

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE

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GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

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GRAND BALLROOM
BEST WESTERN WASHINGTON GATEWAY HOTEL
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THURSDAY, OCTOBER 19, 2000

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PANEL MEMBERS:

ANTHONY N. KALLOO, M.D. Gastroenterologist	Chair
CRAIG F. DONATUCCI, M.D. Urologist	VM
JOSEPH H. STEINBACH, Ph.D. Biomathematician	VM
DIANE K. NEWMAN, RNC Consumer Representative	CR
MICHAEL S. BANIK Industry Representative	IR
ROBERT R. DiLORETO, M.C. Urologist	TVM
RICHARD GORMAN, M.D. Pediatrician	TVM
MARTIN KAEFER, M.D. Pediatric Urologist	TVM
NAIDA B. KALLOO, M.D. Pediatric Urologist	TVM
JEFFREY COOPER, DVM	Executive Secretary

FDA PARTICIPANTS:

DAN SCHULTZ, M.D.

FDA DEFLUX PMA REVIEW TEAM

JOHN BAXLEY, Lead Reviewer
 HECTOR HERRERA, M.D., Clinical Reviewer
 JUDY CHEN, Statistical Reviewer
 RAJU KAMMULA, DVM, Ph.D., Biocompatibility Reviewer
 RAO NIMMAGADDA, Ph.D., Chemistry Reviewer
 CATHY NUTTER, Microbiological Reviewer
 JACK McCracken, Patient Labeling Reviewer
 DON WATCHKO, Manufacturing/QS Reviewer
 BARBARA CROWL, BIMO Contact

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A G E N D A

	<u>PAGE</u>
Open Public Hearing	9
Open Committee Discussion	
1. Sponsor Presentation	
- Dr. Claes Morlin	11
- Dr. Bengt Agerup	12
- Dr. Goran Lackgren	15
- Dr. Nicola Capozza	17
- Dr. Hege Bothner Wik	
2. FDA Presentation	
- John Baxley	55
- Dr. Hector Herrera	65
- Judy Chen	74
Panel Discussion	
FDA charges, recommendations and vote on premarket approval application	82
Open Public Hearing	146
Panel Deliberations and Vote	157
Adjournment	189

PROCEEDINGS

(9:30 a.m.)

1
2
3 DR. ANTHONY KALLOO: Good morning. I
4 would like to call to order the Gastroenterology and
5 Urology Devices Panel. I would like to note for the
6 record that the Voting Members present constitute a
7 quorum as required by 21 CFR Part 14. Would each
8 member introduce him or herself, designate specialty,
9 position title and institution and status on the panel
10 -- that is, Voting Member or Consultant -- starting on
11 my immediate right.

12 DR. COOPER: I'm Jeff Cooper. I'm the
13 Executive Secretary for the Gastroenterology and
14 Urology Devices Panel.

15 DR. NAIDA KALLOO: I'm Naida Kalloo. I am
16 the Primary Reviewer for this and I'm from National
17 Naval Medical Center. I'm a Pediatric Urologist.

18 DR. DONATUCCI: Craig Donatucci. I'm an
19 Associate Professor of Urology at Duke University
20 Medical Center, and I'm a Voting Member of the Panel.

21 DR. KAEFER: I'm Martin Kaefer. I'm an
22 Associate Professor of Surgery, Pediatric Urology,
23 Indianapolis, Indiana. I'm a Voting Member.

24 DR. STEINBACH: Joseph Steinbach,
25 Gastroenterology Section at the University of

1 California at San Diego, and I'm an Associate
2 Biomathematician, and I'm a Voting Member.

3 MS. HARVEY: I'm Elisa Harvey, the Acting
4 Chief of the Urology and Lithotripsy Devices Branch,
5 and I'm sitting in temporarily until our Division
6 Director, Dan Schultz, gets here.

7 DR. BANIK: I am Michael Banik. I am the
8 Industry Rep for the Panel. I'm a Non-Voting Member.

9 DR. NEWMAN: I'm Diane Newman. I'm a
10 Nurse Practitioner and a Visiting Professor at Rutgers
11 and I have a practice in Philadelphia, and I'm a Non-
12 Voting Member. I'm the Consumer Rep.

13 DR. DiLORETO: Robert DiLoreto. I'm an
14 Adult and Pediatric Urologist, Michigan Institute of
15 Urology, Detroit, Michigan, and I'm a Voting Member.

16 DR. GORMAN: My name is Richard Gorman.
17 I'm a Pediatrician in private practice. I hold an
18 appointment as a Clinical Associate Professor at the
19 University of Maryland, and a Voting Member of the
20 Committee.

21 DR. ANTHONY KALLOO: My name is Anthony
22 Kalloo. I'm an Associate Professor of Medicine and
23 Director of Endoscopy at Johns Hopkins School of
24 Medicine, and I'm a Voting Member. I'm a
25 Gastroenterologist.

1 DR. SEGERSON: I'm Dave Segerson,
2 Associate Region Director in the Division of
3 Reproductive, Abdominal and Radiological Devices. I'm
4 sitting in just for a few minutes for Dr. Schultz, and
5 also he is the Acting Division Director, and he's also
6 newly the Deputy Office Director. So he'll be sitting
7 here in a few minutes. He's in another meeting right
8 now.

9 DR. ANTHONY KALLOO: Thank you. I will
10 now turn the meeting over to Dr. Jeff Cooper, who will
11 read the Executive Secretary's statement.

12 DR. COOPER: Good morning. Before we do
13 that, I want to mention that in front of you is an
14 Express Lunch Form. Some have a color version. If we
15 could fill that out, the Panel Members, and we'll pick
16 that up. They will have lunch ready for us. We can
17 pay later on that.

18 Also in front of the Panel Members is a
19 Reader's Digest large-print version of the
20 presentation from the Sponsor, which is this
21 (indicating). It's also included in your packet in a
22 smaller version so that you will all know it's a
23 duplicate, but it's the same essential information.

24 For information, the mikes are on all the
25 time to pick up all your comments. And Dr. Janelle

1 Foote will not be joining us today.

2 Now, to get on, I'd like to read a
3 statement concerning appointments to temporary voting
4 status pursuant to the authority granted under the
5 Medical Devices Advisory Committee Charter, dated
6 October 27, 1990, and as amended August 18, 1999.
7 Drs. Richard Gorman, Martin Kaefer, Naida Kalloo, and
8 Robert DiLoreto have been appointed as Voting Members
9 by Dr. David W. Fiffel, Director of the Center for
10 Devices and Radiological Health, for the October 19,
11 2000 meeting of the Gastroenterology and Urology
12 Devices Panel.

13 For the record, with the exception of Dr.
14 Richard Gorman, these individuals as special
15 Government employees and consultants to this panel or
16 other panels under the Medical Devices Advisory
17 Committee. Dr. Richard Gorman is a special Government
18 employee and a consultant to the Center for Drug
19 Evaluation and Research. They have undergone the
20 customary conflict-of-interest review and have
21 reviewed the materials to be considered this meeting.

22 The following announcement addresses
23 conflict-of-interest issues associated with this
24 meeting and is made a part of the record to preclude
25 even the appearance of any impropriety. To determine

1 if any conflict exists in the Agency review of the
2 submitted agenda and all financial interests reported
3 by the Committee participants, the conflict-of-
4 interest statutes prohibit special Government
5 employees from participating in matter that would
6 affect their or their employer's financial interests.
7 However, the Agency has determined that participation
8 of certain members and consultants, the need of whose
9 services outweighs the potential conflict-of-interest
10 involved, is in the best interest of the Government.
11 We would like to note for the record that the Agency
12 took under consideration a certain matter regarding
13 Mrs. Diane K. Newman. She reported a past interest in
14 a firm at issue, but matters not related to today's
15 agenda. Therefore, the Agency has determined that she
16 may participate fully in today's deliberations. In
17 the event that the discussions involve any other
18 products or firms not already on the agenda for which
19 an FDA participant has a financial interest, the
20 participant shall excuse him or herself from such
21 involvement and the exclusion will be noted for the
22 record.

23 With respect to all other participants, we
24 ask, in the interest of fairness, that all persons
25 making statements or presentations disclose any

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1 current or previous financial involvement with any
2 firm whose products they may wish to comment upon.

3 On another note, we have the 2001
4 Tentative Panel Meeting dates, and they are Friday,
5 March 9, 2001; Friday, June 29; Thursday, September
6 13; and Friday, December 7.

7 DR. ANTHONY KALLOO: We will now proceed
8 with the Open Public Hearing session of this meeting.
9 If there is anyone wishing to address the Panel,
10 please raise your hand and you may have an opportunity
11 to speak. I would ask at this time that all persons
12 addressing the Panel come forward to the microphone
13 and speak clearly as the Transcriptionist is dependent
14 on this means of providing an accurate transcription
15 of the proceedings of the meeting.

16 Before making your presentation to the
17 Panel, state your name and affiliation and the nature
18 of any financial interest you may have in the topic
19 you are going to present. Each presenter can be
20 allotted five minutes. Please provide a copy of your
21 remarks and any visual aids to the Transcriptionist.

22 (No response.)

23 As there are no public comments, we will
24 proceed to the open Committee discussion. We will
25 start with the Sponsor's presentation of PMA000029

1 from Q-Med AB on Deflux Injectable Gel for the
2 prevention of vesicoureteral reflux in children. I
3 would ask at this time that all persons addressing the
4 panel come forward to the microphone and speak
5 clearly. As I said before, the Transcriptionist is
6 dependent on this means of providing an accurate
7 transcription of the proceedings of the meeting.

8 Before making your presentation to the
9 Panel, state your name and affiliation and the nature
10 of your financial interest in that company. Let me
11 remind you that a definition of financial interest in
12 the Sponsor company may include compensation for time
13 and services of clinical investigators, their
14 assistants and staff, in conducting a study and in
15 appearing at the Panel meeting on behalf of the
16 applicant. A direct stake in the product under
17 review, such as invention of the product, patent
18 holder, owner of shares of stock, et cetera, owner or
19 part owner of the company. No statement is necessary
20 from employees of that company.

21 I would like to remind the Panel that they
22 may ask for clarification of any points included in
23 the Sponsor's presentation, but discussion should not
24 go beyond clarification.

25 The first speaker listed on the agenda is

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1 Dr. Bengt Agerup.

2 DR. MORLIN: Ladies and gentlemen,
3 distinguished members of the Panel, good morning. My
4 name is Claes Morlin, actually, and I am the Vice
5 President of Operations and R&D at Q-Med AB, Uppsala,
6 Sweden.

7 I am just going to introduce the other
8 team members from Q-Med and our specialists who are
9 with us. The first speaker will be Bengt Agerup, as
10 I said, founder and Vice President of Exploratory
11 Research at the company. Then the next speaker is
12 Bengt Agerup, who will talk about deflux and some
13 background. Next person to speak will be Hege Bothner
14 Wik. She is Director of Regulatory Affairs at Q-Med.
15 The two following names yo will find on the list over
16 there, Ted Sullivan and Mark Yacura. They are FDA
17 regulatory counsels. The next speaker after Hege
18 Bothner Wik will be Dr. Goran Lackgren, from the
19 University Children's Hospital in Uppsala, Sweden, and
20 he will talk about the concept, the technique, and the
21 first study we call Deflux I. And he will be followed
22 by Dr. Nicola Capozza, from Ospedale Bambino Gesu,
23 Rome, Italy, and he will speak about the two following
24 studies.

25 So, with this, I would like to give over

1 to Bengt Agerup.

2 DR. AGERUP: Members of the Panel, ladies
3 and gentlemen. It is a honor to be invited to make
4 this presentation, of course. May I also add that if
5 we have any patent issues, I am also the inventor of
6 the technology that we will discuss today.

7 Deflux is combination of two polymer,
8 polysaccharide polymers. It is dextranomer -- that
9 means a cross-linked dextran polymer.

10 And we have also hyaluronic acid as a
11 carrier. The hyaluronic acid is, of course, found in
12 the body in basically all tissues.

13 And the dextran has been used quite
14 extensively. So this was deliberately chosen.

15 Hyaluronic acid is repeating disaccharide
16 glucosamine glucide that can be from various sources
17 in various purification levels and also that can be
18 crosslinked, or as we call it "stabilized", to various
19 degrees. So, it's a very common substance.

20 We have chosen for, let's say, the sake of
21 purity mainly, fermentation as the source. There is
22 also tissue extraction mainly which means that you
23 will have a quite difficult mixture of proteins and
24 various tissue components whereas if you use
25 fermentation, you are having a singular cellular

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1 species and you can inhibit and filter off the cells
2 and you have basically a very pure to do your further
3 purifications with.

4 Dextran is glucose, polymerized glucose,
5 which has been extensively used. It is molecular
6 normally that is below -- I would say below 2 million
7 -- and it's produced as a side product from the sugar
8 industry. It's the *Leuconostoc mesenteroides* that's
9 making it. The reason why it was used in the
10 beginning in the medicine is that it was an impurity
11 in sugar that wasn't sweet, so they wanted to remove
12 it. And then the Swedish Company Pharmacia found out
13 the use as plasma volume expander and all these other
14 uses that you see today. So we can look at the usage
15 of Dextranomer products. Plasma volume expander was
16 the first, and then a number of crosslinked forms, and
17 we also find it now in Dextran, that's an iron complex
18 Dextran formulation. You have also various functional
19 groups on the Dextran that's used to reduce
20 cholesterol, for instance. And you also have
21 anticoagulate therapy by Dextran sulfates. So,
22 interestingly, you also see it in the photographic
23 industry, in mining, and also as a food additive you
24 will find this Dextran polymer. It takes up a lot of
25 water, so that's the main reason, it gives more volume

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1 to the ice cream.

2 So, the mechanism of action for this first
3 formulation that we did was -- well, I will also
4 say that the problem with dextranomer beads in product
5 space and the dextranomer beads is that they separate.
6 So you have the beads in the one end of the range and
7 you have the rest of the injections in the other.

8 So the first thing we did was stabilize
9 the carrier hyaluronic acid so that it would keep the
10 dextranomer beads uniformly in the product. So that
11 was the first problem.

12 Then when you overcome that, that means
13 that you can now inject the dextranomer beads. The
14 carrier has to be neutral in the tissue and should
15 disappear quite quickly because -- it is, in fact, the
16 dextranomer beads that will perform the work in
17 tissue, that will make up the new tissue.

18 And next the long-term effects of
19 dextranomer, you will have cell infiltration and you
20 will have, let's say, sort of scar tissue formed
21 around the implant. And in doing so, you will have
22 the tissue augmentation that you are looking for. So
23 that's what Deflux is.

24 In Europe when we looked at this Deflux
25 formulation in the beginning, there were a lot of use

1 in Teflon paste and so on because this was basically
2 unregulated before 1995 in Europe. We also saw today
3 some silicone formulations, and it was detected at
4 about 80 microns below particle product implants could
5 migrate and, in fact, you found Teflon particles as
6 far away as in the brain tissue. And this was
7 considered to be a main safety concern when we did the
8 Deflux. So we cut off the particle size, limited it
9 to 80, and it should be -- could be as big as possible
10 but, of course, any extra would -- so this is a
11 Dextranomer specifications came from this slide.

12 So, with this, I would like to introduce
13 you to our Director of Regulatory Affairs, Ms. Hege
14 Bothner Wik. She also made her thesis on hyaluronic
15 acid, so she is a very experienced person.

16 DR. WIK: Thank you. Members of the
17 Panel, I will try to present the preclinical data made
18 on Deflux which is mainly both in vitro and animal
19 studies.

20 DR. ANTHONY KALLOO: I just want to remind
21 you, if you could, after you introduce yourself, say
22 your relationship with the company and any financial
23 interest.

24 DR. WIK: Okay. I am an employee of Q-
25 Med.

1 The conclusions from the study are that
2 there were no adverse reactions seen in the animal
3 studies and injected material remained stable in
4 study. Histopathological observation showed that
5 Deflux reflected good tissue tolerance with an
6 expected foreign body reaction at the injection site
7 and no significant side effects.

8 From studies in dogs and rats, we could
9 see that the microbeads of the test article induced a
10 fibrous tissue reaction around each microbead without
11 any adverse inflammatory reaction. The fibrous tissue
12 and fibroblasts surrounding each test article
13 microbead act only to occupy space.

14 From the same study, it was also found
15 that implant material does not appear to translocate
16 to other tissues within two years after implantation.
17 Deflux also passed the requirements of the USP Elution
18 test with cytotoxicity grade less or equal to 2.
19 Deflux did not provoke any delayed contact
20 hypersensitivity in guinea pig, and was non-mutagenic
21 in the Ames test.

22 Deflux also gave acceptable induced
23 reactions after implantation in the rabbit muscle and
24 therefore passed the requirements for approval.

25 Deflux also passed the requirements for

1 approval as it only induced a very slight primary
2 irritation with a score of 0.5 in the three rabbits in
3 the intracutaneous test.

4 It also passed the MSI hemolysis
5 requirement for hemolysis value less than 5 percent.
6 In the study, iodine labelled DX-copolymer injected
7 submucosally into the rabbit bladder showed that the
8 dextranomer hyaluron particles do not migrate to
9 distant organs. And the study also showed that no
10 change in DNA profile was observed.

11 This concludes my remarks. I would now
12 like to introduce Goran Lackgren, and he will make the
13 presentation.

14 DR. LACKGREN: Members of the Panel,
15 guests, my name is Goran Lackgren. I am a Pediatric
16 Urologist and head of the Pediatric Urology Department
17 in Uppsala, Sweden since 1987, and I have no financial
18 or personal support from Q-Med, but I hope they will
19 pay my airfare coming here.

20 (Slide)

21 I am going to talk a little bit about
22 reflux. It is a general finding in children with
23 urinary tract infection that they have vesicoureteral
24 reflux. Between 30 to 50 percent of children with
25 pyelonephritis have reflux. We don't know the cause,

1 we don't know what makes it, but the treatment options
2 today are either prophylactic antibiotics to prevent
3 renal scarring, to prevent new infection; open surgery
4 reimplantation of the ureter, with a very high success
5 rate; endoscopic injection of bulking agents, and we
6 have seen that the ones that have been used in Europe
7 is Teflon, Silicone and Bovine Collagen.

8 Current treatment options might be no
9 treatment of the low-grade reflux after a certain age,
10 but we don't know if that is going to be the case in
11 the future. Next slide.

12 (Slide)

13 The endoscopic treatment gives us an
14 alternative which is simple, and it should be an
15 alternative to prophylaxis, and also to exclude
16 patients from open surgery, which I think is the most
17 important reason.

18 It is simple. You use the standard
19 endoscopic technique. If you have safe materials,
20 it's a good method. And it can be performed on a day
21 basis. The patient goes home the same day. It is
22 cost-effective, it is very easy and painless to the
23 children. Next slide.

24 (Slide)

25 The technical aspects -- and we have

1 actually a videotape that may show that, if I am
2 allowed to demonstrate that for a couple of minutes.
3 If you lower the sound, I can explain it.

4 (Videotape shown.)

5 It is injected under the vesicoureteral
6 orifice, to lift up the orifice and elongate the
7 distal part of the ureter to get the mechanism so that
8 the reflux in ureter ceases. These are the particles
9 of the injection. In a couple of seconds, you will
10 see the technique.

11 So this is the end result. And it is
12 general anesthesia. We used a common endoscopic
13 technique with a normal cystoscopy and in the working
14 channel, and we had a stiff needle, and this is just
15 to show that it is very easy to inject with normal
16 hand force, without having special kind of high-
17 pressure. And as you can see, it is very easy to
18 inject like this.

19 It is introduced in the working channel of
20 the normal and the bladder should be semi-thin, not to
21 have too high pressure in the bladder. So this is
22 inside the bladder and the refluxing ureter and the
23 needle is just at the 6:00 o'clock position, and it
24 should go transitionally to the bladder wall because
25 it is very easy to inject too deeply because the

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1 bladder wall is only 2-4 mm in thickness. And we
2 inject between .5 to 1 cc of the substance to get a
3 bolus like that. And we inject until we get a
4 crescent-like orifice. Next slide.

5 (Slide)

6 And I will be going through the Study No.
7 1 where we did a non-randomized study in 50 children
8 with reflux grade III-IV. Next slide, please.

9 (Slide)

10 The objective was for safety reason, but
11 also efficacy. Next slide.

12 (Slide)

13 And the children should be more than one
14 year of age, and basically with persistent Grade III
15 reflux, which means on developing with 6 to 12 months
16 in between, and they have persistent Grade IV reflux,
17 and they should be healthy with normal creatinine
18 levels. Next slide.

19 (Slide)

20 We should exclude patients with history of
21 serious illness, history of endoscopically or
22 surgically treated VUR, and also diverticulum. Next.

23 (Slide)

24 And we examined them before treatment and
25 the day after with an ultrasound or after the

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1 treatment an ultrasound, VCUG after 3 months and one
2 year. Next slide.

3 (Slide)

4 The demographic information. Next slide.

5 (Slide)

6 Adverse events were two patients
7 experienced nausea, vomiting and abdominal pain, more
8 in association with the anesthesia than the Deflux
9 injection. Next slide.

10 (Slide)

11 And the ultrasound findings, two patients
12 had sign of dilatation at one month visit, and one
13 directly after injection. And they resolved
14 spontaneously. And over the year, six periods of UTI
15 was diagnosed. That is positive urinary culture. And
16 no pyelonephritis. Next slide.

17 (Slide)

18 This is the result on 47 ureters and
19 primarily Grade III-IV, and the results after one
20 year, the ones that were followed one year. Next
21 slide.

22 (Slide)

23 And the success of ones correctly included
24 without reflux at 12 months evaluation. And there
25 were some that were correctly included that were clear

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1 after 3 months, but they refused to do the VCUG
2 because they were healthy without reflux, but they are
3 not included in the next slide. Next slide.

4 (Slide)

5 And for safety conclusions, there were no
6 safety concerns at all during the study. And efficacy
7 showed that it is a good treatment for vesicoureteral
8 reflux of at least Grade III-IV. Thank you very much.

9 And I will introduce the next speaker,
10 which is Dr. Nicola Capozza, from Rome. He will
11 present himself.

12 DR. ANTHONY KALLOO: There is a question.

13 DR. DONATUCCI: I want a clarification,
14 please, of something you said. I believe when you
15 described the children, you said there was no dilation
16 of the upper urinary tract in these kids?

17 DR. LACKGREN: No increased dilation.
18 Difference between the first and subsequent.

19 DR. KAEFER: If I could ask a question as
20 well, the children who were fine at 3 months and then
21 didn't have follow-up at 12, did any of them get into
22 trouble in any way for the urinary tract?

23 DR. LACKGREN: No, no infections.

24 DR. DiLORETO: One more question. These
25 were supposed to be Grade III and above refluxers for

1 the treatment?

2 DR. LACKGREN: Yes.

3 DR. DiLORETO: There were some less than
4 Grade III?

5 DR. LACKGREN: Yes.

6 DR. DiLORETO: What was the explanation?

7 DR. LACKGREN: If they were bilateral
8 reflux with at least Grade III on one side and Grade
9 II on the other side, we treated the other side as
10 well when we were in the bladder. So, that's why.
11 But they are not included in the results.

12 DR. CAPOZZA: FDA members, ladies and
13 gentlemen, my name is Nicola Capozza, and I don't have
14 any personal or financial involvement with Q-Med. Of
15 course, I will be paid for coming here.

16 I've been working at Bambino Gesu Hospital
17 in Rome for 20 years as Pediatric Urologist.

18 Regarding this endoscopic treatment of
19 vesicoureteral reflux, I started in 1986 with Teflon
20 in very selected cases. There were a neuropathic
21 bladder with reflux. And then one collagen was used
22 starting in '89. Finally, in '95, following Dr.
23 Lackgren and expanded experience, I decided to use
24 Deflux. And in the last 12 years, about 1,000
25 patients and 1,500 ureters were treated at our

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1 hospital. Can I have the first slide?

2 (Slide)

3 The objective of this study was to
4 investigate the safety and the efficacy of the
5 submucosal injection of a pseudoplastic implant,
6 dextranomer particles, in a 1 percent hyaluronIC
7 solution in children more than 1 year of age with
8 manifest VUR grade II-IV. Next, please.

9 (Slide)

10 The therapy was the same to treat 1 of the
11 patients consecutively found eligible for
12 participation according with the following inclusion
13 criteria.

14 Patients would manifest grade II-IV
15 reflux, patients more than 1 year of age, patients who
16 agreed to refrain from seeking other treatment without
17 first notifying the investigator, and with normal
18 serum creatinine levels, patients or patients with
19 parents with ability to understand and comply with the
20 requirements of the study, and patients who had given
21 their informed consent. Next, please.

22 (Slide)

23 These are the exclusion criteria:
24 Patients who suffered from serious illness, or with a
25 history of endoscopically or surgically treated

1 vesicoureteral reflux, patients with vesicoureteral
2 reflux and a diverticulum, Hutch diverticulum, and
3 patients with duplicated ureters and patients with
4 neurogenic bladder. Next.

5 (Slide)

6 This is the study design. As you see,
7 there is a screening visit with a cystogram. The
8 cystogram could be done at the screening visit or
9 pretreatment. An ultrasound was performed at the
10 prestudy period, a scintigraphy as well. Clinical
11 examination and urinalysis were performed at the
12 screening. As you see the cystogram, the cystogram
13 was repeated at 3 months after treatment and 12 months
14 post-treatment. In the case of persistent VUR Grade
15 II-IV, patients underwent a second treatment.
16 Ultrasound was 1 month after treatment and 12 months
17 after treatment. Clinical examination was done
18 pretreatment, post-treatment, 1 day, 1 month, 3 months
19 and 12 months after treatment. And cystoscopy, of
20 course, at the time of the treatment, and urinalysis
21 at screening, 3 months and 12 months. Next.

22 (Slide)

23 This is a short description of
24 demographics: 120 children, 89 males and 31 males,
25 were found eligible for participation. The children

1 were born between 1980 and 1995, and fulfilled the
2 criteria of being children according to the definition
3 of the hospital. Next.

4 (Slide)

5 And now in terms of safety, we can say
6 that no adverse events were reported in this study.
7 As you can see, serum creatinine was normal, 2 kidneys
8 had no function, and 1 patient had a dilation of the
9 ureter appearing at the 12-month visit. In 2
10 patients, the dilation had increased after 1 month and
11 remained unchanged after 1 year. Next.

12 (Slide)

13 These are the results. In Column 0, you
14 can see the successful results. In grade II, 42
15 ureters were without reflux at 12 months, and 4 had
16 positive results -- that means grade I reflux -- and
17 5 patients had a failure. In grade III, 41 patients
18 successful treatment, 6 with a positive result and 8
19 with failure of the treatment. In grade IV, 12
20 ureters, no reflux; 3 with grade I, and 5 with
21 persistent reflux. Next.

22 (Slide)

23 To explain what we define as success or a
24 positive result, success is no reflux at 12 months
25 evaluation. There is also a group of patients that

1 were correctly included but they didn't show any
2 reflux at 3 months, but they did not perform the 12-
3 month cystogram for the same reasons that Dr. Lackgren
4 said. And in positive results is improvement to grade
5 I at 12-month visit without regard with reflux at 3-
6 month visit. Failure is persistent grade II-IV at 12
7 months. Next.

8 (Slide)

9 This is the summary of the treatment
10 results according to protocol findings. Treatment
11 success was achieved in 98 ureters, that means 68
12 percent of cases. Positive treatment was in 12
13 ureters, 8 percent of the cases, and treatment failure
14 in 24 percent of patients. Next.

15 Finally, these are the conclusions of our
16 study. The Deflux system for local treatment of
17 vesicoureteral reflux is a safe treatment. No safety
18 concerns at all have appeared during this study.

19 And the efficacy evaluation showed that 68
20 percent of the patients had their reflux cured after
21 12 months and another 8 percent of the patients had a
22 reduction to grade I. And this result was essentially
23 obtained already after 3 months. Thank you.

24 If you want, I am going to do the second
25 presentation.

1 DR. ANTHONY KALLOO: You can do the second
2 presentation.

3 DR. CAPOZZA: Thank you. Now I am going
4 to present the results of a randomized comparative
5 study of DX -- that means Deflux -- implantation in
6 children with vesicoureteral reflux. Next.

7 (Slide)

8 The primary objective of this
9 investigation was to investigate the safety of the DX-
10 copolymer implant, and the secondary objective was to
11 compare the efficacy of DX-copolymer implant to long-
12 term prophylactic treatment with antibiotics with
13 regard to cystogram results 1 year after start of the
14 treatment. Next.

15 (Slide)

16 In the first part of the slide you can see
17 the study design. In the first part all patients
18 underwent a prestudy cystogram, ultrasound,
19 scintigraphy and laboratory tests. Then there is the
20 treatment, and 1 month later there is an ultrasound
21 evaluation and clinical evaluation, and 3 months,
22 again, voiding cystogram, and 12 month cystogram,
23 ultrasound, scintigraphy and laboratory tests. The
24 other group, the antibiotic group, were evaluated just
25 the first time at the prestudy period with the

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1 cystogram, ultrasound, the scintigraphy and laboratory
2 tests, and then 12 months later with the same protocol
3 -- cystogram, ultrasound, scintigraphy and laboratory
4 tests. Next.

5 (Slide)

6 Inclusion criteria are the same as the
7 previous study. Next.

8 (Slide)

9 Exclusion criteria doesn't defer from the
10 previous study. Next.

11 (Slide)

12 Patients included were 61 children of both
13 sexes, 24 boys and 37 girls, all of Caucasian origin,
14 with grade II-IV. Sixteen boys and 24 girls were
15 allocated in Deflux group while 8 boys and 13 girls
16 were located in the long-term antibiotic group. Their
17 mean age was 3.1 years. Next.

18 (Slide)

19 In detail, we screened 99 patients, but 38
20 were not included, 8 because they did not match with
21 the inclusion criteria and 14 for the exclusion
22 criteria and 10 without informed consent and 6 for
23 urological malformation associated with urological
24 malformation. So, we randomized 61 patients, 40 in
25 the Deflux group and 21 in the long-term prophylaxis.

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1 One concern was withdrawn. As you can see, this
2 patient was never given any treatment. So we treated
3 39 patients, and 8 patients were out of the protocol
4 after 3 months because they were failure results. So,
5 31 patients ended the protocol at 12 months. In long-
6 term prophylaxis, we have 21 patients, and 21 patients
7 were re-evaluated after 12 months. Next.

8 (Slide)

9 In terms of safety, 1 adverse event, it
10 was a stomatitis was reported. It is unlikely a
11 relationship with the study. And 6 patients in the
12 Deflux group reported 9 results of urinary tract
13 infections. And, finally, the bladder function, the
14 renal function and the serum chemistry did not show
15 any signs of deterioration during the study period.
16 Next.

17 (Slide)

18 So 27 patients -- that means 69.2 percent
19 -- of Deflux group patients were grade II-IV, were
20 cured after implantation or reimplantation. We
21 retreated 18 patients. Eight patients -- that means
22 38.1 percent of patients with grade II-IV, in the
23 long-term antibiotic prophylaxis were cured. So, the
24 difference is 69.2 and 38.1 in the two groups. We are
25 thinking about patients.

1 Now, in this section of the slide, we are
2 talking about ureters. The cure rate per ureter in
3 patients with vesicoureteral reflux grade II-IV was in
4 the Deflux group, 38 out of a total of 62 units, 73.1
5 percent, while now out of a total of 30 renal units,
6 30 percent, were cured in the group on long-term
7 antibiotic prophylaxis. So in this case, the
8 difference is 73.1 and 30 percent. Next, and this is
9 the last slide.

10 (Slide)

11 The use of Deflux for local treatment of
12 vesicoureteral reflux is a safe treatment. And in
13 terms of efficacy, the efficacy evaluation showed that
14 compared to long-term antibiotic prophylaxis,
15 treatment of VUR with Deflux can be expected to result
16 in a higher degree of cessation of the VUR at one year
17 post treatment. Thank you.

18 DR. ANTHONY KALLOO: Thank you.
19 Questions?

20 DR. STEINBACH: When a patient was
21 retreated successfully, was the problem the first time
22 a problem with injection?

23 DR. CAPOZZA: No. Reinjection is not a
24 problem at all. It is more or less as the first time.

25 DR. STEINBACH: I guess my question was

1 misunderstood. Why was it necessary to inject the
2 first time? Is there indication that you had problems
3 with the first injection with directly locating the
4 point of injection?

5 DR. CAPOZZA: You mean after 3 months, or
6 immediately?

7 DR. STEINBACH: After 3 months.

8 DR. CAPOZZA: In case of failure, we
9 decided to give them a second treatment in all
10 patients who failed the first treatment.

11 DR. STEINBACH: How much of this was due
12 to -- you don't know.

13 DR. CAPOZZA: The absorption -- okay --
14 maybe it's out of the study, but we believe that the
15 dislocation of material -- can be a dislocation of the
16 material. Not the misplacement -- could be a
17 misplacement, but we have record of all treatments on
18 a tape, so every time with a failure, we go back to
19 the video and check if it's a misplacement, and it
20 wasn't in any case. It wasn't a misplacement. Maybe
21 a dislocation.

22 DR. STEINBACH: Thank you.

23 DR. KAEFER: Dr. Capozza, a few questions.
24 On page 6 of your handout, the first result slide for
25 Deflux II, and I'm sure I may have misunderstood this,

1 but it says under Results and Safety, glomerular
2 filtration, only 2 kidneys had no function. What does
3 that mean exactly?

4 DR. CAPOZZA: At the scintigraphy, they
5 were near to 0, the glomerular filtration was near to
6 0.

7 DR. KAEFER: So pretreatment, were they
8 also close to 0?

9 DR. CAPOZZA: Yes, this is at pretreatment
10 evaluation. We didn't do a pre and post treatment
11 evaluation in the Study II, just a prestudy.

12 DR. KAEFER: And so they were still
13 treated --

14 DR. CAPOZZA: Yes, because the function,
15 renal function, total renal function was perfectly
16 normal. It was just maybe a kidney with reflux. And
17 I think we should treat this kind of reflux even if
18 there is any problem for renal function, but for the
19 infections, for morbidity.

20 DR. KAEFER: Thank you. And I had two
21 other questions. On Deflux III, you had stated the
22 mean age was 3.1 years. Was there any difference in
23 the mean age between the controls and the patients
24 studied with injection?

25 DR. CAPOZZA: I think there is a

1 difference. It is not significant. It is in the
2 reports. This is just a short presentation.

3 DR. KAEFER: Thank you. Not statistically
4 significant difference.

5 DR. CAPOZZA: No.

6 DR. KAEFER: And the final question, you
7 said this was a randomized study. Was the intent of
8 the randomization to halve the difference, 40 studies
9 and 20 controls, or did it simply balance out that way
10 for other reasons?

11 DR. CAPOZZA: I didn't decide the
12 statistical -- I mean, disposition. It was -- the
13 randomization was based upon previous studies, and the
14 epidemiologists said this is the number of patients to
15 study.

16 DR. KAEFER: Thank you very much.

17 DR. ANTHONY KALLOO: There was 1 patient
18 who had dilatation that appeared at 12 months?

19 DR. CAPOZZA: Yes.

20 DR. ANTHONY KALLOO: Was that patient --
21 did that patient have a repeat cystoscopy to look at
22 potential explanations, or not?

23 DR. CAPOZZA: No, because the ultrasound
24 didn't show any renal damage, and scintigraphy didn't
25 show any renal damage, and the patient was very well.

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1 DR. DiLORETO: The patients, 2 patients
2 that had persistent -- this was in Deflux II,
3 persistent dilatation at a year out, were any other
4 studies done -- lysis, renography, or any --

5 DR. CAPOZZA: Yes. In the literature it is
6 well known that the rate of such complication is not
7 the real complication, but this occurs in about 1-2
8 percent, but these patients were followed up for years
9 and without any problem.

10 DR. DiLORETO: And the same goes with
11 these patients, obviously they've been followed -- I
12 know it's not part of the study, but they've been
13 followed and there's no --

14 DR. CAPOZZA: Yes. The study is just 1
15 year, but we follow our patients, any patient, even
16 patients who undergo o[pen surgery are followed for
17 years in Italy. We can't leave these patients, we
18 have to take care of them for many years.

19 DR. DiLORETO: Thank you.

20 DR. DONATUCCI: I'm not sure who to
21 address this question to, you may not be the
22 appropriate person, and perhaps I missed it in the
23 briefing document. What is the expected longevity,
24 how long do you expect these to last?

25 DR. CAPOZZA: This is a good question, but

1 also from previous experience with other biodegradable
2 materials -- I mean, collagen -- you can see the
3 implants even after 4-5 years by ultrasound.
4 Sometimes it is perfectly visible on ultrasound. So
5 our opinion is that the material, if the injection is
6 correct, lasts for some years, and you know the trend
7 of a basic ureteral reflux is the spontaneous cure.

8 DR. DONATUCCI: I understand that, but I
9 guess I'm asking, do we have data on this product for
10 life expectancy? And, again, you may not be the
11 appropriate person to ask. Is there anyone from the
12 company that could answer that?

13 DR. AGERUP: I am afraid I am the person
14 to ask it. First of all, I think Dr. Capozza pointed
15 an important thing with this material and that is that
16 the bladder is really a muscle that is moving a lot.
17 I mean, it is like -- I would say that displacement
18 could be the most probable reason for treatment
19 failure. Then if you have the material there, we know
20 that the hyaluronic acid, the carrier is leaving the
21 implant very quickly, within 3-6 weeks period, due to
22 the inflammatory reaction that we start with the
23 dextranomer beads. The dextranomer beads have been
24 hydrolyzed to a specific level so that we expect them
25 to be degradable, but in different tissues and

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1 different circumstances we also expect them to stay
2 different times, but they are not forever. They are
3 for -- in animal experiments, we calculate that they
4 could be about 3-5 years. But I wouldn't -- we
5 wouldn't guarantee such figures, but it's a good
6 guess.

7 DR. NAIDA KALLOO: In the report, in the
8 rat study, it mentioned that it lost about 23 percent
9 of its volume between the injection and the 1 year
10 study. Now, were there any studies longer out?

11 DR. AGERUP: No, we did not. I mean,
12 there were studies, but we couldn't analyze them
13 properly because it becomes a matter of defining what
14 is really the initial material, what is the
15 dextranomer and what is the tissue reaction and other
16 secondary things.

17 DR. NAIDA KALLOO: Now, the beads
18 themselves are hydrolyzed prior to injection?

19 DR. AGERUP: Yes.

20 DR. NAIDA KALLOO: Do they still maintain
21 that hydrosolic once they are injected? Do they still
22 increase in size once they are injected?

23 DR. AGERUP: No, not as far as we have
24 seen. They hydrolyze a bit different in tissue
25 because they are more controlled.

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1 DR. NAIDA KALLOO: The beads themselves do
2 not increase in size once they are injected?

3 DR. AGERUP: No.

4 DR. NAIDA KALLOO: The hyaluronic acid is
5 then dissipated but then is replaced by the fibroblast
6 and the fibrous tissue?

7 DR. AGERUP: Yes.

8 DR. NAIDA KALLOO: And in the children, on
9 ultrasound, did you measure the "bleb" (phonetic)?
10 Could that be measured by ultrasound?

11 DR. AGERUP: I must leave that question to
12 our clinicians, maybe Dr. Lackgren.

13 DR. LACKGREN: Goren Lackgren, Uppsala,
14 Sweden. Yes, we have measured the bolus on ultrasound
15 on three levels and tried to measure the volume. And
16 it's possible to see the bolus. It's very easy the
17 day after and after 3 and 12 months, and we have even
18 seen the bolus after several years. And we tried to
19 correlate that to the vesicoureteral orifice to see if
20 it's sufficient with an ultrasound in the future to
21 control the reflux, but it is very hard.

22 DR. NAIDA KALLOO: So it is not possible
23 to measure the side, let's say, the day after
24 injection and 12 months, to see if there's a decrease
25 in size of the bolus?

1 DR. LACKGREN: Well, it's possible to
2 measure, but it's hard to --

3 DR. NAIDA KALLOO: Correlate.

4 DR. LACKGREN: -- correlate that actually.
5 But we have a bolus after --

6 DR. NAIDA KALLOO: One of the studies, one
7 of the references mentioned that in some animal
8 studies the material was still around 3 to 4 years
9 later, but that was a study from 1977. Are there any
10 studies more recently that show that this particular
11 material is around longer than 2 years on a
12 histopathologic -- any histopathologic studies that
13 say that it's around longer?

14 DR. LACKGREN: In Uppsala we have
15 performed histopathological studies, and we did it on
16 rats until they died, which is two years in a normal
17 rat. That's what we know as far as we know, but as I
18 know no other studies were made.

19 DR. AGERUP: This is Bengt Agerup again.
20 The dog study in category, for instance, we kept the
21 implant for two years, and the implant was fully
22 visible and identifiable. So we would guess that the
23 3-5 years is sort of a reasonable estimate. I mean,
24 it's important that we can't hydrolyze them to 0,
25 there is nothing left if you hydrolyze the beads in

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1 vitro.

2 DR. NAIDA KALLOO: Were any surgical
3 reimplants performed on any of these patients during
4 the study?

5 DR. CAPOZZA: Nicola Capozza. Yes, of
6 course we reimplanted with open surgery in some
7 patients with Deflux treatment, and maybe even to know
8 if there is any difficulty in -- isolate the ureter
9 from the surrounding tissue, there isn't any
10 difficulty. If you want, you can remove also the
11 implant, the old implant with the ureter, with the
12 distal part of the ureter, and send it to the
13 pathologist if you want. It's possible.

14 I think to answer, if I can, the previous
15 answer about the failure and displacement and the
16 biodegradability of the material. We think that there
17 are two main reasons for failure. One is too deep an
18 injection. If you inject too deeply, the material can
19 slip away. It doesn't support -- it doesn't affect --
20 it lacks support for the ureter. And the other reason
21 is the displacement. And we saw that this
22 displacement of the implant is always in one
23 direction, the bladder neck. And there is a
24 correlation between the displacement and bladder
25 dysfunction because there are contractions, bladder

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1 contractions, in overactive bladders that push the
2 material. So if we perform endoscopic treatment, we
3 have to think about bladder function as well, and
4 maybe give them some drugs.

5 DR. NAIDA KALLOO: In the briefing, I only
6 saw that 2 patients were placed on Oxybutinin
7 (phonetic) in one of the studies.

8 DR. CAPOZZA: Yes. I am referring to
9 other studies, of course. It's not a part of this
10 study, the bladder dysfunction and correlation with
11 the failure.

12 DR. NAIDA KALLOO: I don't recall all of
13 the information, but I know in one of the studies the
14 12-month success rate for grade IV was less than 50
15 percent. On any of the studies, was it higher?

16 DR. CAPOZZA: It's possible. Not our
17 studies.

18 DR. NAIDA KALLOO: On any of these 3 --
19 Deflux I, II and III -- was it higher than -- I only
20 saw one mention of the specific 12-month success rate
21 for grade IV, and it was 46.7 percent. I don't recall
22 seeing it for any of the other two. Was it ever
23 higher at 12 months for grade IV?

24 DR. CAPOZZA: I have to check my data
25 because I have another slide not in this presentation

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1 about grade IV results.

2 DR. LACKGREN: Goran Lackgren, Uppsala,
3 Sweden. In the first study, there were 7 out of 11
4 ureters that were cured after 12 months, in grade IV.

5 DR. NAIDA KALLOO: And was that after 1 or
6 2 injections?

7 DR. LACKGREN: After -- both, either 1 or
8 2 injections.

9 DR. DiLORETO: In I, II and III, how many
10 ureters were retreated, and what was the
11 success/failure rate based on grade of those that were
12 retreated, and when were they retreated?

13 DR. LACKGREN: Actually, the retreatment
14 was not a part of the first study where we did mostly
15 safety studies.

16 DR. DiLORETO: Well, then II and III?

17 DR. NAIDA KALLOO: There's a mention of a
18 20 percent retreatment rate, and then there was a
19 comment --

20 DR. CAPOZZA: Yes, and in the study III,
21 18 ureters were retreated.

22 DR. DiLORETO: One time, or more than one
23 time?

24 DR. CAPOZZA: No, just one time. The
25 protocol is just one retreatment. Otherwise, they

1 were out of the protocol, out of the study.

2 DR. DiLORETO: In that subset of
3 retreatment, what was the success/failure rate?

4 DR. DiLORETO: Okay, let me see.

5 DR. NAIDA KALLOO: I saw one comment that
6 said -- it said 20 percent retreatment rate at 3
7 months, and the comment was, "They were less likely to
8 improve than the general population if they were
9 retreated". But I tried to tease out the specific
10 number for the retreated and their success rate, but
11 I couldn't tease it out of the data. It just said
12 that they were less likely to improve.

13 DR. CAPOZZA: Okay. I have a slide. In
14 grade II, we didn't have any retreatment -- talking
15 about study No. III. In grade III, we retreated 8
16 ureters, and I have the success rate. After 1
17 injection, is 62.5. After 2 injections, it is 71
18 percent. In grade IV, we retreated 5 ureters, and the
19 percentage after a single injection is 29 percent.
20 After 2 injections, it is 43 percent.

21 DR. DiLORETO: One other question. I had
22 a little difficulty going through the data, and
23 actually I was looking specifically at the timing
24 here. How many -- it seemed to me in actually all 3
25 of the groups, that a significant number of patients

1 were seen, screened, voiding studied, consented, and
2 treated on the same day.

3 DR. CAPOZZA: No, it wasn't the same day.
4 When you see screening in the prestudy, it doesn't
5 mean the same day.

6 DR. DiLORETO: It's not the same day.

7 DR. CAPOZZA: Not the same day. It may be
8 in one month, especially screening. In prestudy,
9 usually one week before treatment. They came back for
10 the treatment.

11 DR. DiLORETO: So there isn't a cohort of
12 patients in here that were handled that way, screened
13 and --

14 DR. CAPOZZA: There are some patients, but
15 considering some geographical problems we have, it's
16 impossible to do at the same time screening and
17 prestudy because they want to come maybe twice, but
18 for one day -- and it is also the policy of ours not
19 to put the children for a long time in hospital.

20 DR. DiLORETO: I understand. Do you have
21 in the last -- particularly the last group of
22 patients, how many of those that were handled that
23 way, that may have been screened, randomized treated
24 the same day?

25 DR. CAPOZZA: The same day -- screening

1 and prestudy, a lot of them are the same day, but the
2 treatment could be a week later.

3 DR. DiLORETO: Not the same day.

4 DR. CAPOZZA: No, not the same day. No.

5 DR. DONATUCCI: One brief clarification,
6 please. Who read the radiographic studies in the
7 randomized trial?

8 DR. CAPOZZA: The radiologist. Because I
9 read about the question. I think it is a blinded
10 evaluation because the radiologist doesn't know
11 anything about which patient is a Deflux patient,
12 which one is antibiotic, which one is another one.

13 DR. DONATUCCI: Was it the same
14 radiologist?

15 DR. CAPOZZA: No, not the same
16 radiologist. The only thing I thought the
17 radiologist, but generally speaking is not -- it is to
18 be very careful with the filling, the bladder filling.
19 We have normal values of bladder capacity, and the
20 tendency -- the trend of the radiologist is to
21 overfill the bladders because if they ask the child
22 when is the moment they want to urinate, and sometimes
23 the children don't say anything because they are
24 afraid because they don't want to -- they don't want
25 to cooperate. So I recommend to the radiologist not

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1 to exceed the bladder filling, but this is just this
2 one general recommendation. And I was not in the
3 radiology department during the examination.

4 DR. GORMAN: At the hospital I practice
5 at, occasionally there are disagreements between
6 clinicians and radiologists. Did that occur in the
7 reading of the studies and, if so, whose assessment of
8 the grade of reflux was put on the clinical report
9 form?

10 DR. CAPOZZA: A successful treatment is
11 grade 0 or I, and the failure is grade II to IV. We
12 can forget the difference between grades II and III
13 and III and IV. We don't need it. It's a failure
14 even if the radiologist says its grade IV and I say
15 it's grade III. And you can't miss the difference
16 between grade I and grade II because grade I is
17 incomplete reflux and grade II is complete. Of
18 course, we had discussions sometimes with the
19 radiologists, and we disagreed just in one case.

20 DR. GORMAN: Can we speak for the same
21 system of radiology and urologists at our hospital in
22 Sweden?

23 DR. LACKGREN: There are several hospitals
24 involved. You should know in our area which is almost
25 two-thirds of Sweden in size, and we serve 3 million

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1 for pediatric urology, and that's about ten county
2 hospitals. Most of our patients come from very far
3 away, which means that we have not made the checkup at
4 our clinic. But the hospitals are very well trained
5 and they know what we want. And the radiology
6 department at each hospital has done the followup on
7 a standardized manner, and we have followed the
8 results from the radiologists, but we have seen all
9 the x-rays afterwards. So that's the way we are doing
10 it, and I fully agree with Dr. Capozza about the
11 results.

12 DR. NEWMAN: It appears it's critical
13 where you place this material. What is the learning
14 curve here? You must have lots of people doing it in
15 Europe, a lot of physicians and thousands of cases.

16 DR. LACKGREN: Actually, I can say that
17 when we started it, we put one of the causes for
18 failure was unexperienced surgeons, and that we have
19 removed because it does not seem to be the case
20 actually because it's very easy to learn, it's very
21 easy to perform for an urologist that has experience
22 with endoscopic technique. So you are actually
23 achieving results immediately because it is easy to
24 inject. So it doesn't seem to be a very long learning
25 curve.

1 DR. CAPOZZA: Nicola Capozza, Rome. We
2 had the same experience. I personally performed all
3 the children in the study, but I took the study --
4 everybody, every physician at our hospital does it
5 without any problem. With the experience, you can
6 save material and you can reduce the number of
7 punctures, of course, but the final result is the same
8 because you have to inject until you see the good
9 configuration, the crescent-like kind of projection,
10 the volcano-shaped bolus. When you see that
11 configuration, you are satisfied and you stop.

12 DR. KAEFER: Are the results of your
13 colleagues in your department as good as yours?

14 DR. CAPOZZA: Sorry?

15 DR. KAEFER: Are the results of your
16 colleagues in your department as good as yours?

17 DR. CAPOZZA: Yes, in this study, of
18 course.

19 DR. BANIK: I have a question going back
20 to the longevity of the implant material and
21 referencing the label copy claims. In your label, you
22 indicate that the material is present for 3 to 4
23 years or more, and I'm assuming you're relating that
24 to some human data. I think you talked about only
25 data available on rats up to 2 years, and we also

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1 talked a little bit about a 20 percent initial
2 degradation in size at the initial implant.

3 Is there other data to back up the
4 duration of the claim for the material being present
5 for bulking in 3 to 4 year range?

6 DR. AGERUP: Bengt Agerup. I'm afraid we
7 have no such data. I think, on the other hand, Dr.
8 Lackgren can comment a little bit about his experience
9 because he has the longest experience with the
10 material, the dextranomer particles.

11 DR. LACKGREN: Yes, we are following the
12 patients the same way after operations, and we have
13 very few late recurrences regarding urinary tract
14 infections, which we see as a sign of durability.

15 If I may comment about durability
16 regarding vesicoureteral reflux, we know that there is
17 a risk of renal scarring in the young patients
18 probably below the age of 4 or 5 years. And if you
19 can be without reflux during that period from 1 to 5
20 years, I think that in many instances is sufficient.
21 So we are not looking at a material that should stay
22 lifelong. Actually, we don't want that. We want
23 during the time of maturation that they shouldn't get
24 an infection, and I think we have achieved that. And
25 looking at when we see the patients is that ones that

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1 are failures, are initial failures, and those are the
2 ones that are going on for further open surgery, and
3 only in occasional cases we have had late failures
4 with pyelonephritis and come back with a significant
5 reflux that had needed operation. So that's our
6 experience.

7 DR. KAEFER: The topic of dysfunctional
8 voiding is hard to define in your patients, especially
9 when your age mean is 3.1 years. But do you see any
10 correlation of dysfunctional voiding, urinary
11 frequency, urgency, and a higher lack of success or
12 lower success rate?

13 DR. CAPOZZA: Nicola Capozza. Yes, you
14 are right, the mean age is low, and in a lot of our
15 cases in this study, we put just diapers in the form
16 because, of course, you can say anything about wetting
17 function between 2 and 3 years. But for adult studies,
18 we can say that there is a correlation. It is very
19 significant between wetting dysfunction and recurrence
20 of reflux. And in those cases, we perform cystoscopy
21 just to reinject the patient. And in those patients
22 we saw a displacement. So there is a correlation
23 between wetting dysfunction, recurrence and
24 displacement.

25 DR. KAEFER: Do you have any different

1 recommendations for the use of this material then in
2 patients who have dysfunctional voiding
3 characteristics?

4 DR. CAPOZZA: Not a particular
5 recommendation, a general recommendation -- any
6 material you want to use maybe you have to wait until
7 maybe 6 months until the bladder is quite normal. In
8 some cases, you can't inject the material. You can
9 see the vesicoureteral orifice. You can see a bladder
10 with a thick wall that it is impossible to inject such
11 kind of a bladder. So the recommendation in case of
12 bladder dysfunction is wait.

13 DR. NAIDA KALLOO: I had another question
14 about urinary tract infections. On page 37, it
15 mentions that 6 patients had urinary tract infections
16 after 12 months. Were those patients patients that
17 had -- were those patients failures, all 6?

18 DR. CAPOZZA: Yes. They are all in Deflux
19 group, and they were failure.

20 DR. NAIDA KALLOO: And then on page 38 it
21 mentions 7 urinary tract infections during the study,
22 and then on page 40 it mentions 9 urinary tract
23 infections during the study.

24 DR. CAPOZZA: Patients and episodes.
25 Seven patients, 9 episodes. Some patients have more

1 than one infection episode.

2 DR. NAIDA KALLOO: Was there a correlation
3 between whether those patients were failures?

4 DR. CAPOZZA: Yes, they were failures.

5 DR. NAIDA KALLOO: So all patients that
6 had urinary tract infections were failures?

7 DR. CAPOZZA: Yes.

8 DR. NAIDA KALLOO: Were these urinary
9 tract infections related to intervention?

10 DR. CAPOZZA: No. No, we don't think so,
11 but you have to think about that all Deflux patients
12 discontinued the prophylaxis after 1 month. So they
13 were without prophylaxis and with reflux because they
14 were failure.

15 DR. NAIDA KALLOO: If they were injected
16 at time 0, they had another radiographic study at 3
17 months, and then at 12 months. Was there a
18 correlation between the radiographic study -- for
19 example, the catheterization -- and the urinary tract
20 infection?

21 DR. CAPOZZA: It could be. We didn't
22 study this correlation. Of course, the day before the
23 cystogram, they ate prophylaxis.

24 DR. NAIDA KALLOO: So you are covering
25 them for the study. Okay.

1 DR. CAPOZZA: Yes. Cystogram is always
2 done under prophylaxis, even if they stop the
3 prophylaxis after the treatment, a month after the
4 treatment.

5 DR. NAIDA KALLOO: They are treated the
6 day before, the day of, and the day after?

7 DR. CAPOZZA: Three days.

8 DR. NAIDA KALLOO: And I had one more
9 question. Theoretically, the higher grades of reflux
10 have a shorter intramural tunnel. Was there more
11 difficulty in getting an adequate crescent shape in
12 the higher grades of reflux, and did you find you used
13 more of the dextranomer?

14 DR. CAPOZZA: Material, yes, you are
15 right. There are some recommendations in grade IV.
16 One is maybe to go inside the ureter, to inject inside
17 the ureter. This is one technique. There was another
18 technique, the balloon catheter, to attract the ureter
19 in the bladder, and then we can inject -- but this is
20 too complicated. The only recommendation is to inject
21 maybe more material and inside the ureter because you
22 don't have a plain in which to perform the injection.
23 So you have to go a little inside, but this is a
24 little tricky in grade IV.

25 DR. NAIDA KALLOO: Do you mention that in

1 your video?

2 DR. CAPOZZA: My video?

3 DR. NAIDA KALLOO: In the video. Do you
4 mention those tricks in the video for the higher
5 grades of reflux?

6 DR. CAPOZZA: I have a video, but not
7 here.

8 DR. LACKGREN: I agree with Dr. Capozza.
9 If you have the high grade reflux severely lateralized
10 and with a short tunnel, of course you have no roof to
11 put the material on. You may see a bolus, but what
12 happens with a failure, they just sink down, which you
13 see when you do the UCG after 3 months. So those are
14 severe cases, but the reason we are doing this is to
15 exclude patients from surgery, and those are the
16 surgical cases. But we don't know initially it's a
17 difficult case because some of them may be cured.

18 DR. ANTHONY KALLOO: Before the next
19 presentation we will take precisely a 10-minute break.

20 (Whereupon, a short recess was taken.)

21 DR. ANTHONY KALLOO: Next, we will proceed
22 with the FDA presentation of the open public hearing.
23 Again, I would like to remind the panel that they may
24 ask for clarification of any points included in the
25 FDA presentation, but the discussion should not go

1 beyond clarification.

2 The first speaker for the FDA is John
3 Baxley, Biomedical Engineer. John.

4 MR. BAXLEY: Thank you. Good morning.

5 (Slide)

6 I'm John Baxley, a Biomedical Engineer in
7 the Urology and Lithotripsy Devices Branch and lead
8 reviewer of the PMA that is before you today, Deflux
9 Injectable Gel for the treatment of vesicoureteral
10 reflux in children.

11 The applicant has presented a thorough
12 overview of the information contained within the PMA.
13 Therefore, FDA will take this time to highlight our
14 comments regarding the information submitted in this
15 application, and bring your attention to the issues on
16 which we are particularly interested in receiving your
17 guidance.

18 (Slide)

19 Our presentation will be divided into
20 three parts. First, I will present some
21 administrative information regarding our review of the
22 PMA, the FDA review team's comments regarding the
23 device description and preclinical testing
24 information, and some background information regarding
25 the clinical studies. Following my talk, Dr. Hector

1 Herrera, Urologist and Clinical Reviewer of the PMA,
2 will summarize his comments regarding the clinical
3 results and conclusions. Lastly, Judy Chen, CDRH
4 Statistician, will briefly summarize her comments
5 regarding the clinical studies and their analyses.

6 (Slide)

7 Before I discuss the information contained
8 within the PMA, however, I'd like to point out that
9 FDA granted this PMA expedited review status.
10 According to the FDA guidance document entitled
11 PMA/510(k) Expedited Review, a submission is eligible
12 for expedited review if (1) the proposed device is
13 intended to treat or diagnose a life-threatening or
14 irreversibly debilitating condition, and (2) it
15 satisfies one of four criteria, one of which is that
16 the device represents a clear, clinically meaningful
17 advantage over existing alternatives. Since pediatric
18 vesicoureteral reflux has the potential to cause
19 irreversible kidney damage, and since FDA believes
20 that an injectable bulking agent for the treatment of
21 vesicoureteral reflux may be significantly safer than
22 open surgery while more effective than observation
23 with antibiotic prophylaxis, we decided that expedited
24 review of this PMA was justified. It is important to
25 note that expedited review does not change the

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1 criteria for approval. Rather, it means that this
2 application takes precedence in the review queue over
3 other PMAs.

4 (Slide)

5 The next two slides list the entire review
6 team for this PMA, whom I'd like to publicly thank for
7 their hard work and expert advice. As I've already
8 mention, Dr. Herrera is the clinical reviewer. The
9 other members of the team are as follows: the
10 statisticians are Judy Chen and T.C. Lu, the
11 toxicologist is Dr. Raju Kammula, the chemist is Dr.
12 Rao Nimmagadda.

13 (Slide)

14 The microbiologist is Cathy Nutter, the
15 patient labeling reviewer is Jack McCracken, the
16 manufacturing and quality systems reviewer is Don
17 Watchko, and the bioresearch monitoring liaison is
18 Barbara Crawl.

19 (Slide)

20 Let me now briefly discuss the PMA and
21 draw your attention to some important issues. I'll
22 begin with the device description and implantation
23 information.

24 As presented earlier, Deflux is a sterile,
25 nonpyrogenic, injectable bulking agent consisting of

1 a suspension of crosslinked dextran particles, or
2 dextranomer, in an aqueous solution of hyaluronic
3 acid. The hydrated particles range in size from 80-
4 250 microns, with an average size of approximately 130
5 microns. The product is filled into 1 ml,
6 polycarbonate syringes, packaged, and moist heat
7 sterilized. The labeling states that Deflux must be
8 stored at 3-15°C to prevent deterioration.

9 (Slide)

10 As stated in the applicant's presentation,
11 the proposed indication for Deflux Injectable Gel is
12 the treatment of vesicoureteral reflux in children.
13 The purpose of this injection is to create increased
14 tissue bulk at the vesicoureteral orifice, causing
15 coaptation and blockage of the flow of refluxing
16 urine. Dr. Herrera will comment in more detail on the
17 injection technique and mechanism of action in his
18 presentation.

19 (Slide)

20 Next I'll say a few words about the chemistry
21 information that was reviewed by Dr. Nimmagadda. The
22 PMA contains detailed chemical information regarding
23 the processing and formulation of Deflux. This
24 information documents that the device has sufficiently
25 low levels of impurities, such as proteins,

1 crosslinking agents, and heavy metals. FDA does not
2 have any significant concerns regarding the chemistry
3 information and testing.

4 (Slide)

5 Now for the preclinical testing
6 information, beginning with biocompatibility testing,
7 which was reviewed by Dr. Kammula. As summarized
8 earlier in the applicant's presentation, the PMA
9 contains the results of a variety of biocompatibility
10 tests to demonstrate that Deflux does not pose a
11 toxicological risk when permanently implanted in the
12 bladder submucosa of children. These tests included
13 cytotoxicity testing, hemolysis testing, sensitization
14 testing, intracutaneous toxicity testing, mutagenicity
15 testing, (slide) 90-day muscle implantation testing
16 in rabbits, 2-year bladder submucosal implantation
17 testing in rabbits and dogs, and a migration study in
18 rabbits.

19 (Slide)

20 This testing did not reveal any concerns.
21 In particular, the risk of migration of the
22 dextranomer particles is adequately addressed within
23 the PMA. Not only did the animal studies fail to
24 demonstrate distant migration, but the likelihood of
25 particle migration is improbable given their large

1 size. After reviewing the chemistry information in
2 detail, we agree with the applicant that
3 carcinogenicity and reproductive/developmental
4 toxicity testing is not warranted given that the
5 ingredients of Deflux are well understood, the levels
6 of impurities are reasonably low, and each of the
7 biocompatibility tests described was successfully
8 passed.

9 (Slide)

10 The PMA also contains the results of
11 additional biocompatibility tests performed on the
12 hyaluronic acid portion of Deflux. This injectable
13 material is legally marketed abroad for facial tissue
14 augmentation under the trade name Restylane. These
15 additional tests were reviewed as supplementary
16 information, and did not raise any concerns regarding
17 the biocompatibility of Deflux.

18 (Slide)

19 The other preclinical tests that I'll
20 discuss address the force and time required to inject
21 Deflux, and the stability of the material over time.
22 The results of injectability testing show that the
23 prefilled syringe can be emptied through the accessory
24 needle in less than 3 minutes with a peak force of
25 about 9 pounds, verifying the use of the manual

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1 injection technique. The stability testing assessed
2 a range of physical, chemical, and microbiological
3 properties in batches of Deflux-filled syringes during
4 both real-time and accelerated aging. Although the
5 long-term results of such testing are either mixed or
6 incomplete, this information demonstrates that Deflux
7 has a shelf life of at least 12 months when stored at
8 3-15°C.

9 (Slide)

10 At this point, let me switch the
11 discussion to the clinical information. As presented
12 to you in detail earlier this morning, the primary
13 evidence submitted in support of the safety and
14 effectiveness of Deflux comes from three, separate
15 clinical studies, which were performed at two European
16 sites: Uppsala, Sweden and Rome, Italy. Although
17 PMAs are usually not entirely based on foreign
18 clinical data, such data are valid and acceptable
19 provided certain criteria are met.

20 (Slide)

21 These criteria, stated in the Code of
22 Federal Regulations, are:

23 - the studies were conducted in accordance
24 with the Declaration of Helsinki or the
25 laws and regulations of the country in

1 which the research was conducted,
2 whichever accords greater protection to
3 human subjects;

4 - the foreign data are applicable to the
5 U.S. population and U.S. medical
6 practice;

7 - the studies were performed by clinical
8 investigators of recognized competence;
9 and

10 - FDA is allowed to validate the data
11 through an inspection or other
12 appropriate means, if FDA considers such
13 an investigation to be necessary.

14 The applicant states that all studies were
15 conducted in accordance with the Declaration of
16 Helsinki, and that informed consent was obtained from
17 the parents or guardians of each child prior to study
18 entry. Additionally, the firm has informed FDA that
19 both sites are open for routine bioresearch monitoring
20 inspection, which has been scheduled. Although it
21 appears that the firm has addressed the other two
22 criteria as well, I ask you to keep them in mind as
23 you discuss the PMA today.

24 (Slide)

25 I'd now like to emphasize a point that the

1 applicant brought up earlier regarding the design and
2 limitations of the three clinical studies. Although
3 the general entry criteria and endpoints are similar
4 among the three studies, there are some important
5 differences:

6 - Studies 1 and 2 did not have control
7 arms, while Study 3 was designed as a
8 randomized, controlled clinical trial to
9 compare the safety and effectiveness of
10 Deflux to observation with antibiotic
11 prophylaxis.

12 - Studies 1 and 2 were designed as safety
13 studies, whereas Study 3 was designed to
14 definitively evaluate the safety and
15 effectiveness of Deflux.

16 - Studies 1 and 2 did not closely monitor
17 patients for signs of renal damage,
18 whereas Study 3 did.

19 - Studies 1 and 2 had some missing data and
20 loss-to-follow-up, while Study 3 followed
21 patients closely.

22 Based on these differences, the firm
23 proposes and FDA agrees that the studies be assessed
24 individually rather than pooled, and that the results
25 of Study 3 be regarded as the primary evidence of

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1 safety and effectiveness with Studies 1 and 2 serving
2 as supplementary data.

3 (Slide)

4 Next, let me point out two potential
5 weaknesses of the primary study, Study 3, which were
6 raised during FDA's statistical review of the PMA. We
7 are specifically requesting the Panel's input and
8 guidance on these times during your deliberations.
9 The first item is that Study 3 was conducted at a
10 single institution. Our specific concerns regarding
11 the lack of multicenter experience with this
12 controlled trial are (1) the study population may not
13 be sufficiently diverse in demographic and baseline
14 characteristics to permit comparison to the U.S.
15 patient population, and (2) the study may not have
16 sufficiently documented the full range of injection
17 techniques and any other physician-dependent outcomes.

18 (Slide)

19 The second general concern is that the
20 comparison of effectiveness between Deflux and
21 antibiotic therapy in Study 3 is based upon a
22 subjective grading system, i.e., the International
23 Classification System, yet the assessment of post-
24 treatment reflux grade was not performed by a blinded
25 evaluator. While the International Classification

1 System is clearly the worldwide standard for grading
2 the severity of reflux, the fact that evaluators were
3 not blinded to the treatment that each patient
4 received introduces a potential source of investigator
5 bias. Even in the most well meaning evaluator, it is
6 possible that such bias can unintentionally occur in
7 the absence of blinding. One possible way to minimize
8 the effect of any such bias with the current data is
9 to restrict the definition of success to grade 0,
10 meaning total absence of reflux, since this grade
11 category is less subjective in nature than grades 1
12 through 5.

13 (Slide)

14 At this point, I'd like to introduce Dr.
15 Herrera, clinical reviewer of the PMA. He will provide
16 his comments regarding the clinical results of these
17 three studies, as well as briefly discuss the concerns
18 that I just presented. Dr. Herrera.

19 DR. HERRERA: Good morning. I am Hector
20 Herrera, a urologist and Medical Officer in the
21 Urology and Lithotripsy Devices Branch. I will go
22 over the history and general safety and effectiveness
23 data of the Deflux Injectable Gel for Vesicoureteral
24 Reflux in Children.

25 (Slide)

1 I will begin with the description of the
2 International Classification of the vesicoureteral
3 reflux, then I will comment on the pivotal clinical
4 study or study 3 and at the end I will comment on the
5 supplementary data or studies 1 and 2. Bulking agents
6 to correct stress urinary incontinence have been
7 investigated in the United States for approximately
8 the past ten years. This is the first bulking agent
9 to request FDA approval for the treatment of
10 vesicoureteral reflux.

11 (Slide)

12 The accepted and established
13 classification scheme for evaluation of vesicoureteral
14 reflux is as follows:

- 15 - Grade I reflux is defined as reaching
16 into a non-dilated ureter.
- 17 - Grade II reflux reaches into the renal
18 pelvis and calices without producing
19 dilatation of the collecting system.
- 20 - Grade III reflux produces mild to
21 moderate dilatation and minimal blunting
22 of the collecting system.
- 23 - Grade IV reflux produces ureteral
24 tortuosity and dilatation of the pelvis
25 and calices.

1 - Grade V reflux produces gross dilatation
2 of the ureter, pelvis and calices with
3 complete loss of papillary impression.

4 As John mentioned, one of the criticisms
5 was that the evaluation of the x-rays was performed
6 unblinded and by only one observer. But with such
7 clear classification of the reflux it is difficult, in
8 the majority of the cases, to confuse or miss the
9 different grades of reflux.

10 (Slide)

11 The tissue bulking effects of Deflux are
12 believed to be after the absorption of the hyaluronic
13 acid, the result of the Dextran microspheres which
14 allow ingrowth of collagen and fibroblasts between the
15 particles that facilitates the bulking.

16 (Slide)

17 The injection technique is very
18 straightforward, and urologists are well familiarized
19 with the procedure. As was mentioned by the applicant
20 it is performed cystoscopically under direct vision
21 through a narrow long cannulae that fits into the
22 cystoscope connected to a video camera. The material
23 is injected submucosally at the 6 o'clock axis of the
24 ureteral opening, patients were treated with up to a
25 maximum total amount of 3 ml of substance averaging

1 0.8-1 ml to obtain the coaptation desired. Normally,
2 one puncture gives satisfactory results, but in some
3 cases 2-3 punctures may be required.

4 (Slide)

5 An improvement to a non-refluxing grade 0
6 urinary bladder was to be classified as successful,
7 and a post-treatment at three months persistence of
8 the reflux was regarded as treatment failure and had
9 the option to be retreated.

10 As John mentioned, Study 3 is regarded as
11 the primary evidence of safety and effectiveness; it
12 was conducted at Italy in a single institution. The
13 Italian study was a randomized comparative study of
14 Deflux in children with vesicoureteral reflux grade
15 II-IV. The control was the continuous prophylactic
16 treatment with antibiotics. The observation period
17 after the initial treatment in both groups was one
18 year.

19 (Slide)

20 A total of 61 patients fulfilled
21 eligibility and were randomized to either Deflux
22 implantation, 40 subjects, or long-term antibiotic
23 prophylactic treatment, 21 subjects.

24 (Slide)

25 Although patients were similar in many

1 baseline demographics such as gender and age, it is
2 noted the great majority of patients were Caucasians,
3 but well known low incidence of VUR in black children,
4 as Askari and Belman have reported in the literature,
5 may closely resemble the demography of the United
6 States.

7 (Slide)

8 All subjects assigned to the long-term
9 antibiotic completed the 12 month study period. Of
10 the 30 ureters in this group evaluated at 12 months,
11 9 were successes and 20 were failures. On a per-
12 ureter basis the success for the antibiotic arm was 30
13 percent, on a per patient basis the success was 33
14 percent.

15 (Slide)

16 On the Deflux arm, one subject withdrew
17 before treatment and 8 discontinued due to persistence
18 of reflux. Thirty-one patients, 40 ureters, were
19 evaluated at 12 months, 35 ureters of them were
20 successes and 3 were failures. Nine other ureters
21 were discontinued at 3 months due to failure. The
22 success rate on a per ureter basis was 71 percent and
23 on a per patient basis was 69 percent.

24 (Slide)

25 And you can see in the overview the

1 effectiveness of Study 3. As I said earlier, Studies
2 1 and 2 were supplementary data only.

3 (Slide)

4 The Swedish clinical study, Study 1, was
5 a non-randomized trial. A total of 50 children, 33
6 females and 17 males with grade III-IV reflux and
7 older than one year of age were injected with Deflux.

8 (Slide)

9 After 12 months of treatment there is a
10 total of 47 ureters evaluated: 30 were grade 0 or
11 successes. The remaining 15 ureters withdrew prior to
12 12 months, of whom 5 were refluxing at 3 months and
13 wee not followed further. Therefore, the 5 ureters
14 are also counted as failures. This study demonstrated
15 that the procedure was successful in 30 ureters, or 57~
16 percent of ureters and 56 percent of patients.

17 (Slide)

18 The Italian clinical study, Study 2, was
19 a non-randomized study of 120 children with
20 vesicoureteral reflux Grades II-IV, receiving Deflux
21 System implant treatment.

22 (Slide)

23 Eighty-nine females and 31 males were
24 eligible leaving 167 ureters to be studied. At 12
25 months, 95 patients, or 127 ureters, were evaluated,

1 resulting in 95 of them becoming successes and 18
2 failures. An additional 40 ureters dropped out prior
3 to 12 months of whom 14 are known to have failed
4 treatment. Including these 14 dropouts with the 127
5 ureters followed at 12 months, the success rate was 67
6 percent on a per ureter basis and 61 percent on a per
7 patient basis.

8 (Slide)

9 As you can see, this is the summary of
10 Studies 1 and 2.

11 (Slide)

12 As you heard earlier, the patients were
13 allowed one retreatment. The retreatments were 18
14 percent, 16 percent and 27 percent at the three
15 studies.

16 (Slide)

17 It is noted that there is a strong trend
18 of decrease effectiveness with increasing baseline
19 grade.

20 (Slide)

21 As you can see in the slide, safety.

22 (Slide)

23 The safety evaluation Study 3, included
24 scintigraphy and serum-chemistry to assess kidney
25 function. Ultrasonography and intravenous pyelography

1 was performed to assess kidney status.

2 (Slide)

3 Subjective symptoms and urine culture were
4 performed if dipstick were suggestive of urinary tract
5 infection. Bladder function and adverse events were
6 also documented.

7 (Slide)

8 Bladder function, renal function and the
9 serum chemistry did not show any signs of
10 deterioration during the study. Only one adverse even
11 occurred that required hospitalization, which was
12 fever and diagnosed as stomatitis in the control arm.
13 Nine urinary tract infections were detected in 6
14 implanted patients of whom 4 had asymptomatic
15 bacteriuria, 4 had cystitis and 1 had pyelonephritis.

16 (Slide)

17 From the safety standpoint in Study 1 and
18 2, the serum parameters were within normal limits, but
19 many values were missing. The same can be said of the
20 ultrasound investigations at later visits.

21 (Slide)

22 Ultrasound revealed no increase of
23 ureteral obstruction. Two patients in Study 1 and 17
24 patients in Study 2 with dilatation had this resolved
25 at last ultrasound. In contrast in both studies, the

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1 rate of de novo dilatation was less.

2 (Slide)

3 No urinary tract infections reported for
4 Study 1. Seven patients in Study 2 experienced 8
5 urinary tract infection. Both studies were prescribed
6 antibiotics during the entire study period.

7 (Slide)

8 Only two cases of nausea, vomiting and
9 pain post-injection were reported in Study 1, and none
10 in Study 2.

11 (Slide)

12 To conclude, this particular bulking agent
13 appears to show efficacy, but there are outstanding
14 questions we look forward to hearing the Panel
15 deliberate, including the evaluation of blinding and
16 the fact that the pivotal study was performed at one
17 site.

18 The demographics seem not to be as
19 different as in the United States when we consider the
20 low incidence of VUR in black children. I think that
21 the administration procedure is simple and requires
22 minimal learning curve. In light of this, we are
23 interested in the Panel's opinion regarding whether a
24 physician training program is required.

25 The safety profile is good. The long-term

1 effects are unknown, but I do not think in this
2 particular entity is as critical.

3 There are some statistical points that
4 need clarification and now Judy Chen will address
5 these. Thank you.

6 MS. CHEN: Good morning. I am Judy Chen,
7 the reviewing statistician for this submission. I am
8 from the Division of Biostatistics in Office of
9 Science and Biometrics.

10 (Slide)

11 We have all heard there are three studies
12 in this submission. In the first two of them are non-
13 randomized single arm study of 50 patients performed
14 in Sweden, and another one is 120 patients and it is
15 in Italy. The third study is the pivotal study, and
16 it is a randomized controlled study of 61 patients in
17 Italy.

18 (Slide)

19 For the first two uncontrolled studies, I
20 am concerned about whether observed improvement were
21 due to the device or part of it can be due to
22 spontaneous improvement over time, or even due to
23 regression to the mean which actually is a random
24 fluctuation of the disease state, or it is due to a
25 combination of all of the above.

1 (Slide)

2 You have seen the effectiveness are all
3 measured based on a ureter. Each success rate will
4 have a larger variance because outcomes of within-
5 patient ureters are likely to be correlated. So it
6 really cannot be counted as an independent unit.

7 (Slide)

8 Now, for the randomized controlled study,
9 there are also protocol deviations. First, there were
10 two centers specified in the protocol, but only one
11 center entered patients. So the question is whether
12 this good result can be reproduced in another center.

13 Second, an independent masked evaluation
14 was indicated in the protocol, but endpoint evaluation
15 was not masked in the study.

16 Third, also in the control antibiotic
17 treatment compliance was poor. In fact, only 62
18 percent of patients did not return diaries concerning
19 their antibiotic treatment.

20 (Slide)

21 Further, for this randomized controlled
22 study, the data were also evaluated on a ureter basis,
23 and actually the data from both device and control
24 group cannot really rule out a correlation between the
25 outcomes of 2 ureters in the same patient being

1 correlated. In fact, there were 10 patients in the
2 device group who had both ureters treated, and 9 out
3 of 10 had same outcome. And in the control group, 9
4 patients had two ureters treated, and 8 of 9 had same
5 outcome. So these ureter based observations are not
6 really independent observations.

7 (Slide)

8 Ureters in the same patient are seen to be
9 correlated, the statistically highly significant
10 treatment difference, or the highly significant p-
11 value is not reliable.

12 (Slide)

13 Further, covariable adjustment was
14 specified in the protocol, but no adjustment was done
15 in the sponsor's per-ureter analysis or per-patient
16 analysis.

17 (Slide)

18 Therefore, we do not know whether Deflux
19 treatment will benefit children over the entire age
20 range or entire disease grade included in the study.
21 Thank you.

22 (Slide)

23 My conclusions are given the deficiencies
24 listed, the data should be reanalyzed by both the
25 sponsor and FDA to validate the sponsor's statistical

1 conclusion. And also the results need to be
2 interpreted with the other deficiencies in mind.
3 Thank you.

4 DR. ANTHONY KALLOO: Thank you. Any
5 clarifications from the Panel for FDA?

6 (No response.)

7 If not, Dr. Schultz?

8 DR. SCHULTZ: Thank you very much. My
9 name is Dan Schultz. I am the Acting Director for the
10 Division and the Deputy Director for the office.
11 First of all, let me say I welcome you all here and I
12 appreciate you all being here.

13 In my new positions, I basically don't get
14 to say very much, don't get to be involved in the
15 scientific discourse, so it is a pleasure to get to do
16 this, although it is somewhat of a mixed pleasure.

17 My purpose here today, rather than just
18 sitting here, is to present Dr. Craig Donatucci with
19 a plaque. As I talked to him before, I mentioned to
20 him that I heard that this was going to be his last
21 meeting in this round as a Voting Member, and he said,
22 well, he knew he would be done when he was given a
23 plaque. So we have a plaque. So, Craig, there's your
24 plaque. I guess that makes it official.

25 I would like to make a couple of comments

1 and express our appreciation both on behalf of the
2 Division, the Office and the Center, to Dr. Donatucci.
3 He's been here on this Panel since 1992 and has served
4 with distinction. He has been involved in a number of
5 difficult decisions and has always been looked upon as
6 someone in whom we could rely on a very comprehensive
7 and detailed as well as clear and meaningful
8 discussion, and we thank him for that.

9 In addition to being a member of this
10 Panel, Dr. Donatucci also, by the way, is a Professor
11 of Urology down at Duke, and has managed that part of
12 his career as well, although we all recognize that
13 this is really the important thing in terms of his
14 medical career.

15 That's all sort of public information.
16 What is somewhat private information is the fact that
17 Dr. Donatucci's career started -- and I probably know
18 this to the exclusion of almost everyone else -- Dr.
19 Donatucci's medical career started in San Francisco at
20 the Public Health Hospital where he interned as a
21 general surgery intern, and had the good fortune at
22 that time to serve under the tutelage of a junior
23 resident in general surgery who had just come off the
24 Indian Reservation and was going into public health as
25 a full-time career. And I take some pride in the fact

1 that not only has Dr. Donatucci decided to go into a
2 surgical career, albeit urology, but he also has
3 maintained an interest in public health as evidence by
4 his performance on this panel. So, for all those
5 things, we thank you, and it's been a pleasure working
6 with you.

7 And I would say one more thing, please
8 don't leave the country because we do intend to call
9 you back. So that's part of your new assignment.
10 Thanks, Craig.

11 DR. DONATUCCI: Thank you, Dan. Just a
12 point of clarification, that senior surgical resident
13 was Dan.

14 DR. SCHULTZ: I also have a second
15 pleasure today -- again, sort of a mixed pleasure --
16 and this one is kind of a surprise because if she knew
17 that we were doing this, she probably wouldn't have
18 shown up for the meeting.

19 As you may or may not have noticed,
20 there's a new face sitting in the Executive Secretary
21 position, Dr. Jeffrey Cooper, who has replaced a face
22 that you have all grown to know and love over the last
23 many, many years -- Mary Jo Cornelius. And Mary Jo
24 has been in this position for 9 or 10 years. It was
25 very difficult to get information. We tried to get

1 some data, and every time we asked her -- how many
2 meetings have you done? How many new chair people
3 have you trained? How many new reviewers have you
4 recruited? It was always, "Well, it's not really
5 important, it doesn't matter". So, let me just say to
6 all of those things, it's a lot. And as all of you
7 know as well as I do, not only does she do it, does
8 she do it competently, does she do it well, but she
9 does it with great distinction, with grace, and making
10 it look easy, and basically making that position not
11 appear apparent is the measure of her success in how
12 well she's done.

13 And I can say from a personal standpoint,
14 when I first came to the Agency several years ago, I
15 was made an Executive Secretary, and I sort of asked,
16 "Well, how do you do this job", in addition to not
17 knowing everything else, and they said, "Well, just
18 watch the way she does it", and that's turned out to
19 be probably the best advice I ever got.

20 So, Mary Jo, we're going to embarrass you
21 a little bit and give you this nice plaque. I do need
22 to say, though, that Mary Jo isn't going to go
23 anyplace either. She'll be around both to help Jeff,
24 to help me, to help you, and to continue doing the
25 great work in the branch that she's always done. Mary

1 Jo.

2 (Applause.)

3 It says, "Certificate of Appreciation,
4 Mary Jo Cornelius, C.N.B.S.N.,CGRN, for outstanding
5 contributions as Executive Secretary to the
6 Gastroenterology and Urology Devices Advisory Panel",
7 and it's signed by Dr. David Pfeigel.

8 MS. CORNELIUS: I was taught you're never
9 too old to learn when I came here, and today I found
10 out you're never too old to blush.

11 DR. ANTHONY KALLOO: Thank you. We will
12 now have a 45-minute lunch break, and reconvene at
13 12:30. Thank you.

14 (Whereupon, at 11:45 a.m., the luncheon
15 recess was taken.)

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AFTERNOON SESSION

(12:50 p.m.)

1
2
3 DR. ANTHONY KALLOO: Good afternoon. The
4 meeting will reconvene with the Panel Discussion
5 portion of the meeting. Although this portion of the
6 meeting is open to public observation, public
7 attendees may not participate except at the specific
8 request of the Panel.

9 The first speaker is Dr. Naida Kalloo
10 primary Panel review lead Discussant.

11 DR. NAIDA KALLOO: I think, in summary --
12 and it's already been brought up before -- we know
13 that reflux alone does not necessarily cause the
14 damage after birth, it's the infection. And I think,
15 as stated before, that our goal is to prevent
16 infection and to prevent further damage to the
17 kidneys.

18 I think one of the things that's been
19 brought out is that this does have a success rate in
20 preventing the reflux, but it does not prevent the
21 infection, and I think we need to keep that in mind.
22 Again, we're going to get input from everybody, but
23 the one thing that I think we need to discuss among us
24 is whether or not we should go along with the same
25 type of followup as was done in Europe by stopping the

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1 antibiotics. I don't think, based on this study with
2 the urinary tract infection that occurred in these
3 patients, that stopping the antibiotics was
4 necessarily part of the goal -- it did not achieve the
5 goal of preventing infection. So that's one thing
6 that we probably need to discuss, is the role of
7 antibiotics with and without endoscopic treatment in
8 these patients.

9 The other thing is that there was about a
10 10 percent decrease in the success rate from the 3-
11 month VCUG to the 12-month VCUG, and there was
12 actually -- if I'm reading it correctly -- in those
13 patients that were retreated, the final VCUG was at 9
14 months post final treatment, or post second treatment,
15 rather than 12 months after the treatment. So there
16 is a decrease in the success rate from the 3-month
17 initial VCUG to the final VCUG, and in that time those
18 patients that are not successful have to be covered to
19 prevent infection.

20 The other points that I would like to
21 discuss would be the long-term management of these
22 patients since we don't know what the long-term
23 effects are of this device, and we don't know the
24 long-term success and failure rate of this device.

25 So I would like to open this up to the

1 Panel for any discussion or questions, if we may, if
2 there are any questions that anybody thought of during
3 the lunch period. Does anybody have any comment about
4 the antibiotic prophylaxis with this device?

5 DR. STEINBACH: The design of the third
6 experiment was to (1) the placebo one was to use
7 antibiotics only, and according to the stack, it said
8 nobody in Europe would sign up -- pardon me -- I'm
9 sorry, I didn't mean to kick Italy out of Europe -- no
10 one in Sweden would sign up for this because of
11 current fears of antibiotics.

12 Now, in California we hear all kinds of
13 strange things, so this didn't surprise me, that
14 patients -- or parents of patients would say, "I don't
15 want my child exposed to long-term antibiotics". So
16 the question is, how would they do your test?

17 DR. NAIDA KALLOO: Well, compliance is
18 certainly an issue, and in those patients where this
19 device is not successful, those patients still have to
20 be covered by something. Do they automatically jump
21 to open surgery, or do they need to be covered at some
22 point until we know whether or not they are
23 successfully treated or not. I mean, these patients
24 were all discontinued after one month. No
25 confirmatory studies were done until 3 months, and

1 then there was another 10 percent drop in success rate
2 from 3 months to 12 months.

3 So, what happens? How do we make sure
4 that those patients are adequately treated?

5 DR. STEINBACH: I'm an engineer, so I get
6 to ask this. How do doctors know when there's an
7 infection going on?

8 DR. NAIDA KALLOO: We do surveillance
9 during cultures, and we check urine based on symptoms.
10 So if a patient has a change in urinary habits, it
11 doesn't necessarily have to be symptoms, but if there
12 is a change -- it doesn't have to be dysuria, burning
13 on urination, or anything like that, it can just be
14 all of a sudden they start bedwetting. So, if there
15 is a change in urinary habits -- if they all of a
16 sudden are using the bathroom more frequently, if they
17 have tummyaches, if they get a fever -- all those may
18 indicate that there's a urinary tract infection.

19 DR. KAEFER: Or if they just have
20 irritability because some of these children are too
21 young and they are not totally trained yet.

22 DR. NAIDA KALLOO: That's right. And so
23 if they are just fussy. So, before they get a fever,
24 there certainly are other indications that there may
25 be a urinary tract infection going on. So I think

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1 that that was one thing that struck me is the only
2 group that got urinary tract infections which could
3 eventually lead to permanent renal damage was the
4 group where the antibiotics were stopped. And so we
5 need to make sure that we address that issue.

6 DR. DONATUCCI: Just a comment. From my
7 memory, I think part of the problem with defining the
8 incidence of urinary tract infection in the pivotal
9 study is that 62 percent of the patients in the
10 antibiotic control arm did not return diaries, and we
11 really don't know what the incidence of infection was
12 in that group.

13 DR. NAIDA KALLOO: And there was some
14 mention about the patients who were coming from far
15 away, and were they really -- were they being treated
16 locally instead of coming back to the host
17 institution, did they get infections? We don't know -
18 - those in the antibiotic arm.

19 But that's one point. If anybody has any
20 comments.--

21 DR. KAEFER: I think I have a comment, if
22 I can make it, just how I treat patients when I treat
23 them surgically, because I don't treat them this way.
24 I keep them on antibiotics until I prove the reflux is
25 gone because they could develop an infection in the

1 interim. And I think your point is very well taken.

2 DR. NAIDA KALLOO: I think the majority of
3 pediatric urologists in America do that, if I can make
4 that leap based on what the discussions are at the
5 American Academy of Pediatrics meeting and all the
6 meetings I've been to, that once we prove that the
7 reflux is gone, then we take them off antibiotics.
8 But the success rate for surgery is over 95 percent in
9 good hands, and so you know if that VCUG is negative
10 when you do that followup VCUG, we don't necessarily
11 worry about a 10 percent drop in success rate after
12 that. Once it looks cured from surgery, it's cured.

13 DR. KAEFER: You're right, I'm agreeing
14 with you completely that even with a very high success
15 rate we're doing that, and here you have a lower
16 success rate and you don't know what's going to be
17 long-term. So I'm backing up your statement.

18 DR. DiLORETO: That's absolutely true, and
19 there's a point of definition of success rate. Before
20 I get to that, maybe patients are managed differently
21 in different areas, but I believe, having been doing
22 this 21 years, if there's reflux, they're medically
23 covered and they're followed until such time, either
24 early or later, that they are deemed surgical
25 candidates because of progression of breakthrough

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1 infections or renal damage initially or whatever
2 reasons, they are covered. They are not left
3 uncovered. And I think that's probably -- it's not a
4 leap -- that is the norm, and that's how patients are
5 managed here.

6 The other issue is endpoint or what you
7 are considering success. If I do an antireflux
8 procedure and there is reflux, even grade I, that is
9 not success, that's a failed reimplant. And those
10 kids need to be followed for -- now, they may outgrow
11 that grade I reflux, but they need to be followed and
12 covered with antibiotics. I wouldn't consider that
13 grade I to be a success in either an implant or
14 injection or, for sure, an antireflux surgical
15 procedure. That's a failed case. And in this
16 particular consort that was considered one of the
17 successes, if they decrease --

18 DR. NAIDA KALLOO: Or positive result.

19 DR. DiLORETO: -- or positive result but,
20 again, I don't consider that to be a success when you
21 look at at least the way we are managing patients
22 here.

23 DR. KAEFER: It would only make sense
24 based on now there's a reflux. If there's any avenue,
25 whether it's a huge bolus or a small bolus, they may

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1 still --

2 DR. DiLORETO: And they're covered with
3 antibiotics. The -- I'll just make a general
4 statement -- and Mary Jo will support me -- I probably
5 will be grandfather of this Panel because I've been
6 sitting here for 10 or 11 years -- and sat through the
7 Teflon PMA, the Collagen PMA, and a lot of the others,
8 and have looked at a lot of submissions. I have a
9 little bit of a problem, particularly if we are basing
10 the issues of yes or no on 61 patients, if we are
11 looking at that last category per the FDA's
12 suggestion, group 3 being the group to base the
13 decision on. That's not enough. It's not enough
14 patients. There's issues of data collection, and
15 there's issue of long-term. You know, a year out
16 isn't -- when you're dealing with kids, that's not
17 enough time.

18 And one of the comments that came up at
19 the Teflon Panel -- and it may have been mine, I don't
20 remember. -- was issues of having lots of study
21 subjects that happened to be humans running around
22 with teflon injected into them, what was going to
23 happen over the long-run -- not a year, but 5, 10, 15
24 years -- and, obviously, you have to weigh that
25 against the issue of reflux and renal damage and the

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1 other things. And this particular product doesn't
2 appear to have that biochemical issues that some of
3 the other things had that we looked at before, but
4 there still is the long-term issues of what is going
5 to happen with these kids from the standpoint of
6 changes, reflux reaction, reflux down the road. A
7 year isn't enough time.

8 DR. NAIDA KALLOO: The other comment I
9 have is maybe the intervention, it is felt,
10 predisposed these kids to urinary tract infection, the
11 VCUG at 3, and then another procedure 3 months later
12 if it failed, and then another VCUG at a year. Even
13 though they were covered at the time of the procedure,
14 some of these kids, as we know, can be very
15 challenging to get to use the bathroom. And so it may
16 be that the effects, the irritability, or something
17 that had to do with the actual injection, may have had
18 effects on bladder instability or dysuria or something
19 that may have lasted a little bit longer than the
20 antibiotics covered them for, and that may have
21 actually predisposed them slightly. It changed their
22 habits enough to predispose them to a urinary tract
23 infection.

24 The other -- again, for the long-term, we
25 don't know what the effects on the body are, and we

1 don't know what the success rate is long-term. We
2 just don't know that.

3 The other thing that I'd like to bring up
4 is the fact that the biostatistician sort of echoed --
5 or you are echoing her comments that there's just not
6 enough information over the long-term, and she
7 recommended a reanalysis of the data based on -- and
8 I'm not quite -- would you mind repeating what your
9 comments were about the reanalysis?

10 MS. CHEN: Yes. This is Judy Chen again.
11 My focus for the reanalysis is through other
12 ineffectiveness. There is no clear statistical
13 analysis of the effect of covariables, and also the
14 per patient analysis has not been thoroughly done.
15 And that's what my point is, but I certainly agree
16 with you that we only have 40 patients treated with
17 the device, and only have one year followup data. In
18 fact, it is 39 patients.

19 DR. STEINBACH: We have the data in our
20 handout, so you could have done the simple analysis of
21 per patient success in study 3. Did you do this and
22 find it not significant?

23 MS. CHEN: Yes, per patient analysis
24 probably is statistically significant, but then the
25 covariables of age and disease grade cannot be done

1 just by looking at the data. So that is the point
2 that reanalysis need to be done.

3 DR. GORMAN: Would there be other
4 covariables you would like to look at, such as gender
5 or race?

6 MS. CHEN: Yes, that is also a
7 possibility. And also the effect of retreatment can
8 be looked at again.

9 DR. NAIDA KALLOO: I think those are all
10 the big points that I wanted everybody to have an
11 opportunity to speak on.

12 DR. ANTHONY KALLOO: I would like to thank
13 the Panel for their comments, and then what I would
14 like to do is to direct the Panel on discussion points
15 and establish a consensus for each issue. Dr. Naida
16 Kalloo will summarize the Panel comments. At the end
17 of the discussion of each question at the close of the
18 discussion. If I could have the first question,
19 please.

20 . Based on the patient population
21 enrolled in the clinical investigation of
22 Deflux Injectable Gel and reported in the
23 PMA, should the intended use statement
24 specifically limit the use of Deflux
25 Injectable Gel to patients with

1 particular grades of vesicoureteral
2 reflux, VUR: For example, grades II-IV
3 reflux as enrolled in the clinical
4 studies?

5 I will start with Dr. Kalloo, and go
6 around for comments.

7 DR. NAIDA KALLOO: I think based on the
8 results of grade IV reflux, I'm not sure that I would
9 use this as a treatment without covering them with
10 antibiotics and making sure that the parents -- I
11 would consent, or I would inform all parents that the
12 success rate that we have is less than 50 percent.
13 There are certainly those parents who would like to do
14 everything possible short of open surgery, and I think
15 that certainly this could be an option for those
16 parents, but with a success rate less than 50 percent
17 for grade IV reflux -- and I believe it was the first
18 treatment it was only 29 percent success rate, if I'm
19 not mistaken -- but I'm not sure that I would include
20 grade IV reflux as a specific indication. I think
21 maybe grades II and III, with a qualifier that the
22 parents would need to be thoroughly informed that the
23 success rate is less than 50 percent and that those
24 children may ultimately come to surgery.

25 DR. DONATUCCI: I would like at this point

1 to limit my comments on this question until the next
2 one.

3 DR. KAEFER: I agree with the statements
4 and I really strongly feel the patients should be on
5 antibiotics regardless of the grade until we prove
6 that it is gone.

7 In discussing the potential for
8 dysfunctional voiding resulting in a lower success
9 rate, I think that one may put a comment in there that
10 a patient should first be screened for dysfunctional
11 voiding and treated appropriately for that before they
12 are considered adequate candidates for the therapy.

13 And the other problem I had, which was
14 only those 2 patients in the study, but the 2 patients
15 who had a nonfunctioning kidney and who were treated
16 with the antireflux agent. I had potential problems
17 with that because we are potentially obstructing a
18 unit that has no function, and there is no way to test
19 whether or not it drains later because one can't do a
20 functional study in an actual renal scan to look for
21 drainage. You may have a fully obstructed system by
22 this Deflux going under a nonfunctional ureter that's
23 observing -- a nonfunctional kidney, rather. And so
24 I have real reservations regarding that, and of course
25 there were only 2 patients in the study that were

1 treated that had no function, so I think that would be
2 one limitation that I would include.

3 DR. STEINBACH: I think Dr. Kalloo has
4 correctly pointed out that for grade IV this is only
5 going to correct 40 percent, but our charge to the
6 Panel is that if a device is effective in a
7 substantial fraction, then the FDA can approve it.
8 And I think that for many people, they would choose
9 nonsurgery first and find out if it works. Certainly,
10 there has to be warning to the physician and the
11 family that there's a good chance this won't work and
12 that surgery or something else will be required later.
13 But it seems that even in this group there will be
14 enough people who would benefit from it that it should
15 be allowed.

16 DR. KAEFER: Can I make another comment?
17 I think potentially it should be allowed as well, it's
18 just, again, with those certain stipulations and with
19 the antibiotics being given. If it does give a chance
20 and the risks and benefits are presented to parents
21 and caregivers, then it's their decision ultimately,
22 and if it does have a possible benefit, then I think
23 it potentially should be allowed.

24 DR. SCHULTZ: I just wanted to point out
25 that one of the later charges asks you to discuss the

1 risk-benefit tradeoff.

2 DR. BANIK: Based upon the discussions
3 that we've had, I feel that in grade IV reflux, that
4 there is a potential for risk there associated with
5 the patient ultimately going to surgery -- and not get
6 into the last question -- but the benefit here is
7 significant in terms of giving this as an avenue -- as
8 an alternative treatment. And because of that, and
9 looking at the particular data, I am not necessarily
10 in favor of limiting the range to the low of class of
11 grading.

12 DR. NEWMAN: I think as long as you form
13 the patients' family, I think it should be all grades.
14 I think that you have enough support here saying that
15 it can possibly work. I would not exclude the fourth.

16 DR. DiLORETO: I would agree with what's
17 been discussed, and particularly Dr. Kaefer's
18 comments, however, I will defer, as did Dr. Donatucci,
19 to the next question.

20 DR. GORMAN: I feel comfortable with a
21 grade II-IV labeling, if that's what we're talking
22 about, in effect, but maybe to change the wording from
23 antibiotic therapy to a total system of care or
24 urologic followup of ultrasonography, something that
25 allows the progress of these patients in their

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1 diseased state to be monitored and treated
2 appropriately as complications or successes are noted
3 in the charts.

4 DR. ANTHONY KALLOO: Dr. Kalloo, will you
5 summarize the Panel comments.

6 DR. NAIDA KALLOO: I think that the
7 majority of the Panel would agree that this is a
8 viable option based on the considerable success rate,
9 and it is a viable option for those parents who may
10 not want to continue antibiotic therapy for a long
11 period of time, and for those that don't want surgery.
12 I think that overall there is an adequate benefit for
13 grade IV that it should not be excluded, but that
14 informed consent is mandatory, and that covering the
15 patients -- making sure that this is not utilized as
16 a sole treatment initially -- in other words, patients
17 should be covered with antibiotics and other means of
18 monitoring them to decrease the risk of urinary tract
19 infection and potential damage to the kidney.

20 DR. ANTHONY KALLOO: The second question:
21 2. The primary study, Study 3, was conducted
22 at a single center -- Rome, Italy.
23 Typically, pivotal clinical trials are
24 performed at multiple institutions to
25 evaluate the outcome of device use on a

1 divers patient population in the hands of
2 a variety of clinicians. Are the results
3 from Study 3 sufficient to assess device
4 safety and effectiveness given (i)
5 possible differences between the
6 demographics and baseline characteristics
7 of the study and the intended U.S.
8 patient population, and (ii) the possible
9 differences in device use across
10 physicians?

11 Starting with Dr. Kalloo, we'll go around
12 the table for comments.

13 DR. NAIDA KALLOO: I think the physician
14 from Italy made it clear that he was the only one that
15 did the procedure, so I don't think that we know about
16 the learning curve for other physicians. I think
17 that's definitely an issue. I think that most trained
18 endoscopists would be able to pick this up relatively
19 quickly but, again, we don't have that proof in the
20 study.

21 In terms of the patient population and
22 demographics, I think that, as mentioned before, these
23 are all Caucasian and there's a risk that certainly
24 different demographics and different groups but, as
25 was mentioned, we don't really see a lot of reflux in

1 African Americans. We don't have any -- I don't know
2 of any results in the Asian community -- so it doesn't
3 cut across all barriers, but I think that it's
4 adequate for the group that's most at risk.

5 The differences in use of the device, we
6 certainly haven't assessed that.

7 DR. DONATUCCI: I'd like to begin by
8 saying that as a clinician, I have had the frustrating
9 experience of treating a child with reflux with
10 antibiotics and had them return with an infection
11 which, on culture insensitivity, is sensitive to the
12 antibiotic that I've given them. So there's a real
13 issue with compliance.

14 I also have a different perspective
15 because I've been the parent of a child with reflux,
16 and I've taken them through the process of evaluation.
17 I've squirted the antibiotics down my daughter's
18 throat when she was a year old, so I know what that's
19 like for a parent. So, I'm sensitive to the need for
20 an alternative for these children. However -- and I
21 compliment the physicians who did this trial for their
22 efforts -- however, I do still feel that the data that
23 we have before us today is not sufficient to document
24 the effectiveness of this therapy for these children.
25 In particular, I would question, first, whether

1 radiographic improvement alone is the appropriate
2 endpoint, since we know it's the infection that causes
3 the damage.

4 The other thing I have a significant
5 concern about is the lack of long-term data. We know
6 that approximately 20 percent of these children with
7 lower grade reflux at least will each year grow out of
8 this condition. We don't know the long-term effect of
9 this device. If it's 75 percent will last 2 years,
10 there's still 25 percent who will start refluxing
11 again, theoretically.

12 I just think we need to see more data
13 before we judge the effectiveness of this therapy,
14 particularly in the children with lower grade reflux,
15 who will be the ones most likely to get antibiotics,
16 and that's why I withheld my comments on the first
17 question until now.

18 DR. KAEFER: I would echo your concerns,
19 and then I would also add to point (ii), the possible
20 differences of device use across physicians. I don't
21 think it was adequately assessed in the study.

22 DR. STEINBACH: First of all, I think it
23 would be very difficult to conduct an experiment where
24 everybody gets antibiotics. I mean, how do we -- what
25 is the control group? Do we say there is a group of