatment and diagnosis of diseases,
3 and conditions that affect or manifest in less than
4 4,000 individuals in the U.S. per year.

5 The device received a humanitarian device
6 exemption on September 20th, which allowed for the
7 marketing of the HUD. During the HDE, the indications
8 for use were identical to that of the PMA currently
9 being reviewed.

10 The patient population for the HDE was the
11 same as that for the PMA, and the number of implant to
12 patients in the follow-up period were less at the time
13 of approval, and the HUD was approved based on
14 demonstration of safety and probable benefit, and
15 copies of that were included in the panel mail out.

16 I am going to just very, very briefly go
17 over the clinical implications of fecal incontinence.
18 Mr. Worrell touched on much of this. Fecal
19 incontinence is defined as the inability to control
20 gas or stool, and to some degree it can affect up to
21 7 percent of the U.S. population in general, and more
22 than 50 percent of nursing home patients.

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1 It is a leading cause of U.S. nursing home
2 placement, and a substantial social problem for those
3 affected. In the United States, it is a significant
4 public health burden, with over \$400 million a year
5 being spent on incontinence appliances.

6 The associated conditions in etiology as
7 you are all aware include diarrheal states, including
8 fecal impaction, or short cut syndrome, neurological
9 injury or impairment from a stroke, and spinal cord
10 injuries, and mass or other neuropathies, obstetric
11 sphincter injury following delivery, surgical
12 sphincter injury which may occur after a fissile
13 repair, pelvic trauma, rectal prolapse, and collagen
14 vascular disease.

15 Current treatment concerned with medical
16 therapy which centers around treating the underlying
17 disorder using anti-diarrheal medications, changes in
18 diet, especially fiber; disimpaction, and scheduled
19 toileting.

20 Biofeedback, which in certain sub-
21 populations can benefit 70 to 90 percent of people.
22 Surgery, including sphincter repair, has a 70 to 90

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1 percent success rate in those with sphincter defects.

2 Skeletal muscle transposition of the
3 gluteus or vercilis muscle, rectal prolapse repair,
4 which has been anywhere from 45 to 85 percent success
5 rates; and then finally almost as a treatment of last
6 option would be a diversion ostomy.

7 Other investigational methods which are
8 not apparently through the United States include
9 muscle transposition, plus stimulation, sacral nerve
10 stimulation, and injection of bulking agents.

11 As Mr. Worrell and Dr. Wong pointed out,
12 this is a picture of the device, consisting
13 essentially of three components. There is the
14 inflatable inclusive cup, which is placed around the
15 anal canal, connected with kink resistant tubing to
16 the pump control.

17 The pump is placed either in the labia in
18 the female, or the scrotum in males. This can contain
19 a septum for adding fluid post-operatively, and the
20 bulb which the patient squeezes to operate the device.

21 The pump is connected with kink resistant
22 tubing to a pressure regulating balloon, which is

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1 placed in the pre-vesical space. That controls the
2 amount of pressure exerted on the anal canal by the
3 cuff.

4 When a patient wishes to defecate as Dr.
5 Wong explained, the patient presses the bulb several
6 times, which moves fluid from the cuff through the
7 mechanisms in the control pump, to the regulating
8 balloon, opening the cuff and allowing the person to
9 defecate.

10 The balloon then repressurizes the anal
11 canal by way of the cuff over the next several
12 minutes. Right now I would like to introduce Kathy
13 Olvey, who we affectionately call our fecal focal
14 point, to discuss the pre-clinical studies.

15 MS. OLVEY: Good afternoon. I am going to
16 present a brief overview of the pre-clinical testing.
17 This information was submitted in the HDE for the
18 Acticon. That HDE was approved in September of 1999.

19 The same testing requirements are needed
20 in an HDE as in an PMA. Pre-clinical testing included
21 the results of material safety testing, evaluation of
22 device performance, and sterilization.

1 The components of the Acticon Neosphincter
2 are identical in design and materials to the American
3 Medical Systems artificial urinary sphincter. The
4 artificial urinary sphincter has been marketed since
5 1973, and it received PMA approval in June of this
6 year.

7 While the corresponding components of the
8 two devices are not identical, they differ only in
9 size. The two devices are assembled using equivalent
10 methods and sterilized under the same conditions. The
11 largest percentage of material in the Acticon, almost
12 95 percent, is solid silicon.

13 Biocompatibility testing of the raw
14 silicones was performed by the silicones manufacturer
15 in accordance with FDA requirements. Testing on the
16 finished sterilized device included identification and
17 quantification of extractable compounds, and in vitro
18 and in vivo biological testing.

19 Extracted testing was a risk analysis to
20 identify and quantify compounds that may lead from the
21 silicon, and that evaluate the potential risk to
22 implant recipients based on available toxicity

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1 information.

2 Extracted data was obtained for the
3 artificial urinary sphincter, and then extrapolated to
4 account for the larger mass of the Acticon. The
5 results of this testing showed that a recipient of the
6 Acticon is potentially exposed to measurable amounts
7 of several extractable compounds, monomers, and low
8 molecular weight siloxanes (phonetic), catalysts
9 images, and soluble silicon.

10 The potential exposure levels were
11 compared in published results from toxicity studies to
12 assess the possibility of significant health risks due
13 to the extractors. The potential doses of extractable
14 substances associated with the implant were negligible
15 compared to doses observed to be toxic in animals.

16 The comparisons demonstrated that these
17 extractors do not present significant health risks to
18 Acticon patients. In addition to the risk assessment
19 conducted on the potential extractors,
20 biocompatibility testing was conducted using extracts
21 or device materials collected from samples of the
22 finished sterilized device.

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1 This testing was conducted in accordance
2 with the FDA guidance use of International Standards,
3 ISO 10993. The results of this in vitro testing
4 indicate that the materials are biocompatible.

5 To evaluate whether there were any
6 systemic effects of the implanted material on the host
7 system, studies were conducted in which ground
8 silicone was implanted subcutaneously in rats. There
9 were no findings of toxicological or immunogenic
10 significance associated with the implantation of the
11 silicone.

12 Non-clinical bench testing was conducted
13 to assess the physical and performance characteristics
14 of the Acticon. The testing was grouped into three
15 categories; performance characteristics, reliability,
16 and component strength.

17 Testing was conducted to assess the
18 performance characteristics for each of the device
19 components, and examples of the type of testing
20 conducted include pump squeeze force, pump refill
21 time, kink resistant tubing performance testing, cuff
22 balloon inflation/deflation characterization; and

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1 impact of septum access on balloon pressure.

2 Reliability testing repeated the tests
3 conducted for performance characteristics testing, but
4 was intended to evaluate the reliability of the long
5 term use of the device.

6 Component strength testing assessed the
7 integrity of the various components used in the
8 system. This testing demonstrated that the components
9 adequately performed the early estimated life cycle of
10 the Acticon.

11 The components of the Acticon are
12 sterilized for sterility assurance level of 10 to the
13 minus 6. The pressure regulating balloon and attached
14 tubing are sterilized using ethylene oxide. The cuff
15 and control pump, with attached tubing, are steam
16 sterilized.

17 The sterilization protocols were adequate
18 to determine that the device is sterile, and the
19 method of sterilization is identical to that used in
20 the artificial urinary sphincter.

21 The Acticon is labeled with a 5 year shelf
22 life, and an accelerated agent study was performed ont

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1 he package configuration, and results from the study
2 show that the packaging will provide physical
3 protection and a sterile barrier for a five year shelf
4 life, with a 2 year safety margin.

5 Now, Dr. Yustein will continue with the
6 presentation of the clinical data.

7 DR. YUSTEIN: The PMA pre-Acticon
8 Neosphincter was supported by two prospective clinical
9 trials performed in the United States. The first one
10 was G880037, which was a feasibility study, and the
11 second, G960116, was the pivotal trial.

12 With respect to the feasibility study,
13 this was used in an earlier version of the Acticon
14 Neosphincter, which was adapted from the AMS 800
15 urinary sphincter.

16 This was a multi-center prospective study
17 which took place from August 1988 to April of 1995.
18 Quickly, the objectives of this study, number one,
19 were to demonstrate that the device could be
20 surgically implanted without adverse sequelae to
21 demonstrate the device providing an acceptable level
22 of continence to demonstrate that the anticipated

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1 adverse events had a low incidence, and could be
2 managed without long term sequelae, and to demonstrate
3 that there were no unanticipated adverse responses
4 associated with the device.

5 Now, 21 patients, including 10 males and
6 11 females, were enrolled at three sites. The ages
7 ranged from 15 to 68. As you can see, over 50 percent
8 of the etiology were either anorectal trauma or
9 obstetric injury.

10 With respect to results and safety, 12 out
11 of the 21 patients, or 57 percent, experienced adverse
12 events. This included five patients with infection,
13 and five with a mechanical malfunction, and two with
14 pain.

15 And 9 out of the 21 patients, or 43
16 percent, required surgical revisions, and this
17 included all five patients with malfunction, and 4 out
18 of the 5 with infection.

19 And 5 out of the 21 patients, or 24
20 percent, required permanent device explanation. This
21 was 2 out of the 5 patients with malfunction, and 3
22 out of the 5 patients with infection.

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1 With respect to the effectiveness, the
2 outcomes were based on the patient continence diaries
3 that were kept, and the follow-up ranged anywhere from
4 7 to 76 months. And 10 out of 16, or 64 percent,
5 achieved complete continence to liquid and solid
6 stool, and an additional 18 percent, or 3 out of 16,
7 achieved continence to solid stool, but experienced an
8 occasional leakage of liquid stool.

9 If looked at with an intent to treat an
10 analysis under five patients that were explanted and
11 are included, this number becomes number becomes 48
12 percent, and this number becomes 14 percent.

13 Following the feasibility study, several
14 modifications were made on the device. This included
15 a reenforced longer cuff for improved pressure
16 transmission, a larger pressure balloon, and the
17 addition of a septum port to the control pump for the
18 addition of fluid post-operatively.

19 The pivotal trial, and this was a multi-
20 center perspective, non-randomized trial, with each
21 patient serving as his or her own control. As Dr.
22 Wong pointed out, 19 sites, mostly in the United

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1 States, and three in Canada, and three in Europe.

2 The study started enrollment in February
3 of 1997, and ended enrollment in December of 1999.
4 The objectives briefly were to demonstrate that the
5 Acticon Neosphincter could be surgically implanted
6 without serious adverse sequelae.

7 And to demonstrate that the device
8 provided an acceptable level of continence as
9 determined through the use of a fecal incontinence
10 scoring system questionnaire, which was discussed by
11 Dr. Wong.

12 And to report the adverse events
13 associated with the implantation of the device, and to
14 demonstrate that these events could be managed without
15 serious sequelae.

16 The inclusion criteria briefly included
17 fecal incontinence for greater or equal to 6 months.
18 The patient had to have failed at least one non-
19 surgical treatment, and have a FISS score of greater
20 or equal to 88.

21 The other inclusion criteria are listed up
22 there. The exclusion criteria notable for a FISS

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1 score of less than 88; irritable bowel syndrome is the
2 only cause of incontinence; and inflammatory bowel
3 disease, active pelvic sepsis; pregnant patients;
4 history of extensive pelvic radiation; scarred and
5 fragile perineum; patients who engage in anal
6 receptive intercourse; and patients enrolled in
7 another study involving investigational products.

8 Approximately 115 patients were enrolled,
9 and 112 of them are implanted, and the average age was
10 49, ranging from 18 to 81. The average age of the
11 females was 53, and the average age of the males'
12 enrollment was 36.

13 As pointed out the majority of the
14 patients were female and a large majority were
15 caucasian. The etiology of incontinence, as Dr. Wong
16 pointed out, again the number one is obstetric trauma
17 or injury.

18 Previous treatments, also show on a slide
19 by the sponsor, all had undergone other treatments,
20 including medical bowel management and other surgical
21 procedures.

22 The primary study end-point. The device

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1 effectiveness was assessed by analyzing the difference
2 between the pre-implant FISS score, which could range
3 anywhere from 88 to 120, and the score at 12 months,
4 post-implant, which could range from zero to 120.

5 A clinically significant improvement was
6 defined as a reduction in score of greater than 24
7 points. The FISS score was validated in a study by
8 Vaize, et al, which was published in Gut in 1999.

9 This is an example of the FISS
10 questionnaire. As you can see, it consists of five
11 questions. The top four relate to how often a patient
12 experiences various symptoms, including accidental
13 bowel leakage of gas, soiling or seepage, leakage of
14 liquid stool, and leakage of solid stool.

15 The fifth question assesses the general
16 effect on the lifestyle of incontinence. Each answer
17 had a unique point system assigned to it, and the
18 total is obtained by taking the highest score from the
19 top four and adding the score from question number
20 five.

21 So for this patient, the highest score is
22 85 in question number three, and three would be added

1 to it to obtain a score of 88, which would enroll this
2 patient in the study.

3 You have seen this slide as well. This is
4 the breakdown of what the numbers correlate to as far
5 as the definition. I just wanted to also point out
6 that 25 patients pre-implant were in this category,
7 and 35 patients were in this category, and 38 patients
8 were incontinent to liquids or solids greater than
9 daily.

10 Also of note, 23 patients had a maximum
11 score of 120. The second end-points as mentioned
12 included anal rectal manometry, mean resting pressure
13 pre-implant versus 12 months.

14 And fecal incontinence quality of life
15 questionnaire, and the health status questionnaire,
16 and the adverse device effects.

17 Following implantation, this was the
18 follow-up schedule for the patients. At 6 to 8 weeks,
19 the patients were activated; and at 6 months, FISS
20 score, and the quality of life questionnaire and
21 manometry were performed.

22 And at 12 months, those same studies were

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1 performed, as well as the health status questionnaire
2 and/or anal ultrasound. With respect to results
3 effectiveness, Dr. Wong presented these results.

4 The pre-implant, the average FISS score
5 was 106; and at 6 months, 50; and at 12 months, 49.
6 The average drop was 57 points, and just for your
7 reminder, 49 corresponds to seepage or soiling daily.

8 This slide depicts the breakdown of FISS
9 scores at 12 months for 67 patients, with scores at
10 that time, and if you will notice the other slide was
11 61, and this also includes six stoma patients, which
12 made the 12 months time period, and had scores at that
13 point.

14 Basically what this shows is that about 70
15 percent of patients had incontinence to liquid or
16 solid on a less than monthly basis at 12 months, for
17 those that did meet the 12 month criteria.

18 This is just a graph depicting the
19 breakdown of FISS scores, both pre-implant in green,
20 and post-implant at 12 months in those patients that
21 did make the 12 months.

22 And 67 patients did have 12 month follow-

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1 ups, and six of these started with stomas, and
2 therefore, they had 12 month scores on the FISS
3 system, but no pre-implant score to compare to.

4 Of the remaining 61 patients, 52 had a 24
5 point reduction at 12 months, and this corresponds for
6 variable patients, and this corresponds to 85.2
7 percent.

8 There was a FISS significant difference
9 between 12 month scores for females, versus males, and
10 no other differences between other sub-groups were
11 noted.

12 An adjusted ITT was presented by the
13 sponsor earlier, and these are the breakdown of those
14 numbers. The FDA's ITTs differ slightly, and we have
15 added the three patients lost to follow-up, and the
16 six with no 12 month follow-up in the failure
17 category.

18 And based on this, our success rate is 59
19 out of 115, with all 115 being accounted for, with a
20 success rate of 51.3 percent. This slide goes back to
21 a question that Dr. Woods asked before. This is just
22 some raw data that I had compiled.

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1 In the intent to treat analysis, you had
2 asked about the three sub-categories and how well each
3 patient in that category did, and this is the rough
4 breakdown for patients with pre-implant scores of 97
5 or below, and 17 out of 28, or 61 percent met the
6 success criteria.

7 And for the patients in the category of 97
8 to 108, 23 out of 49, or 47 percent. And for 109 to
9 120, 50 percent. Now, this category also includes the
10 14 stoma patients which were assigned a pre-implant
11 score of 106.

12 DR. TALAMINI: Is there any statistical
13 data?

14 DR. YUSTEIN: I don't have the statistical
15 analysis on that, no, I'm sorry. So, I can't answer
16 either way. With respect to secondary end-points, Dr.
17 Wong already showed this. The statistical significant
18 change in manometry from pre-implant to 12 months.

19 The fecal incontinence quality of life
20 questionnaire, which he also discussed, I presented
21 the data in a little bit form. The patients, when
22 they answered these questions, answered such things as

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1 most of the time, some of the time, strongly agree,
2 and somewhat agree, and I chose to take only the
3 patients that responded most of the time, or strongly
4 agree, and compare pre-implant and 12 months.

5 Again, as you recall, this is at 113 and
6 this is at 67 patients as was discussed earlier. So,
7 for example, 89 percent of the patients pre-implant,
8 felt that they had no control of their bowels most of
9 the time; whereas, 9 percent of the patients who had
10 12 months, said the same thing.

11 The other secondary end-point was the
12 health status questionnaire. As was mentioned before,
13 the average, the 457 average, pre-implant, and 555
14 post-implant, with a score of 800, represent an ideal
15 functioning.

16 DR. TALAMINI: Can I just ask a question
17 about the slide before that one. I'm sorry, but I
18 didn't catch the end numbers of 113 and 67, but they
19 are there.

20 DR. WOODS: Did you happen to break it
21 down and look at the 67 at 12 months, and look at
22 their answers to the questions, pre-implant?

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1 DR. YUSTEIN: No, I don't have that. This
2 is the eight scales for the HSQ, showing that 6 out of
3 the 8 significantly improved. The other two which did
4 not, there were limitations, emotional problems, and
5 bodily pain did show some improvement, however.

6 With respect to safety, much of this was
7 gone over before. A total of 456 adverse events were
8 reported, and 395 were believed to be either device
9 related or potentially device related, which account
10 for 87 percent of the total adverse events.

11 And 67 or 17 percent required no
12 intervention; and 142 or 36 percent required surgical
13 intervention, including 81 surgical revisions in 56
14 patients.

15 This chart depicts the common adverse
16 events which affected greater than 10 percent of the
17 patients. As you can see, things to note are
18 infection as we have discussed, and 36 patients
19 experiencing 41 events, and 33 of which required
20 surgery.

21 Erosion occurred in 24 patients, and a
22 total of 28 events, and 27 of which required surgery.

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1 The alterations in bowel habits all were approximately
2 20 percent changes, and fecal incontinence,
3 constipation, and compaction.

4 I wanted to spend just a minute on
5 revisions. A definition of a revision was a
6 repositioning, removing, and/or replacing one or more
7 device components subsequent to initial implantation,
8 and as was mentioned before, the overall rate was 50
9 percent, or 56 out of 112 implanted.

10 And Dr. Congilosi already described the
11 other data. The indications for revision, the two
12 most common being infection, which required 30
13 procedures in 28 patients; and erosion, which required
14 27 revisions in 24 patients.

15 Also, it is important to note that 13 of
16 these were overlapping, and in 13 patients, infection
17 and erosion combined were the indication for revision.

18 As far as infection and revision, as I
19 already stated, 28 patients, or 25 percent, required
20 30 revision procedures for infectious complication,
21 and a fair number of these occurred within 30 days or
22 60 days after implantation.

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1 No significant differences in rates of
2 infection were noted among the sites, gender, or
3 length of operation. With respect to erosions and
4 revision, 27 out of the 28 events required surgical
5 revision to correct. And as has already been pointed
6 out, the most common erosions were cuff to rectum and
7 perineum, and in pump erosion, and in tubing
8 accounting for less.

9 Explanations. A total of 34 patients, or
10 30 percent of those implanted underwent 38 total
11 device explanations, and that includes four patients
12 who underwent explanation, followed by reimplantation,
13 and a second explanation.

14 The mean time to explanation was 4.2
15 months, and as noted with the revisions, a large
16 majority were due to either infection, erosion, or a
17 combination of the two.

18 The other three reasons for explanation
19 was, one, a patient with recurrent incontinence, one
20 patient with pain, and one patient that developed an
21 anal urethral communication.

22 No unanticipated adverse events occurred

1 during the course of the study, and no deaths occurred
2 during the course of the study. In summary, fecal
3 incontinence is a common health issue which can have
4 a major impact on a patient's quality of life.

5 There are several treatment alternatives,
6 both surgical and non-surgical, each with its own risk
7 benefit profile. The Acticon Neosphincter has been
8 studied under two IDEs in the United States, involving
9 approximately 135 patients.

10 When patients are considered in an intent
11 to treat analysis, 51.3 had a clinically significant
12 -- I'm sorry, 51.3 percent had a clinically
13 significant improvement in fecal incontinence one year
14 after implantation as defined by the FISS score.

15 And 50 percent of the patients implanted
16 required at least one surgical revision within one
17 year, and approximately 30 percent of patients
18 required total device explantation within one year.

19 The majority of these revisions and
20 explanations were as a result of infection and/or
21 erosions. Thank you for your attention, and that's
22 all I have.

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1 CHAIRMAN KALLOO: Are there any questions
2 or any clarifications from the panel to the FDA? If
3 not, thank you very much. Are the sponsors prepared
4 to provide some of the data before we break for lunch?

5 DR. CONGILOSI: Susan Congilosi again
6 speaking. I can give one clarification on the
7 questions regarding explanations. Again, there were
8 38 explants, and 11 were reimplanted, and 7 remain
9 candidates. That means that there are 27 patients
10 that are permanent explants.

11 These are detailed in long histories in
12 our notes, but in general nine of those went permanent
13 stomas, typically after 1 or 2 attempts at revision,
14 and then a decision to go to a permanent stoma.

15 Four had preexisting stomas. That leaves
16 14 patients who were judged as not candidates, or will
17 not go on to another implant. The various reasons
18 included a judgment that they were at an increased
19 risk of infection because they had had two times that
20 implant and both had eroded.

21 Technical reasons that they were judged by
22 the surgeons that they were not able to attempt

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1 another implant, and two patients were decided that
2 they were eligible, but that they did not want to
3 undergo this further treatment.

4 Development of new medical conditions,
5 such as cancer, cardiac disease, patient choice, which
6 also came out with ones with preexisting stoma, and
7 three patients who you would probably categorize as
8 poor patient selection for their general health, and
9 not mental status.

10 MS. NEWMAN: Which were men versus women?
11 You said that the majority of your patient population
12 were women, it is interesting that you show the men.
13 So how many were men?

14 DR. CONGILOSI: We can find that out. It
15 is going to be a variety.

16 CHAIRMAN KALLOO: Do you have information
17 on the co-morbid conditions?

18 DR. CONGILOSI: Co-morbid conditions? I
19 don't have that either.

20 MS. BEAURLINE: Analyses of risk factors?

21 DR. CONGILOSI: No, other co-morbid
22 conditions pre-operatively.

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1 DR. SMITH: One question. When you have
2 the --

3 CHAIRMAN KALLOO: Let her see if she can
4 finish this, and then we will ask further questions.
5 Are you ready to respond?

6 DR. CONGILOSI: The question about their
7 status, the best way at this point that we can tell
8 you is their FISS score preoperatively to the last one
9 obtained before explanation, and in those the number
10 didn't make it to the 12 month score.

11 But of those that did, only one was worse.
12 So in general they hadn't improved, and then it went
13 on possibly to infection and explanation, and that is
14 the best that I can give you on that, because patients
15 are not studied after explanation with that
16 questionnaire.

17 CHAIRMAN KALLOO: Question?

18 DR. SMITH: Yes. When you had an erosion,
19 could you not put the cuff in transabdominally at a
20 higher position?

21 DR. CONGILOSI: That is not recommended at
22 the time of the use of this device. It has in

1 selected cases in the HDE been placed above the
2 levators, and that may be an option for the more
3 difficult patients, where they are placed in a prone
4 position, and the incision is done differently, and it
5 is done above the levator muscle.

6 DR. SMITH: Thank you.

7 DR. KOLTUN: Tell me if I am wrong, but
8 aren't there different sized balloons or reservoirs
9 that provide different degrees of pressure?

10 DR. CONGILOSI: Yes, but that was not
11 found to be significant with risk of erosion or
12 infection.

13 DR. KOLTUN: It was not?

14 DR. CONGILOSI: That was one of the
15 categories that they looked at with both infection and
16 erosion, and it was not significant.

17 DR. KOLTUN: So what makes you decide as
18 to what sized reservoir or balloon that you use?

19 DR. CONGILOSI: In general, if we are
20 placing a larger cuff, we would place the larger
21 reservoir.

22 DR. KOLTUN: But that does not relate to

1 erosion at all?

2 DR. CONGILOSI: Right.

3 DR. KOLTUN: Does it relate to changes in
4 the anorectal manometry pressures?

5 DR. CONGILOSI: I don't know if we
6 specifically looked at that.

7 DR. WOODS: Would it be an absolute
8 recommendation that a woman who has one of these
9 placed and who becomes pregnant be delivered by C-
10 Section?

11 DR. CONGILOSI: In my mind, yes; just as
12 I would advise a woman who has had an overlapping
13 sphincteroplasty to seriously consider a C-Section
14 rather than run the risk of reinjury, yes.

15 And we don't know that someone could not
16 choose to do that, but my recommendation would be a C-
17 Section.

18 DR. CONGILOSI: Okay. If there are no
19 further questions, we will break for 45 minutes for
20 lunch, and return at 1:15. Thank you.

21 (Whereupon, at 12:27 p.m., a luncheon
22 recess was taken.)

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

(1:17 p.m.)

1
2
3 CHAIRMAN KALLOO: I would like to begin by
4 asking the sponsor if they have managed to put
5 together a response to the questions that were still
6 outstanding? Again, please identify yourself by your
7 name and affiliation.

8 MR. GETLIN: Yes. My name is Larry
9 Getlin, and I am with American Medical Systems. We
10 are still putting together a couple of slides. So we
11 need a couple of more minutes, and if there is other
12 business that needs to move forward, we do have some
13 answers to the questions that you have raised.

14 CHAIRMAN KALLOO: About how much time do
15 you need?

16 MR. GETLIN: Larry Getlin again. They are
17 just finishing up making slides. I would imagine
18 about 5 minutes or so.

19 CHAIRMAN KALLOO: What I will do then is
20 have Dr. Talamini make some general comments, and then
21 we will go into the specifics of each of the
22 questions. Dr. Talamini.

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1 DR. TALAMINI: Well, I was asked to be a
2 lead panel reviewer for this device, and I don't have
3 prepared slides, but I do have a couple of thoughts,
4 and I think they are thoughts that would be shared
5 certainly by the surgeons, and probably the
6 gastroenterologists in the room as well.

7 This certainly is a field -- the avoidance
8 of ostomies and the continence issues is a field of
9 great interest to surgeons for many, many years, and
10 the field of trying to come up with an alternative to
11 a stoma, or a continent stoma, has been an endeavor
12 that surgeons have been in the forefront really for
13 many, many years now.

14 But unfortunately as we all know, it has
15 been a very stubborn problem, and medical history is
16 littered with attempts to succeed here that did not
17 succeed.

18 It is probably going to become worse in
19 the next number of years as the baby boom generation
20 ages, and the women in that generation in particular
21 begin to have their child birth related continence
22 problems.

1 It is estimated by most people that the
2 number of women with these problems is going to
3 continue to grow. So it is certainly an important
4 topic, and I would congratulate the company and the
5 panel members this morning really for bringing up most
6 of the issues that I think we need to deal with this
7 afternoon as we discuss this particular product.

8 The one additional comment that I would
9 make is that as surgeons, when we talk about
10 procedures, we always talk about risk benefit ratio,
11 and that question has already come up this morning.

12 And when the alternatives, such as
13 incontinence, or stoma, are as extreme as they are,
14 that certainly makes you think a little bit
15 differently about what the risk issues are.

16 And I think it is going to be in that
17 framework that we are going to need to discuss the
18 relative merits of the application today. It looks as
19 if our team might be ready.

20 CHAIRMAN KALLOO: Okay. Mr. Getlin, are
21 you ready?

22 DR. CONGILOSI: Okay. Susan Congilosi.

1 I will address some previous questions. One was a
2 question about patient dissatisfaction as a possible
3 sole reason for explanation. It was not. It was
4 patient dissatisfaction listed as a reason for four
5 patients with revisions.

6 They all had other reasons for the
7 revision. There is no patient who had an explanation
8 solely for patient dissatisfaction. The other
9 question was regarding co-morbidities, and I guess
10 there were variations of that question with regard to
11 co-morbidities, and patients who had infection or
12 erosion, and also success.

13 When we go through those who were
14 explanted, in general, you can find that they all had
15 infection erosion at some point. The co-morbidities
16 were looked at in patients who had infection and
17 erosion.

18 So there is only one patient explanted who
19 did not fall into this study as far as knowing what
20 their co-morbidities are, and that is a patient with
21 other medical problems.

22 So the co-morbidities, if you want me to

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1 list them off, are these 47, but in general it does
2 address the issue of age, gender, previous
3 pregnancies, previous vaginal deliveries,
4 musculoskeletal condition; previous conditions, such
5 as GU condition, diabetes, allergies, respiratory
6 conditions, CV condition, neurological, psychiatric
7 conditions.

8 And previous surgeries, such as rectal
9 prolapse sphincteroplasty, circulus, transposition,
10 gluteus transposition, post-anal repair, pelvic
11 radiation, Gyn-Surgery.

12 The only significant factor for co-
13 morbidity again was diabetes. For factors after
14 implantation, preoperative stay, volume in the cuff,
15 the preoperative antibiotics used or not used, and the
16 preoperative bowel prep.

17 And whether they had a stoma. As you
18 know, in one case that did fall out. The surgical
19 approach, and whether we did a lateral incision or an
20 anterior incision.

21 Anal canal length, and anal canal
22 circumference; cuff width, cuff length, and none of

1 these factors were significant.

2 CHAIRMAN KALLOO: Thank you.

3 MR. WORRELL: David Worrell, AMS. A
4 couple of other points of clarification. The question
5 was asked what was the gender breakdown in patients
6 who were explanted.

7 Out of 98 activated patients, there were
8 24 explants, and 20 of the patients were female. That
9 is 83 percent of the 98. Four of the patients were
10 males, 17 percent, and so 75 percent of the patients
11 in the study were female.

12 And then a little more information. I
13 direct you to your panel packs, and to follow up on
14 risk benefit. Another way that everyone on the panel
15 I am sure is familiar with analyzing risk benefit is
16 life table analysis.

17 And on pages 54 and 55 of your panel
18 packs, we have life table analysis. At 12 months the
19 probability of remaining revision free with the device
20 is 73-1/2 percent.

21 CHAIRMAN KALLOO: Which section is that?

22 MR. WORRELL: Section 3, clinical summary,

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1 pages 54 and 55. Table 20, there is a figure in a
2 table, and quickly at one year, your probability of
3 remaining revision free if treated with the device is
4 73-1/2 percent. That is Table 20 on page 54.

5 Table 21 on page 55 addresses explants,
6 and the probability of remaining explant free at 12
7 months is 80 percent.

8 DR. TALAMINI: That is based on 98
9 patients? It says that at the top of page 54, is that
10 correct?

11 MR. WORRELL: That is correct.

12 DR. TALAMINI: Which 98 is that, because
13 that sounds like a different number from either the
14 150 that we started with, or the --

15 MR. WORRELL: Those would be patients that
16 we have activation times on, and either an explant, or
17 a revision time on.

18 CHAIRMAN KALLOO: Thank you. We will now
19 begin with the panel discussion portion of the
20 meeting. Although this portion of the meeting is open
21 to public observation, public attendees may not
22 participate, except at the specific request of the

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1 panel.

2 Do any of the panel members have any
3 general comments or questions before we proceed to the
4 panel discussion points?

5 DR. STEINBACH: I do, and I think it shows
6 up several ways. This is understandably not a
7 randomized control double-blind placebo test. I think
8 that anyone would have a hard time getting through an
9 IRB, saying that we are going to do patients who have
10 failed preliminary alternative studies, and we want to
11 just watch some of them for a year, and others we will
12 give this treatment to.

13 I suspect that this option would not be
14 approved by institutional review boards. So as a
15 result, things like intention to treat, we don't have
16 a real comparison. And the one where it is most
17 important is quality of life assessments.

18 This measure has a very strong placebo
19 effect, and so we don't know what the quality of life
20 improvement would be in, for example, the stoma group,
21 or the people who had an explant because they were not
22 followed.

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1 And whether they said, okay, I gave it my
2 best shot, and now I feel better about having to wear
3 pads. So there is no question that these people have
4 a better quality of life.

5 What I don't think we have a handle on,
6 because it is not part of the study with a real
7 control group, what another group of patients not
8 given this treatment, how their quality of life would
9 improve.

10 I think in San Diego that we are well
11 aware of the fact that you can play professional
12 football with a stoma, and so I think with -- and
13 everyone here is aware that stomas create problems.

14 But with proper management the patient
15 would -- I think many would report a quality of life
16 and just pulling studies out of the literature are not
17 fair comparisons for this group.

18 And so we really don't know how much the
19 quality of life was improved by this procedure. And
20 I think the other point is that in two of the
21 literature cited they suggested a control group would
22 be dynamic -- recilioplasmy, if I am pronouncing that

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1 right.

2 This, however, is another experimental
3 procedure, and the FDA rules say that we can't use
4 this as a comparison. So that we are going to have to
5 let the sponsor do this test. We can't require that
6 it be part of this PMA.

7 CHAIRMAN KALLOO: Any comments about that,
8 the issue of the quality of life?

9 DR. KOLTUN: I have a comment that relates
10 to that a little bit. There seems to have been a
11 group of patients who went through both this
12 procedure, and then a stoma, right? That would have
13 been an interesting group of patients to evaluate from
14 that, at least the QOL standpoint.

15 But it would have been interesting. I
16 know that there are studies in the literature that
17 talk about how patients frequently after they get the
18 stoma have a very different opinion of it having now
19 had it.

20 So the issue of quality of life is a real
21 one, because frequently the perception preoperatively
22 of what the stoma is like is not accurate enough, and

1 in fact after the fact patients are surprised by their
2 ability to function in that fashion.

3 I am not sure at what point in this forum
4 or this meeting that we should offer maybe the ability
5 to ask a question of the person who presented the
6 layperson who had the sphincter.

7 But what was her educational process, and
8 what was her understanding of what stomas were about,
9 and the experience that she had with regards to
10 knowing really what a stoma was like.

11 In other words, what did you think about
12 a stoma, and what had been taught you about a stoma,
13 and what experiences have you had to absolutely delete
14 it from your mind.

15 MS. LOITZ: It wasn't deleted from my mind
16 at all.

17 CHAIRMAN KALLOO: Madam, if I could ask
18 you to come to the microphone, and again please just
19 repeat your name.

20 MS. LOITZ: Nancy Loitz. The option of a
21 stoma was not eliminated as an option for me at all,
22 and my life was bad enough in dealing with this

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1 problem, and it was bad enough that I would have gone
2 in that direction, I think, and that it would be there
3 today had I not gotten an implant and had it been a
4 success.

5 DR. KOLTUN: Wouldn't you feel that right
6 now the impression that you have is that --

7 CHAIRMAN KALLOO: Can you speak into the
8 microphone, please.well,

9 DR. KOLTUN: My impression would be that
10 you would be exercising now, and you would be dynamic,
11 and you would be jogging, and you would be doing all
12 those things. You would be a person much like you are
13 now, even with a stoma.

14 MS. LOITZ: I think that is probably true,
15 but I would not want to have only that as my option,
16 because this option has worked so well, and this
17 option is completely under my skin. It functions as
18 normally as I functioned, or any of you function.

19 So while I don't think I would have been
20 embarrassed by that option, or would have said, no, I
21 won't do that because it is a stoma. I am not that
22 type of person.

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1 I don't want it to be my only option if
2 there is another option that could also be successful.
3 I want to consider both of them.

4 DR. KOLTUN: I think from my standpoint,
5 getting back to the more professional aspect of this,
6 is that the issue in my mind is do no harm. And I
7 would like to see a more thorough analysis of the
8 failures.

9 In other words, I want to know that in
10 fact those patients were as bad as they could have
11 been, and in fact were not harmed by a failed attempt
12 at this option; though we see a very healthy, dynamic,
13 and great success in front of us. But I want to know
14 that the people who are on the other side of the story
15 are not worse off.

16 CHAIRMAN KALLOO: Thank you, Ms. Loitz.

17 MS. NEWMAN: This is not so much maybe
18 here, but in the whole process. I have been coming
19 here often, and sometimes we include European data,
20 and last year they had thousands, and thousands, and
21 thousands of people that had that procedure.

22 And so why aren't we including that? And

1 then we go to panel where all you do it on is European
2 data. And I think that this goes along with what we
3 are saying, is that if there is more data in the world
4 on this -- and again I am bias, because I have had --
5 done something with the urinary sphincter device, and
6 we put those in every week.

7 And why isn't that stuff included? Is it
8 because the FDA doesn't ask for it, or the company
9 doesn't want you to? There is more people than just
10 in the U.S. So I think we can learn a lot whenever we
11 understand the whole history of these kinds of things.

12 And I don't understand why because there
13 is a couple of meetings, and we go back and forth over
14 this.

15 CHAIRMAN KALLOO: That is something that
16 I myself have personally asked about -- and I guess
17 that it is not available as best as I --

18 DR. STEINBACH: And as a statistician, I
19 would say that the Europeans are not following your
20 protocol in general. And so if you are setting up a
21 controlled trial, you want control of what is done to
22 the patients to be more than just -- well, I think

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1 that is the reason.

2 CHAIRMAN KALLOO: A under reporting of
3 complications and adverse events would be issues that
4 would make that data very questionable as well. Any
5 other comments by any of the other panel members?

6 DR. SMITH: One question. Are we going to
7 discuss anything about the labeling?

8 CHAIRMAN KALLOO: Yes. Yes.

9 DR. SMITH: We just have not come to that
10 yet?

11 CHAIRMAN KALLOO: Yes. That is going to
12 be in the group of questions that will be following
13 that we will be discussing. So now I guess we will go
14 to the questions to the panel.

15 And what I will do is ask each of you to
16 comment on this question, and then Dr. Talamini will
17 summarize the panel comments at the end of the
18 discussion on each question.

19 And again you can ask for clarifications
20 from the sponsor and from the FDA. Do you want to put
21 up the first question, please.

22 A total of 395 device related or

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1 potentially device related adverse effects events were
2 reported among implanted patients, including 43 events
3 which required surgical intervention.

4 Half of those implanted required at least
5 one surgical revision, and 30 percent underwent
6 explanation of the device. A significant portion of
7 these surgical interventions were a result of
8 infection and/or erosion.

9 Please discuss the safety profiles of this
10 device overall, as well as in relation to other
11 treatments of fecal incontinence. And if Dr. Smith
12 could please comment, and we will go around the table.

13 DR. SMITH: I don't think that this device
14 is the device where you are simply putting in a
15 sphincter and that is going to solve all the patient's
16 problems.

17 And this is a device that is associated
18 with recognizable risks, and again I think the
19 important thing is to recognize the benefit that these
20 patients can have from the device, as opposed to
21 whether that would make it worthwhile for them.

22 So, I am not particularly concerned about

1 the higher incidents of complications. I would be
2 concerned if the patients were not aware of this risk
3 before they had the procedure done.

4 If they are fully aware and they are
5 cognizant of all the risks that are associated with
6 the procedure, then I think that this is something
7 that is acceptable to be done.

8 And also the other factor is that in this
9 group, again this is cohorts of patients and who are
10 very small in each group. And we have found in the
11 neurological devices that the better that you get at
12 it, and the more devices that you put in, the lower
13 your complication rate. And I think that the
14 statistics will improve over the course of time.

15 CHAIRMAN KALLOO: Dr. Woods.

16 DR. WOODS: I agree with what Dr. Smith
17 has said with respect to the complication rate. I
18 think that is something that would not naturally be
19 unexpected working in this area.

20 I also agree very strongly with what Dr.
21 Kolten echoed earlier about the options that patients
22 have with an ostomy, and the fact that there is often

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1 a psychological barrier to an ostomy that is probably
2 the most difficult thing to overcome for patients.

3 And as was pointed out by the patient
4 herself, knowing that she had another option to
5 explore I think is a very important one for patients
6 in making the right choice for that individual.

7 So I think it is a good think to have
8 options. I think it is very important that a patient
9 understand at the outset what those two options are
10 and what the complication rate is with this device,
11 and that there is at least a 50 percent chance that
12 they are going to have to have another operation if
13 this device is used.

14 But if they understand that at the outset
15 and make that choice, I am comfortable with the
16 complication rate.

17 CHAIRMAN KALLOO: Dr. Steinbach.

18 DR. STEINBACH: I agree with what has been
19 said that this high rate is acceptable if the patients
20 are prepared for the consequences emotionally, if no
21 other way, and that they are -- that this is being
22 restricted to a use of patients who are at risk for

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1 complications.

2 DR. KOLTUN: I don't have much to add.
3 Simply, I think that the degree or number of
4 infections is such to be expected to a large degree
5 based upon the anatomic considerations.

6 That is really about it. I think the
7 issue once again becomes one of trying to minimize
8 those complications, and I think it would be up to the
9 clinician largely to recognize the appropriateness of
10 this kind of operation in the patients that they are
11 dealing with.

12 There are clearly going to be risk factors
13 that worsen the possibility of complication, and other
14 risk factors that may in fact get so close as to be a
15 contraindication.

16 MS. NEWMAN: I agree. I don't have
17 anything more to say on this.

18 MR. BANIK: I also agree

19 DR. EPSTEIN: I think this brings up
20 several points, and one is exactly who is going to be
21 implanting this device. It seems like there is a
22 learning curve here to avoid some of the

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1 complications, particularly the cuff erosion into the
2 rectum, or vagina.

3 And a discussion of the fragile perineum
4 came up a number of times as to maybe being a little
5 bit more careful in selecting the patients who are
6 going to undergo the procedure.

7 And the question that comes up in my mind
8 in relation to this is in how are the surgeons going
9 to be trained, and what kind of requirements are going
10 to be there.

11 Is it going to be done just in selected
12 centers where these things can be monitored and
13 observed, and the outcomes further defined? Clearly,
14 there is a role for a specific antibiotic regimen, and
15 all those issues I think need to be addressed to
16 improve what was learned in this study, in terms of
17 the safety profile.

18 CHAIRMAN KALLOO: Dr. Gellens.

19 DR. GELLENS: Well, I am like the rest of
20 the panel. I am very concerned with this rate of
21 complications to tell you the truth, especially in a
22 small number of patients, and in this well-controlled

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1 and supervised trial.

2 My concern is that when this device is
3 released the number of patients that it will be used
4 on will obviously be much greater, and the number of
5 co-morbid conditions that the patients have will
6 likely become much greater.

7 Someone has already mentioned the fact
8 that the population is aging, and as you start having
9 older patients to deal with, and in which many more
10 complications, including diabetes as was mentioned,
11 and hypertension, and vascular disease and what not,
12 even though we saw no deaths in this study, I think it
13 is quite possible that with the current level of
14 understanding with this device that it could be a
15 significant risk to the population.

16 I think we have already seen that advances
17 have already been made during the study here as far as
18 antibiotic choice, and have improved the complication
19 rates significantly. And I think it needs to be
20 evaluated further before it is released on the gender
21 population basically.

22 DR. MCCLANE: I think the complication

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1 rate is high, and again I think you really need to
2 look at who is going to do this operation. It
3 probably needs to be done in certain centers at least
4 initially, or if you are not going to do it in certain
5 centers, keep it from those centers coming out to the
6 hospitals to train some of the physicians in doing
7 this operation.

8 I know that once it is in the public that
9 it is hard to restrict surgeons from doing it, and it
10 is hard to know really whether this is a high
11 complication rate, because there is nothing really to
12 compare this particular procedure to.

13 I mean, you can take other operations, but
14 then in those patients you don't have an opened bowel,
15 or even colonic resections which they are referred to
16 in the packet, the compared complication rate, and to
17 the bowel resections.

18 But then again in those procedures, you
19 don't have a mesh. And even anorectal operations
20 generally don't put mesh in or foreign bodies. So
21 this is a high complication rate, but it is hard to
22 compare it to anything because nothing else is really

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1 similar to this.

2 So it may be a mesh in a colostomy, or
3 colostomy hernias, but again I don't know what the
4 data is, and I know that they have high complication
5 rates for that procedure.

6 So it is going to be hard to decrease the
7 infection rate and the complication rate, because it
8 is a dirty field, and you are putting in foreign
9 material.

10 But then the idea is that you are doing a
11 lot of good for the patient, and as long as you tell
12 the patient that they are going to have a high rate of
13 a complication, it is probably worth pursuing.

14 CHAIRMAN KALLOO: Okay. Dr. Talamini,
15 would you summarize the panel comments.

16 DR. TALAMINI: Mr. Chairman, I think the
17 opinion of the panel as a whole is that they recognize
18 that this study reflects a high complication rate, but
19 with one vocal exception, it appears that the panel is
20 willing to accept those high complications relative to
21 the perceived high level of benefit to many of these
22 patients.

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1 The other summary point would be concern
2 about the indications, which I think may well speak to
3 labeling issues that we will get to discuss a little
4 bit later, and a further summary point would be a
5 consideration for who puts these devices in, and how
6 they are trained, and where they are put in.

7 CHAIRMAN KALLOO: Thank you. Question 2.
8 Currently, there is no gold standard for the measure
9 of fecal incontinence. The fecal incontinence scoring
10 system, FISS, was developed by the American Medical
11 Systems, Incorporated, and used as a primary end-point
12 in this study.

13 Patients were considered to have a
14 successful clinical response if scores dropped by 24
15 or more points 12 months after device implantation.
16 Please discuss the clinical significance of the 24
17 point score reduction on the scale. Dr. Smith.

18 DR. SMITH: Well, I think that is quite a
19 dramatic improvement in the clinical condition, and I
20 think it is an effective way of assessing them.

21 DR. WOODS: I tend to agree. I had the
22 same question myself as I read the protocol, but when

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1 you look at what a 24 point reduction means, going
2 from daily incontinence, and even to weekly
3 incontinence for some patients, I think that is still
4 a fairly dramatic improvement for the patient who is
5 incontinence daily.

6 As has already been mentioned, this is a
7 pretty devastating problem for the patients who suffer
8 from this, and so I would think that a patient would
9 be very, very pleased to be incontinent weekly versus
10 daily.

11 And many of the patients I think improved
12 even more than that, having incontinence less than on
13 a weekly basis with the device. So I think it is a
14 reasonable assessment tool.

15 DR. STEINBACH: I forwarded a question to
16 the sponsor, and it was the fecal incontinence scoring
17 system is new and we are not sure that it is a nice,
18 normally distributed, random variable.

19 And a hundred patients is not enough to
20 establish that. However, we are not left in the
21 lurch, because there is non-parametric statistics that
22 as long as we can say that a fecal incontinence score

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1 of 60 is not as bad as a fecal incontinence score of
2 70, that it correctly orders the problem.

3 Then an appropriate test would be the
4 Wilcoxon ranking test, and the sponsor did it for the
5 67 patients that still had it implanted, and found a
6 very significant P value.

7 I did it and included the stoma patients,
8 and their value was a mean of 106 before, and if I
9 transpose that 106 to the other end of the column, and
10 looked at the 114 patients, because three weren't
11 transplanted, it was still highly significant.

12 There were only 25 percent of the group
13 that was worse off with this. So there is concern
14 that the T test and F test that are used throughout
15 the study are appropriate, but in the event that if a
16 less restrictive test was used, this difference still
17 is significant.

18 CHAIRMAN KALLOO: Dr. Koltun.

19 DR. KOLTUN: I think the scoring system is
20 intuitively correct, and the difference that they
21 found was from a clinical perspective, and from an
22 intuitiveness perspective, something that was real and

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1 meaningful.

2 I think, however, that my concern in that
3 regard is that again what about the patients who
4 failed? Were they made worse? I don't want to sort
5 of belabor the point, but we have looked at a study
6 that has about a 50 percent failure rate, and we have
7 been favorably impressed by the successes, or the
8 quality of the improvement in the fecal continence
9 were deemed successes.

10 So that begs the question a little bit in
11 the context of what happened to the patients who were
12 not successfully treated with this device. So I think
13 that the system that they instituted, the fecal
14 incontinence scoring system, I have no problems with.

15 But I would like to have seen that data
16 similarly applied in evaluating the failures.

17 CHAIRMAN KALLOO: Ms. Newman.

18 MS. NEWMAN: I agree with that, because
19 then I want them to put that information in labeling
20 for informed consent. I would have liked to have
21 known, well, what if I fail, and what would happen, so
22 that the individual patient can make the decision.

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1 If my quality of life or my symptomatology
2 is so severe that I can't live with this, there is an
3 "X" percentage of people that fail with this, and then
4 what would happen, and I just think that should be
5 part of this, because I really believe in a hundred
6 percent informed consent.

7 CHAIRMAN KALLOO: Mr. Banik.

8 MR. BANIK: I felt that the model was a
9 good model. I do agree that the model probably needs
10 some more validation as we discussed earlier. But I
11 do think it was significant that the 24 point movement
12 on the scale is significant.

13 Many of the patients I think moved much
14 more than 24 points, and that movement from an
15 individual perspective is quite measurable and easily
16 determinable. So I felt comfortable with the model
17 being used.

18 Relative to the patients that were not --
19 that there was no data collected on, I share the same
20 concern, and would like to see some data so that
21 patients would know, well, what happens if the
22 procedure fails.

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1 I think we concentrated a lot, or the
2 company concentrated a lot on the outcome of a
3 positive result. I think there is data that can be
4 obtained from the patient population that can be
5 helpful in understanding the risk and benefits of
6 those that the product had to be explanted from.

7 CHAIRMAN KALLOO: Dr. Epstein.

8 DR. EPSTEIN: I think more telling than
9 the 24 was the issue of the patients wearing pads and
10 diapers, and just looking here, the comment that in
11 pre-implant that 88 percent were using pads, and 52
12 percent, and that was 88 percent per-implant, to 52
13 percent at 12 months.

14 And that the use of diapers fell from 51
15 percent to 15 percent. And there was also improvement
16 in the quality of life from 30 percent enjoying their
17 life less, as compared to 81 percent prior.

18 So I think to me that has more clinical
19 significance than the scale itself, and I think that
20 the biggest thing is the use of the diapers, and the
21 rate of diaper use going down.

22 MS. NEWMAN: If I could comment on that.

1 The technology of these products have changed so much
2 in the last 10 years that that does not mean a lot,
3 because there are four different sizes of absorbencies
4 in pads.

5 And the wrap around adult briefs, which
6 are diapers, are not even for incontinence, where you
7 have much more fluid leakage, are really only used in
8 the very frail, elderly, bed bound. So the technology
9 is used.

10 You are going from an undergarment, to a
11 perennial pad, to a slide pad, and so which of those
12 slides are we talking about?

13 If you are talking about undergarments,
14 that is not much of a difference change in absorbency.
15 So I think that -- well, I am not sure what that
16 really means, as far as that change, because that is
17 a big change. You know, which pad.

18 DR. GELLENS: I don't have any problem
19 with this scoring system. I thought that it was
20 informative and very descriptive, and told a pretty
21 good story of what was going on with the patients.

22 It is unfortunate that it has not been

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1 validated in any other setting, but I think for
2 purposes of this study that it was informative and
3 that it was okay.

4 DR. MCCLANE: I am also a little
5 uncomfortable with the fact that there is not that
6 gold standard for fecal incontinence, and the scoring
7 system was developed by the manufacturer.

8 However, I do think that there was a
9 significant difference in these patients pre-and-post
10 implant, and when you see a drop of 24, and it is much
11 more than that. So even though you don't have a
12 validated system, I do think there was a real
13 improvement in patients based on this system.

14 CHAIRMAN KALLOO: Dr. Talamini, will you
15 summarize, please.

16 DR. TALAMINI: Mr. Chairman, I think the
17 consensus of the committee is that the 24 point
18 reduction reported is significant, using the fecal
19 incontinence scoring system, and that it appears to
20 concordant with other measures within the study, and
21 perhaps most importantly our statistician expert feels
22 that it has a basis as well.

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1 So I think the answer to question two
2 would be that the panel thinks that the 24 point score
3 reduction is significant.

4 CHAIRMAN KALLOO: Question Three. Two
5 quality of life questionnaires were used as secondary
6 end-points during the pivotal trial. Please discuss
7 the clinical significance of the overall changes in
8 the perimeters contained in these questionnaires.
9 Dr. Smith.

10 DR. SMITH: I think that all clinical
11 quality of life questionnaires are very suspect. It
12 depends on how much the patient likes you, and most
13 people feel that whatever decision they have made in
14 life is the right one.

15 So it is seldom that people would say --
16 well, it had to be very bad for them to say that they
17 made the wrong decision. I think the more important
18 aspect of the whole thing was the objective data that
19 we have previously looked at, rather than the quality
20 of life.

21 DR. WOODS: I completely agree and I
22 especially have a little more trouble evaluating the

1 effectiveness of the fecal quality of life score, that
2 three page questionnaire. It is almost impossible to
3 really decipher exactly what happened with every
4 patient through that.

5 It is interesting to see the numbers look
6 like they are better, but there is no statistics that
7 are gleanable from that sort of data. So I agree with
8 what Dr. Smith said.

9 DR. STEINBACH: I agree with my colleagues
10 that -- and I guess that I am restating the point, but
11 that without a control group, a change in quality of
12 life is awfully hard to interpret.

13 DR. KOLTUN: I agree, and again harping,
14 I would have liked to have known what the failures
15 would have said about their experiences, and what the
16 people who went through a failure, and then a
17 successful stoma placement said about their quality of
18 life.

19 And I think that there is literature, and
20 there could have been control groups in regards to
21 assessing alternatives to the operative procedures and
22 placement of this prosthetic device.

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1 You probably would find a significantly
2 improved quality of life response in patients who go
3 through a colostomy without having gone through a
4 procedure like this.

5 So I think that trying to interpret this
6 quality of life data is very difficult without a
7 control group, and without the approximate control
8 group.

9 MS. NEWMAN: I agree with that, too,
10 because again it would be nice if you had these
11 options, and what is the data on both options. And I
12 think this is a significant procedure, and we don't
13 have all of that data in this area.

14 MR. BANIK: I also agree. I felt that the
15 quality of life information was good, but wasn't
16 something that we could really draw any definitive
17 conclusions from. But I do think it was helpful in
18 having it there.

19 CHAIRMAN KALLOO: Dr. Epstein.

20 DR. EPSTEIN: Well, I think in a little
21 bit of a different approach, and that is simply just
22 looking at straight outcomes and not looking at it

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1 scientifically.

2 What was important to me was that there
3 was an improvement overall in the quality of life just
4 amongst this group itself, and understanding the
5 severe limitations of that.

6 But I think that it is a significant non-
7 negative, and that there was not a worsening. So in
8 that way I think the data is helpful both at the 6
9 month and 12 month follow-up to at least give you an
10 overall sense that there was a feeling of patient
11 well-being and patient satisfaction, notwithstanding
12 the limitations that we do not have with this control
13 group of an ostomy or whatever other control group
14 there might be.

15 CHAIRMAN KALLOO: Dr. Gellens.

16 DR. GELLENS: I agree with what Dr.
17 Epstein said about the fact that it certainly was not
18 a negative report. But the data that was presented
19 here was a little skewed I would say, since a lot of
20 the quality of life data was initially presented on
21 all of the participants of the trial, but the follow-
22 up data was just presented on people who actually got

1 the implants.

2 So I thought that the data was a little
3 bit skewed in that sense.

4 DR. MCCLANE: I don't think that that is
5 the most important part of the study either. I think
6 that the numbers are very low. There were only 48
7 patients in the HSQ than any other. In the FIQL there
8 were only 67 patients at 12 months.

9 So again that is really less than half of
10 the initial patients. So I think it would be better
11 if you looked at all of the patients in these follow-
12 up questionnaires, and you would have better data.

13 CHAIRMAN KALLOO: Dr. Talamini, a summary,
14 and I know it is not an easy one.

15 DR. TALAMINI: Mr. Chairman, I think the
16 panel's opinion is that the clinical significance of
17 the quality of life data is not as powerful as perhaps
18 other aspects of the study, and they have inherent
19 weaknesses, which the panel has outlined, such as lack
20 of a control group, and the omission of the initial
21 patients that were explanted.

22 However, the data do seem to reflect and

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1 agree with the other parts of the study. So they are
2 not without some significance.

3 CHAIRMAN KALLOO: Thank you. Question
4 Number 4. The intent to treat analyses as submitted
5 by the sponsor and the FDA are shown in the
6 accompanying chart. Please comment on these analyses,
7 and also the effectiveness of the advice for the
8 treatment of severe fecal incontinence when analyzed
9 by this method.

10 So we have the intent to treat analyses in
11 the chart as seen on your right, and I would like for
12 you to treat on these analyses, and the effectiveness
13 of the device for treatment of severe fecal
14 incontinence using this method. Dr. Smith.

15 DR. SMITH: Well, I think that this is
16 very similar to the first question that we do oppose,
17 and actually it is a matter of risk-benefit ratio, and
18 I think that if we have success with a fair percentage
19 of patients, 56 percent, I think that provided that
20 the patients know this beforehand, I think that one
21 can live with it.

22 I think it is very hard to know the exact

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1 follow-up of the people that drop out of the trial,
2 and there are failures, and it is very difficult, and
3 as was mentioned earlier, we would like to know what
4 happened to these people.

5 And those of us who have done these trials
6 know that when people fail that they often disappear,
7 and it is very hard to get them to come back and to
8 report any additional data.

9 DR. WOODS: The six patients that are
10 included in the failure rate for FDA, because of no 12
11 month follow-up, is it our understanding that there
12 was no 12 month follow-up available, and that's just
13 because they have not reached the 12 month mark?

14 If so, I see very little difference
15 between 51 percent and 56 percent when it boils down
16 to clinical applicability of this device. And I don't
17 have anything else to say other than what has already
18 been stated.

19 DR. STEINBACH: I agree that 51 percent is
20 a demonstration of effectiveness.

21 DR. KOLTUN: Again, I think the success
22 rate of 51 or 56 percent is irrelevant. It is what

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1 happened, and it has been shown, but my concern,
2 because we are thinking risk benefit, we are looking
3 at benefit.

4 But I really want to know what the actual
5 risk is in the context of what happened to the
6 patients who did not succeed, although they may not
7 come back for follow-up, and QOL isn't what I am
8 talking about.

9 I am talking about the length of hospital
10 stay for sepsis, or complications, or things like that
11 associated with these prostheses, and whether that
12 represents so high a risk that at least the
13 indications for placing such a device, which as
14 someone has already mentioned, will start to become
15 more commonly done, whether those indications, or
16 contra-indications, should be more carefully spelled
17 out.

18 Because right now with the number of
19 patients that have been put into this study, though we
20 see this success rate, the issues of which patients
21 specifically should not be considered candidates, and
22 which patients represent excellent candidates, is not

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1 clear to me, and I think there needs to be some
2 guidance in that regard.

3 Because I think the experience yet with
4 this device is still very much in its infancy. So the
5 success rate I am very happy about. I think it is
6 fine. But I would like to know for a fact that
7 patients that did not succeed not represent such a
8 high cost to pay for the success rate.

9 MS. NEWMAN: I don't have anything to add
10 to that and I agree.

11 MR. BANIK: I also see very little
12 difference between the 56 and the 51 percent. I agree
13 with all the comments made thus far. The idea here is
14 that there is some concern that probably will be
15 discussed relative to label copy, and that my
16 interests are the other part of the population that
17 was not successful.

18 DR. EPSTEIN: I basically agree, but the
19 thing that strikes me again is the failure rate, and
20 I think it speaks back to the point where, for
21 example, when laparoscopic colocholecystostomy first
22 became available, there was a higher complication

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1 rate, and that has gone down over time.

2 And particularly the surgeons that were
3 trained in that went to various specific training
4 programs, and I think the information that the
5 colorectal surgeons here, the most experienced ones,
6 have pointed out needs to be communicated to the
7 physicians that are going to be doing this in some
8 form or way.

9 And I believe that with their experience
10 in transmitting that that the failure rate could go
11 down further with very carefully selected patients,
12 and meticulous attention to surgical detail,
13 appropriate antibiotic selection, and all the things
14 that they have talked about, and how they have learned
15 just in this early study.

16 And that information needs to be applied
17 in some form or way to the surgeons here who are going
18 to be implanting this. And perhaps it does need to be
19 limited initially to some centers where they can
20 really get excellent clinical results.

21 DR. GELLENS: I overall agree with what
22 has been said so far, except for the failure rate, and

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1 that I still have major concerns with, and when it is
2 available for use.

3 I mean, the expertise in using a device
4 will increase, and I think that will help decrease the
5 failure rate. But the patient population that it is
6 used on will also increase, and a lot more illnesses,
7 and that could increase the failure rate.

8 So I don't think just because there is
9 going to be more experience with its use that that
10 automatically will mean that the failure rate is going
11 to go down.

12 DR. MCCLANE: I think that the 50 percent
13 success rate is a pretty good number again as long as
14 the other 50 percent aren't worse off. I agree again
15 that we really have to try and do these in certain
16 centers, at least initially, and the 50 percent is a
17 good number when you compare it to the other surgical
18 procedures that are done for fecal incontinence.

19 And in particular sphincter repairs, where
20 the success rate a year, or year-and-a-half, or two
21 years out, is around the same number as these patients
22 are having some problems down the line, even with the

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1 sphincter repair, which I guess is right now the best
2 operation for fecal incontinence.

3 So I think these numbers are pretty good
4 when you start coming them to other things that are
5 available.

6 DR. STEINBACH: Mr. Chairman, can I speak
7 out of order?

8 CHAIRMAN KALLOO: Yes.

9 DR. STEINBACH: There is a paper referred
10 to by the sponsors by Maloof that was in Lancet last
11 year, and it looked at the United Kingdom experience
12 outside clinical trials with this device, and I think
13 that their general conclusion was that the community
14 was less willing to do revisions of the device.

15 That if it failed once, they said, okay,
16 we will take it out. I will jus say that for what it
17 is worth.

18 CHAIRMAN KALLOO: Thank you. Dr.
19 Talamini, will you summarize the panel's comments.

20 DR. TALAMINI: Mr. Chairman, the intent to
21 treat analysis that we are looking at now doesn't
22 appear to have altered the committee's opinion

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1 regarding the general effectiveness of the device.

2 However, it does underscore for most
3 committee members a concern about the failures that we
4 will probably have the opportunity to discuss further
5 in labeling and in other issues.

6 CHAIRMAN KALLOO: I will ask the panel to
7 help Dr. Talamini and the FDA to try to specifically
8 answer the question that has been posed, and to feel
9 free to provide us with your wisdom and experience.

10 But at a very minimum to try to answer the
11 very specific question that we are being asked to
12 answer. Question Number 5. Based upon the data in
13 the PME, please identify whether there are any patient
14 populations or subgroups that you feel would either
15 clinically benefit more from the device, or be at a
16 higher risk for adverse events from implantation.

17 So, patient population of subgroups that
18 would either clinically benefit or be of a higher risk
19 of adverse events. Dr. Smith.

20 DR. SMITH: I think it has been clearly
21 stated in the PMA.

22 DR. WOODS: I think they have been fairly

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1 clearly stated as well. I would point out that it
2 seems fairly repetitive that the surgeons who have
3 done this have said that patients with very thin
4 parineums, or who have had multiple repeated
5 procedures previously, seem to be at higher risk for
6 maybe erosion and perforations during the surgical
7 procedure.

8 Also, I think it should be very clearly
9 stated that patients who only have severe fecal
10 incontinence should be considered for implantation of
11 this device, so that we don't see the device being
12 offered to patients with more minor degrees of
13 incontinence.

14 Or to those who have not yet tried other
15 alternatives to solve their incontinence problem
16 before getting to this point. I think that should be
17 very clearly labeled.

18 DR. STEINBACH: I asked the sponsor to
19 break down the revision rate and the explant rate
20 based on the etiology of fecal incontinence, and the
21 obstetric was the highest, and this is part of your
22 handout, but was not significantly different.

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1 CHAIRMAN KALLOO: So you are saying if
2 there was no difference -- I'm sorry, I missed what
3 you said.

4 DR. STEINBACH: The conclusion on the
5 numbers available was that the etiology of the fecal
6 incontinence does not change the explant or the
7 revision rate.

8 DR. KOLTUN: My feeling is that I don't
9 think anybody can say -- I mean, based on the data
10 that has been presented, there just aren't that many
11 patients in the subgroup analysis, in any one subgroup
12 analysis, to be able to be definitive in this regard
13 is my impression.

14 I mean, they have not specifically looked
15 at patients who are in some way or another being
16 compromised. Are there issues with regard to
17 underlying medical conditions in any one group, and
18 things like that.

19 So, I think that there probably will
20 develop a sense of who should and who should not get
21 these devices preferentially as experience is
22 gathered.

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1 There is always a balance between how long
2 do you wait so that that experience can be gathered
3 more rapidly, versus mandating a need for such
4 documentation in advance.

5 I have concerns about implanting such a
6 device in some one who is at high risk, and yet use it
7 as something that they have to have. And I think the
8 clinicians who have been involved in the study would
9 not do such. But I think some guidance in regards to
10 possibly labeling is necessary here.

11 MS. NEWMAN: I have concerns, and you have
12 women who have multiple pelvic procedures, and you
13 have those that are menopausal, and with thin
14 parineums, and should they go on estrogen? I don't
15 know. These people age, and the biggest group they
16 did was women.

17 So I think there is a lot of questions to
18 be answered, and you see women who have multiple
19 pelvic procedures by different specialists. So I
20 don't think there is a lot of information there. I
21 would like to see more fine tuning of which population
22 this would benefit, and what do you do with those

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1 individuals.

2 MR. BANIK: I would like to agree with Dr.
3 Woods' comments earlier. I particularly would be
4 concerned about any patient that has had pelvic
5 surgery, and I think it was voiced in some of the
6 presentations earlier whether that could definitively
7 be outlined in labeling copy, and all the adverse
8 kinds of events could be thought out through so that
9 it could be more clearly defined.

10 And I don't know if at this point that is
11 possible. I sort of doubt it based upon the limited
12 experience that people have had with the device. But
13 combining that with the successful outcome of 50
14 percent or more, I think we have to weigh all those
15 alternatives in the decision process.

16 And so it is a rather complicated
17 decision, and I don't think the information is clear
18 for us to determine wholeheartedly what should be put
19 in here. But nonetheless something should be done.

20 CHAIRMAN KALLOO: Dr. Epstein.

21 DR. EPSTEIN: Yes, I have a little bit of
22 a different opinion about this question. I think in

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1 a way this goes into the practice of medicine, and we
2 do have board-certified trained colorectal surgeons
3 who will be implanting these devices.

4 And it is certainly part of their
5 prerogative. We make the information available to
6 them as to what the risk and benefits are, and
7 certainly the information -- I think what I have heard
8 everybody say is the information from this study, and
9 the information that the colorectal surgeons have
10 presented should be incorporated in the labeling.

11 But after that this becomes a medical --
12 becomes the surgeon's prerogative to work up the
13 patient carefully, and to ensure that his own or her
14 own outcomes are appropriate and adequate, and it goes
15 again back to the question of training.

16 And I think just putting the information
17 about the problems with erosion and infection into the
18 labeling very specifically, and I think it should be
19 left at that.

20 DR. GELLENS: The only -- one of the main
21 groups that I am concerned about is the
22 immunosuppressed patients, either because of

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1 medications they are on, or because of underlying
2 medical illness.

3 Because of the high infection rate in this
4 device, that is my major concern as far as the high
5 risk group.

6 DR. MCCLANE: I think that this is based
7 on the data and the PMA and that we don't really know
8 who are the best patients and those with the highest
9 risk, because really the only two groups that are at
10 a higher risk were those with allergies, and those
11 with musculoskeletal abnormalities which intuitively
12 wouldn't be the two groups that we would try to
13 exclude from this type of a device.

14 So I think we have to wait until we get
15 more data on it, and more patients, until we really
16 know for sure on what patients would be at a higher
17 risk.

18 CHAIRMAN KALLOO: Dr. Talamini, would you
19 summarize the panel's comments.

20 DR. TALAMINI: Mr. Chairman, I believe the
21 panel's opinion would be that based upon the data in
22 the PMA, there are not groups that we can clearly

1 identify that would benefit or be at a high risk.

2 But many panel members believe that such
3 groups probably do exist, and will exist, and we will
4 have more information as more of these are implanted
5 over time, if they are.

6 CHAIRMAN KALLOO: Question Number 6. As
7 proposed in the PMA submission, the indications for
8 the use statement recommends the use of this device in
9 post-pubescent males and females.

10 The pivotal study, however, only enrolls
11 subjects 18 years of age or older. Please discuss
12 whether the device should be labeled for use in post-
13 pubescent patients under the age of 18 years. Dr.
14 Smith.

15 DR. SMITH: I would be somewhat reluctant
16 to employ such a device such as this in younger people
17 that are developing, and I would be even more inclined
18 at this stage until there is more experience with the
19 device to use in the post-pubescent patient over the
20 age of 18.

21 DR. WOODS: You know, I have no idea
22 whether or not there is a lot of change or growth in

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1 this area after puberty is reached. I would rely on
2 the comments from the colorectal surgeons here, but
3 intuitively, I would think that there is not a lot of
4 difference here in that age group.

5 And that the social impact of fecal
6 incontinence in a teenager would be enormous. I would
7 think that if we had something to offer them that we
8 felt would be of success that we should offer it to
9 them.

10 But I would like to hear the rest of the
11 comments from the panel about the anatomy in the post-
12 pubescent group.

13 DR. STEINBACH: There is some concern
14 whether a child under 18 can give informed consent,
15 and this is sometimes hard for the parent to
16 understand whether this would benefit their child or
17 not.

18 DR. KOLTUN: I share the concern that the
19 children or youths probably would be more beneficially
20 affected by the successful implantation for their long
21 term psyche, and I think that would be someplace where
22 this device would be a great, great benefit.

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1 But unfortunately I get the impression
2 that a lot of the success associated with this device
3 relates to the actual physical nature of the device;
4 the size of the cuff, and the length of the sphincter,
5 and the way it is placed, and the various mechanical
6 arrangements involved.

7 So I wonder in fact if that -- well, I
8 won't wonder. I basically have a strong suspicion
9 that the mechanical nature of it in a youth therefore
10 will play all that much greater a role in regards to
11 technical failure.

12 So I think probably there would have to be
13 additional studies to prove this, and continued for an
14 equivalent success rate in children, or in youthful
15 individuals.

16 MS. NEWMAN: I agree, because I think,
17 too, it is only the device that will release all those
18 things. And I think that since the studies are done
19 on those 18 and above, unless there are other studies
20 of younger individuals, that it should just stay at 18
21 and above.

22 CHAIRMAN KALLOO: Mr. Banik.

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1 MR. BANIK: I also agree. I think
2 additional information would be required to consider
3 what role the population below 18 would have at this
4 time.

5 DR. KOLTUN: Can I speak out again?

6 CHAIRMAN KALLOO: Yes.

7 DR. KOLTUN: I was going to say that I
8 think probably the criteria by which it would be
9 decided would be sort of a physicality criteria. It
10 would not be age criteria. It would be size criteria.

11 I am saying that I have seen 16 year olds
12 who were 200 pounds, and looked like they had reached
13 maturity. I think the issues would be the
14 appropriateness of the size and the physicality of the
15 device in relationship to the size, and the
16 physicality of the subject.

17 So I know that we could probably say on
18 age and things with regard to the legality of it, but
19 I would be more akin to linking the appropriateness of
20 using this device to the size of the individual, and
21 the maturity of their physical development.

22 DR. TALAMINI: So you would be okay with

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1 somebody under 18 if they were the appropriate size?

2 DR. KOLTUN: Yes. I am not sure how you
3 would define that, but I am sure that there are
4 studies that can define whether someone has reached
5 their finite mass of bone growth, et cetera. I would
6 think it more than that in terms of the success rate.

7 CHAIRMAN KALLOO: Dr. Epstein.

8 DR. EPSTEIN: Yes, I have a little bit of
9 a different opinion again. I think that if you have
10 a child that has fecal incontinence that it is
11 absolutely devastating to that child, and to their
12 growth and development.

13 And I think that if this device is
14 successful at least 50 percent of the time, that is a
15 worthwhile endeavor. And we have heard that it can be
16 removed, and the wounds heal, and I do think that it
17 is going to be very difficult to do a study, because
18 you saw how slow the accrual was in this study in
19 adults.

20 So you are talking about a relatively
21 smaller number of individuals, but individuals who may
22 be affected in a very severe way. And if the device

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1 works in those children, then certainly it would be
2 beneficial.

3 I think though that it would need to have
4 a very strict control, and if it is possible -- and I
5 don't know if that is possible, it should be applied
6 for in each case, and should be kept experimental
7 under 18.

8 But it shouldn't be automatically
9 disallowed, because there are children who are
10 physically probably able to accept the device, and who
11 may therefore benefit from it.

12 So I think that if it is possible to have
13 that stipulation that I wouldn't necessarily restrict
14 it.

15 CHAIRMAN KALLOO: Dr. Gellens.

16 DR. GELLENS: It has not been studied in
17 people less than 18, and so I don't think it should be
18 labeled for use in people under the age of 18.
19 However, it is already being used as a humanitarian
20 device, and so with careful evaluation of people who
21 are under 18, it still could be used in that setting
22 without putting it on the labels.

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1 DR. MCCLANE: I think there is no problem,
2 and there shouldn't be any problem using it in post-
3 pubescent patients under 18. The only issue would be
4 the consent issue, but then again we operate on a lot
5 of patients under 18 in the past, and get the consent,
6 and that's fine.

7 The pre-pubescent patients, it probably
8 should be okay to use them, but again they have to
9 understand the problems that may exist, and in
10 relation to their growth.

11 CHAIRMAN KALLOO: Dr. Talamini, can you
12 summarize the comments?

13 DR. TALAMINI: Mr. Chairman, I believe the
14 panel was split evenly down the middle on this
15 question, and with half saying they thought it was
16 okay under 18, and half saying it should be restricted
17 to those over 18.

18 CHAIRMAN KALLOO: Thank you. The next
19 question is Question Number 7. Please discuss whether
20 the patient labeling as submitted is adequate to
21 accurately involve the users of the risk and potential
22 benefits of using the device. Dr. Smith.

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1 DR. SMITH: I think that there needs to be
2 more detail, and that all of the results be included,
3 and I hoped that we were going to discuss this at a
4 later time. You said we were going to discuss
5 labeling as such?

6 CHAIRMAN KALLOO: This is the moment.

7 DR. SMITH: This is the moment?

8 CHAIRMAN KALLOO: Yes.

9 DR. SMITH: Well, I would like to see very
10 specific details of labeling for the device. I would
11 like to see that the patient is given a whole
12 information kit supplied to the patient, and that this
13 kit be given to them 72 hours before the procedure,
14 and that they sign a form saying that they have read
15 and understood the implications of this procedure, and
16 that goes with part of the consent for the operation.

17 I think that is the one part of it that I
18 think is very important. And the other part of it, I
19 think, is that we should stipulate that people who are
20 implanting the device should undergo a course of
21 training as well to be adequately schooled in the
22 whole technique of this device.

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1 DR. WOODS: I agree with that, and I also
2 think that it should be very, very clearly indicated
3 what the expected outcomes are, be it a success or a
4 failure. It has already been reiterated many times
5 here that we are concerned about the failures.

6 And I think that those numbers need to be
7 well defined in the labeling, and you need not to say
8 27 failures. You need to say what happened to those
9 people.

10 I also think you should tell us in the
11 labeling why the 10 people who had the implant for 12
12 months were deemed as failures. In other words, the
13 ones that can keep the implant, and who aren't
14 successful, we need to understand why they may not be
15 successful.

16 I think it needs to be very well defined
17 who is capable of putting in this device, and as has
18 already been mentioned, a training course or something
19 to that effect needs to be offered and completed, I
20 think, before a person is credentialed or allowed to
21 put this device in.

22 I think that patients who are being

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