FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

JOINT MEETING OF THE ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

AVEED (TESTOSTERONE UNDECANOATE)

NDA 22219

Thursday, April 18, 2013

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center (Room 1503)

Silver Spring, Maryland

Reported by: Natalia Thomas

Capital Reporting Company

1 Meeting Roster

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9 ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

10 (Voting)

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1 MEETING ROSTER

2 (Continued)

3 ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

4 (Voting)(cont.)

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16 Rochester, New York

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1 MEETING ROSTER

2 (Continued)

3 ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

4 (Voting)(cont.)

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10 University of Massachusetts Medical School

11 Worcester, Massachusetts

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15 University of Colorado Denver

16 Aurora, Colorado

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18 Michele J. Orza, ScD

19 (Consumer Representative)

20 Senior Advisor to the Executive Director

21 Patient-Centered Outcomes Research Institute

22 Washington, District of Columbia

1 MEETING ROSTER

2 (Continued)

3 DRUG SAFETY AND RISK MANAGEMENT

4 ADVISORY COMMITTEE MEMBERS

5 (Voting)

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8 Professor of Pediatric and Preventive Medicine

9 Vanderbilt University School of Medicine

10 Nashville, Tennessee

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12 Brian Erstad, PharmD

13 Professor

14 University of Arizona College of Pharmacy

15 Department of Pharmacy Practice & Science

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19 Associate Professor

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21 University of Colorado, Anschutz Medical Campus

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1 MEETING ROSTER

2 (Continued)

3 DRUG SAFETY AND RISK MANAGEMENT

4 ADVISORY COMMITTEE MEMBERS

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8 Barnts Family Distinguished Professor

9 University of Texas MD Anderson Cancer Center

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1 MEETING ROSTER

2 (Continued)

3 DRUG SAFETY AND RISK MANAGEMENT

4 ADVISORY COMMITTEE MEMBER (Non-Voting)

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9 Pfizer, Inc.

10 New York, New York

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12 TEMPORARY MEMBERS (Voting)

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1 MEETING ROSTER

2 (Continued)

3 TEMPORARY MEMBERS (Voting) (cont.)

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12 Lewis Nelson, MD

13 Director, Fellowship in Medical Toxicology

14 New York University School of Medicine

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17 Dennis R. Ownby, MD

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1 MEETING ROSTER

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3 TEMPORARY MEMBERS (Voting) (cont.)

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1 MEETING ROSTER

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3 FDA PARTICIPANTS (Non-voting)(cont.)

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16 Mark Hirsch, MD

17 Medical Team Leader

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21

22

1 MEETING ROSTER

2 (Continued)

3 FDA PARTICIPANTS (Non-voting)(cont.)

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10 ODE II, OND, CDER, FDA

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13 Medical Team Leader

14 Division of Pulmonary, Allergy, and Rheumatology

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17 ODE II, OND, CDER, FDA

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12 Designated Federal Officer, ACRHD

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

2 Call to Order and Opening Remarks

3 Introduction of Committee

4 DR. JOHNSON: Okay. Well, good morning,

5 everyone. To everyone, if you could please take your

6 seats, we'll go ahead and get started. I would like to

7 remind everyone present to please silence your cell

8 phones, your BlackBerries, or any other device that you

9 haven't already done so.

10 I would like to identify the FDA press

11 contact for this meeting, Andrea Fischer. Ms. Fischer

12 is over there. My name is Julia Johnson. I'm the

13 Chairperson of the Advisory Committee for Reproductive

14 Health Drugs. And I will now call this joint meeting to

15 order. This includes the Advisory Committee for

16 Reproductive Health Drugs and the Drug Safety and Risk

17 Management Advisory Committee to order.

18 We'll start now by going around the table and

19 introducing ourselves, if we could start on my right.

20 DR. CAVAZZONI: I'm Patrizia Cavazzoni. I am

21 the industry representative to DSaRM.

22 MR. ZAAYER: I'm Bob Zaayer, PA, in emergency

1 medicine.

2 DR. SWENSON: Erik Swenson, pulmonary and

3 critical care medicine.

4 DR. OWNBY: Dennis Ownby, pediatric

5 allergist, Georgia Regents University.

6 DR. NELSON: I'm Lewis Nelson. I'm an

7 emergency physician and a medical toxicologist at New

8 York University School of Medicine.

9 DR. McCAMMON: Kurt McCammon. I'm a

10 urologist at Eastern Virginia Medical School.

11 MR. LUSTIG: I'm Craig Lustig. I'm the

12 patient representative.

13 DR. ERSTAD: Brian Erstad. I'm a pharmacist

14 at the University of Arizona College of Pharmacy.

15 DR. SUAREZ-ALMAZOR: Good morning. I'm Maria

16 Suarez-Almazor, University of Texas, MD Anderson Cancer

17 Center.

18 DR. WOODS: Good morning. I'm Mark Woods.

19 I'm the clinical coordinator and residency program

20 director in the pharmacy department at Saint Luke's

21 Hospital in Kansas City, Missouri.

22 DR. MORRATO: Good morning. I'm Elaine

1 Morrato. I'm an epidemiologist and health services
2 researcher at the Colorado School of Public Health.
3 DR. COOPER: I'm William Cooper. I'm a
4 pediatrician and a pharmacoepidemiologist at Vanderbilt
5 University.
6 DR. JOHNSON: And I'm Julia Johnson. I'm a
7 reproductive endocrinologist and Chair of OB-GYN at the
8 University of Massachusetts Medical School.
9 MS. BHATT: Good morning. I'm Kalyani Bhatt.
10 I'm with the Division of Advisory Committee Consultants
11 Management.
12 DR. HOEGER: Good morning. Kathleen Hoeger,
13 reproductive endocrinologist, obstetrics and
14 gynecology, University of Rochester.
15 DR. CLARKE: Good morning. Bart Clarke,
16 endocrinologist, Mayo Clinic, Rochester, Minnesota.
17 DR. ORZA: Good morning. Michele Orza,
18 Patient Centered Outcomes Research Institute. I'm the
19 consumer representative.
20 DR. KITTELSON: And good morning. John
21 Kittelson, University of Colorado, Denver,
22 biostatistics.

1 DR. CURTIS: Good morning. I'm Kate Curtis.
2 I'm a health scientist in the Division of Reproductive
3 Health at the Centers for Disease Control and
4 Prevention.
5 DR. BOCKMAN: Thank you. I had a moment of
6 lapse.
7 DR. BOCKMAN: Richard Bockman. I'm an
8 endocrinologist and professor of medicine at Weill
9 Medical College in New York City.
10 DR. OUELLET-HELLSTROM: Good morning. I'm
11 Rita Ouellet-Hellstrom, Associate Director of the
12 Office of Surveillance and Epidemiology, Division of
13 Epidemiology.
14 DR. DURMOWICZ: I'm Tony Durmowicz, a
15 pediatric pulmonary and critical care physician from
16 the Division of Pulmonary, Allergy and Rheumatology at
17 the FDA.
18 DR. CHIN: Stacy Chin. I'm a pediatric
19 allergist/immunologist in the Division of Pulmonary,
20 Allergy and Rheumatology Products at the FDA.
21 DR. HIRSCH: Mark Hirsch, Medical Team Leader
22 in Urology, Division of Reproductive and Urologic

1 Products.

2 DR. GASSMAN: Good morning. I'm Audrey

3 Gassman. I'm the Deputy Director for the Division of

4 Reproductive and Urologic Products.

5 DR. BEITZ: And I'm Julie Beitz, Director of

6 the Office of Drug Evaluation III.

7 DR. JOHNSON: Well, welcome to everyone. Now

8 I would like to allow Ms. Bhatt to give us the conflict

9 of interest statement. Conflict of Interest Statement

10 MS. BHATT: The Food and Drug Administration

11 is convening today's Joint Meeting of the Reproductive

12 Health Drugs and the Drug Safety and Risk Management

13 Advisory Committee under the authority of the Federal

14 Advisory Committee Act of 1972.

15 With the exception of industry -- oh, sorry.

16 There is a page missing here. Sorry about that.

17 The following information on the status of

18 this Committee's compliance with federal ethics and

19 conflict of interest laws covered by, but not limited

20 to, those of 18 U.S.C. Section 208 is being provided to

21 participants in today's meeting and to the public. FDA

22 has determined that members and temporary voting

1 members of the Committees are in compliance with
2 federal ethics and conflict of interest laws. Under 18
3 U.S.C. Section 208, Congress has authorized FDA to
4 grant waivers to special government employees and
5 regular federal employees who have potential financial
6 conflicts when it is determined that the Agency needs
7 for a particular individual's services outweighs his or
8 her potential financial conflict of interest.
9 Related to the discussion of today's meeting,
10 members and temporary voting members of the Committee
11 have been screened for potential financial conflicts of
12 interest of their own as well as those imputed to them,
13 including those of their spouses or minor children, and
14 for purposes of 18 U.S.C. Section 208, their employers.
15 These interests may include investments, consulting,
16 expert witness testimony, contracts/grants/CRADAs,
17 teaching/speaking/writing, patents and royalties, and
18 primary employment.
19 Today's agenda involves discussion of the
20 efficacy and safety of new drug application (NDA) 22219
21 AVEED (testosterone undecanoate) intramuscular
22 injection, submitted by Endo Pharmaceutical Solutions,

1 Incorporated, for the proposed indication of
2 replacement therapy in adult males for conditions
3 associated with a deficiency or absence of
4 testosterone. The safety discussion will focus on
5 post-marketing reports of oil microembolism in the
6 lungs and potential anaphylactic reactions. In
7 addition to AVEED, other approved testosterone
8 injectable products will be referenced, especially in
9 regards to oil microembolism and potential anaphylactic
10 reactions reported for those products.
11 Based on the agenda for today's meeting and
12 all financial interests reported by the Committee
13 members and temporary voting members, no conflict of
14 interest waivers have been issued in connection with
15 this meeting. To ensure transparency, we encourage all
16 standing Committee members and temporary voting members
17 to disclose any public statements that they have made
18 concerning the product at issue.
19 With respect to FDA's invited industry
20 representative, we would like to disclose that Dr.
21 Patrizia Cavazzoni is participating in this meeting as
22 a non-voting industry representative. Acting on behalf

1 of regulated industry, Dr. Cavazzoni's role at this
2 meeting is to represent industry in general and not any
3 particular company. Dr. Cavazzoni is employed by
4 Pfizer, the sponsor of Depo-Testosterone, a competing
5 product. Dr. Cavazzoni oversees the safety and
6 regulatory activities worldwide for this product.
7 We would like to remind members and temporary
8 voting members that if the discussion involves any
9 other products or firms not already on the agenda for
10 which an FDA participant has a personal or imputed
11 financial interest, the participants need to exclude
12 themselves from such involvement, and their exclusion
13 will be noted for the record.
14 FDA encourages all participants to advise the
15 Committee of any financial relationship that they may
16 have with the firm at issue.
17 Thank you.
18 DR. JOHNSON: Excellently read.
19 Now to Audrey Gassman.
20 Dr. Gassman. Member Appreciation
21 DR. GASSMAN: Good morning, everyone. My
22 name is Audrey Gassman, and I'm the Deputy Director for

1 the Division of Reproductive and Urologic Products. At
2 this time, I would like to welcome everyone to this
3 joint advisory committee to discuss NDA 22219 for a
4 testosterone undecanoate product, which is an
5 injectable testosterone product.
6 At this time, I would like to take a moment
7 and thank one of our Committee members, Dr. John
8 Kittelson, for his service to the Advisory Committee
9 for Reproductive Health Drugs. Dr. Kittelson has
10 served on our Committee since June of 2010. We, in the
11 Division and Agency, would like to thank you for your
12 service. I have a certificate for you, and a plaque
13 from the Advisory Committee will be on its way to you
14 shortly.
15 DR. KITTELSON: Thank you very much. I think
16 this is very meaningful work. It's been my pleasure to
17 be involved.
18 DR. GASSMAN: And now with the Chair's
19 permission, I would like to turn this over to Dr. Gary
20 Slatko, who is the Director of the Division of
21 Medication Errors and Risk Management in the Office of
22 Surveillance and Epidemiology.

1 DR. SLATKO: Thank you, Audrey.
2 We would also like to recognize three members
3 of the Drug Safety and Risk Management Advisory
4 Committee, DSaRM, whose terms will be expiring at the
5 end of May. During their years of service, their
6 expertise has contributed to the deliberations of the
7 DSaRM Committee and has provided us with very valuable
8 advice important to the regulatory review process. In
9 appreciation for their service, FDA would like to ask
10 each member to come up and receive a certificate as I
11 call your name. And they're all conveniently located
12 at this corner.
13 Dr. William Cooper is Cornelius Vanderbilt
14 Professor and Vice-Chair of the Department of
15 Pediatrics at Vanderbilt University. He served on the
16 Committee from February 2011 to today, and he has
17 provided us very useful expertise in the areas of
18 epidemiology and pediatrics.
19 Dr. Cooper?
20 DR. SLATKO: Dr. Elaine Morrato is Associate
21 Professor, Department of Health Systems Management and
22 Policy at the Colorado School of Public Health,

1 University of Colorado. She is our longstanding
2 veteran serving from June 2009 until today and has
3 provided us expertise in risk communications and
4 epidemiology.
5 Dr. Morrato?
6 DR. SLATKO: And, finally, Dr. Mark Woods is
7 Clinical Coordinator and Residency Program Director of
8 the Pharmacy Department at St. Luke's Hospital in
9 Kansas City, Missouri. Dr. Woods has served since
10 February of 2011 and has provided us expertise in
11 therapeutics and pharmacy services.
12 Dr. Woods?
13 DR. JOHNSON: And now for our opening
14 remarks.
15 Dr. Gassman. Opening Remarks
16 DR. GASSMAN: Thank you, Dr. Johnson.
17 That's interesting. Apologies. We're having
18 some technical difficulties here. Okay. Could you
19 advance to Slide 2, please? Okay.
20 Again, welcome to our Joint Advisory
21 Committee. Today we are going to be discussing briefly
22 why we're bringing testosterone undecanoate to the

1 Advisory Committee, and I am also going to briefly
2 review the questions to the Committee.
3 Next slide, please.
4 So why are we bringing testosterone
5 undecanoate to the Joint Advisory Committee meeting?
6 Testosterone undecanoate is an intramuscular
7 preparation that is being developed for the indication
8 of testosterone replacement therapy in men with a
9 deficiency or absence of endogenous testosterone. This
10 product is approved as a 4 milliliter solution for
11 injection under the names Nebido and Reandron overseas.
12 Both the Agency and the applicant agree that the
13 efficacy of this product has been demonstrated using
14 serum testosterone levels. During the Agency's review
15 of this product, severe post-injection reactions,
16 including anaphylaxis and pulmonary oil microembolism
17 were identified. After review, we would like the
18 Committee's assessment and input for this product.
19 Next slide.
20 The objective of today's meeting is to ask
21 the Advisory Committee members to provide their views
22 on the risk-benefit profile for testosterone

1 undecanoate injection. We would ask the Advisory
2 Committee members to focus on the data for this
3 injectable testosterone product and provide advice
4 specifically for this application rather than provide
5 global recommendations on the use of testosterone.
6 Next slide, please.
7 I will briefly now review the questions for
8 the Committees.
9 The first question is: Given the severe
10 post- injection reactions that were reported with
11 testosterone undecanoate in clinical studies and post-
12 marketing experience, do you believe that testosterone
13 undecanoate is safe for the proposed indication? If
14 you vote yes, please provide your rationale. If you
15 vote no, please provide your rationale.
16 Next slide, please.
17 Whether you voted yes or no for Question 1,
18 please vote as to whether the applicant's proposed
19 instructions for use in product labeling, that a
20 testosterone undecanoate injection be administered
21 using a slow 30- to 60-second injection, and that
22 patients remain in the office for 30 minutes post-

1 injection would be sufficient to ameliorate the risk of
2 several post- injection reactions. If yes, please
3 provide your rationale. If no, please provide other
4 measures you would recommend to the Agency.
5 And now I will turn the meeting back to the
6 Chairperson, Dr. Johnson.
7 DR. JOHNSON: Thank you very much.
8 For topics such as those discussed at today's
9 meeting, there will be a variety of opinions, some of
10 which can be strongly held. Our goal of today's
11 meeting will be to have a fair and open forum for
12 discussion of these issues, that individuals can
13 express their views without interruption. Thus, as a
14 gentle reminder, individuals will be allowed to speak
15 into the record only if recognized by the Chair. We
16 look forward to a very productive meeting.
17 In the spirit of the Federal Advisory
18 Committee Act and the Government in the Sunshine Act,
19 we ask that Advisory Committee members take care that
20 their conversations about topics at hand take place
21 only during the open forum of the meeting. We are
22 aware that members of the media may be anxious to speak

1 with the FDA about these proceedings; however, the FDA
2 will refrain from discussing the details of the meeting
3 with the media until the conclusion.
4 Also, the Committee is reminded to please
5 refrain from discussing meeting topics at breaks and
6 lunch.
7 Thank you for that.
8 Now we can proceed with the sponsor's
9 presentations. Let me say just a few words as they're
10 gathering to the podium. Both the FDA and the public
11 believe that a transparent process for information
12 gathering and decision making is critical. To ensure
13 such transparency at the Advisory Committee meeting,
14 the FDA believes that it's important to understand the
15 context of an individual's presentation. For this
16 reason, the FDA encourages all participants, including
17 the sponsor's non-employee presenters, to advise the
18 Committee of any financial relationship they may have
19 with the firm at issue such as consulting fees, travel
20 expenses, honoraria, and interests in the sponsor,
21 including equity interests and those based on outcome
22 of the meeting.

1 Likewise, the FDA encourages you, at the
2 beginning of your presentation, to advise the Committee
3 if you do not have any such financial relationships. If
4 you do choose not to address these financial
5 relationships, it does not preclude you from speaking.
6 So now shall we go forward with the sponsor
7 presentations. Sponsor Presentation Introduction
8 DR. CASTY: Good morning. My name is Dr.
9 Frank Casty, Chief Medical Officer of Endo
10 Pharmaceuticals. I am pleased to be here to present
11 data from our complete response submission to
12 testosterone undecanoate injection, a testosterone
13 replacement therapy with the proposed brand name of
14 AVEED.
15 Our proposed indication is shown here. AVEED,
16 testosterone undecanoate, injection is an androgen
17 indicated for replacement therapy in adult males for
18 conditions associated with a deficiency or absence of
19 endogenous testosterone due to primary hypogonadism or
20 hypogonadotropic hypogonadism, whether congenital or
21 acquired.
22 There are several areas of agreement between

1 Endo and the FDA that are important for today's
2 meeting. Both Endo and the FDA conclude that AVEED has
3 met the regulatory requirement for efficacy for a
4 testosterone replacement product. Both Endo and the
5 FDA regard the general safety profile of AVEED is
6 consistent with other testosterone replacement
7 therapies. And both Endo and the FDA agree that
8 pulmonary oil microembolism events, or POME, and
9 anaphylaxis can occur with AVEED.
10 Where we do not agree is how the data are
11 used to formulate an overall benefit-risk assessment.
12 Specifically, as you've read in the
13 respective briefing books, there are three major
14 differences in the interpretation of the AVEED benefit-
15 risk: one is the benefit of AVEED over other available
16 testosterone products; another is the risk and severity
17 of acute post- injection events; finally, the impact of
18 a plan for risk management.
19 Our goal today is to provide contexts to the
20 benefit-risk interpretation to best support patients
21 requiring long-term replacement therapy. First, there
22 is a need for an injectable testosterone replacement

1 therapy with a longer dosing interval to best support
2 those patients who require long-term testosterone
3 replacement.
4 Second, while we acknowledge that immediate
5 post-injection reactions can and do occur, the events
6 are infrequent and are not all the same. Our
7 investigations show that most post-injection events can
8 be identified and treated. Additionally, it's
9 important to note that these events, including those
10 that are considered serious by the patient or
11 physician, have not resulted in long- term sequelae or
12 death.
13 Third, in order to mitigate these events, we
14 are proposing a comprehensive and systematic risk
15 management plan which is much more than a 30-minute
16 wait to assist physicians and patients in the
17 recognition and treatment of immediate post-injection
18 reactions should they occur.
19 Fortunately, for today's discussion, there is
20 extensive international experience which provides a
21 large safety database. Testosterone undecanoate was
22 first approved outside the United States in 2003 and

1 launched under the brand name of Nebido. The Nebido
2 formulation is identical to AVEED but dosed as 1,000
3 milligrams in a 4 ml IM injection whereas AVEED is 750
4 milligrams in a 3 ml injection and is the dose that met
5 the FDA criteria for efficacy. These clinical trial
6 results will be presented shortly.
7 Today, Nebido is approved in 94 countries,
8 including the European Union, Australia, and New
9 Zealand. Over 3.1 million doses have been sold during
10 the first 9 years through November 2011, which is the
11 date of cutoff date for our NDA resubmission. We
12 estimate that more than 1.2 million patients have been
13 treated, representing over 700,000 patient-years of
14 experience.
15 We also have a lot of experience from
16 clinical trials. AVEED's safety profile is supported
17 by clinical data from 18 clinical studies conducted in
18 3,556 patients. These studies include the pivotal U.S.
19 study called IP157 and six European
20 hypogonadism studies. There are also five male
21 contraception studies and six post-approval safety
22 studies. This amounts to a total of 3,556 patients

1 that translate into 4,222 patient-years of exposure
2 data.
3 The AVEED database is supported by over
4 20,000 injections from these clinical trials and more
5 than 9 years of post-marketing experience during which
6 time more than 3.1 million doses have been sold outside
7 the United States.
8 Our NDA resubmission focused on thorough
9 investigations of immediate post-injection events in
10 the clinical studies and the post-approval experience
11 to address the FDA's complete response and questions
12 about post-injection adverse reactions. In order to
13 augment our understanding of the risk of adverse
14 events, Endo reviewed all reported adverse events
15 occurring in development as well as the post-marketing
16 experience, seeking to identify potential cases of POME
17 as well as any symptoms that might suggest anaphylaxis.
18 We then asked two independent adjudicators
19 who are former FDA reviewers and experts in pulmonary
20 medicine to review the safety database to identify
21 cases of POME and anaphylaxis. Their independent
22 clinical review provides support for the AVEED safety

1 profile and will be presented shortly.
2 We will also present an analysis of the 137
3 cases the FDA defined as severe in their briefing book.
4 This analysis is very important to our discussion
5 today, since we believe that once we describe the
6 frequency of post-injection reactions, it's important
7 to appreciate the clinical severity of them as well.
8 Finally, we take these events seriously. In
9 order to support awareness and recognition and allow
10 informed decisions, we have proposed a detailed risk
11 management plan that includes both REMS components and
12 additional activities, which will be reviewed at the
13 end of our discussion.
14 So let's review our agenda today.
15 Dr. Ronald Swerdloff, from Harbor UCLA
16 Medical Center, will provide an overview of
17 hypogonadism and a need for longer interval therapies.
18 Then Dr. Theodore Danoff will discuss the
19 benefit of 10-week dosing and our pivotal PK data.
20 The rest of the presentation will focus on
21 our extensive analyses and characterization of post-
22 injection reactions, including investigations of over 9

1 years of data.

2 Dr. Robert Meyer, a pulmonologist with the

3 University of Virginia and former FDA reviewer, will

4 review the pulmonary oil microembolism, or POME,

5 adjudication results and the clinical characteristics

6 of these cases.

7 Then Dr. Larry Borish, an allergist from the

8 University of Virginia and former Chair of the Allergy

9 Products Drug Advisory Committee, will discuss the

10 clinical spectrum of anaphylaxis.

11 Dr. Marianne Mann, a pulmonologist and former

12 FDA reviewer, will review the anaphylaxis adjudication

13 results and the clinical characteristics of these

14 cases.

15 Dr. Danoff will review the 137 cases

16 identified by the FDA in their briefing book. It is

17 important to remember that these cases are a subset of

18 the cases adjudicated by Drs. Mann and Meyer.

19 Dr. Neil Shusterman will next review the

20 AVEED risk management plan and how it addresses the

21 risk of immediate post-injection reactions.

22 Finally, I will return to summarize the

1 overall benefit-risk of AVEED.

2 In addition to our presenters, we have

3 invited other subject matter experts to assist us in

4 answering your questions. All of our outside experts

5 have been compensated for their time and assisting us

6 in preparation for this meeting.

7 I would now like to invite Dr. Swerdloff to

8 present.

9 Dr. Swerdloff. Hypogonadism

10 DR. SWERDLOFF: Good morning. I am Ronald

11 Swerdloff, Professor of Medicine and Chief of

12 Endocrinology at the Harbor UCLA Medical Center. And I

13 was a member of the Endocrine Society Guidelines

14 Committee on Androgen Deficiency Syndrome.

15 I appreciate the opportunity to review the

16 literature and clinical practice standards of

17 hypogonadism. I want to present to you three key

18 points that I believe are essential for understanding

19 the diagnosis and treatment of hypogonadism. First,

20 hypogonadism is usually a chronic condition with a

21 broad spectrum of clinical manifestations. For many

22 patients, it's a serious condition with profound

1 effects on them both physically and mentally.
2 Secondly, the diagnosis and treatment of
3 hypogonadism is described in the Endocrine Society
4 Guidelines published in 2006 and then revised in 2010,
5 which provides treatment recommendations based upon the
6 best available information at that time.
7 Thirdly, there are several testosterone
8 treatment options, and selection of each option is
9 based on the demonstration of efficacy, safety profile,
10 and the patient's individual needs and preferences for
11 treatment.
12 So let's look at the clinical need. Some
13 people think that men are only treated for hypogonadism
14 for sexual symptoms like reduced libido. However,
15 testosterone replacement therapy is used by some men
16 for that reason, but there are many other clinical
17 manifestations that may benefit from testosterone
18 treatment.
19 Testosterone works in a number of tissues. So
20 hypogonadism can be thought as a systemic disorder.
21 Testosterone is required to induce and maintain
22 secondary sexual characteristics. Hypogonadism can

1 lead to decreased muscle mass and strength as well as
2 increased adiposity. Low testosterone and obesity are
3 risk factors for cardiovascular disease. In addition,
4 hypogonadism leads to altered bone metabolism, which
5 results in osteopenia, osteoporosis, and an increased
6 rate of bone fractures.
7 The Endocrine Society Guidelines emphasizes
8 that testosterone replacement is warranted in an adult
9 man with clinical symptoms and reproducibly low
10 testosterone levels, and I would emphasize symptoms and
11 low testosterone levels. For the young patients with
12 genetic causes for testosterone deficiency, like
13 Klinefelter syndrome, treatment can induce and maintain
14 their secondary sexual characteristics. For them,
15 long-term therapy and adherence is particularly
16 important.
17 The Guidelines also state that testosterone
18 therapy is indicated in hypogonadal men to improve
19 their sexual function and sense of well-being, increase
20 their muscle mass and strength, and increase their bone
21 mineral density. The available interventional clinical
22 studies are positive and suggest a long-term benefit,

1 but large- scale, well-controlled studies are needed to
2 define the full spectrum of efficacy.
3 The recently approved testosterone
4 replacement therapies are gels and solutions. There
5 are several factors that may be influencing the
6 persistence on these therapies. The main factors are
7 probably the need for daily application and the need to
8 let the product dry before getting dressed.
9 Additionally, these therapies are associated with skin
10 irritation at the application site in up to 15 percent
11 of patients. Topical application of testosterone also
12 carries the risk of transference of testosterone from
13 the application site on the patient to women or
14 children who are in contact with the patient.
15 Transference can also result in virilization of women
16 and children and other irreversible effects on the
17 children. These products now require a REMS and carry
18 a black box warning on their package inserts that warn
19 about transference.
20 The short-acting injectables have been
21 available since the 1950s. For men treated with these
22 agents, the Endocrine Guidelines recommend inquiring

1 about mood fluctuations which may occur related to the
2 peaks and troughs in testosterone concentration that
3 occur during shorter dosing intervals. To address
4 these PK characteristics, endocrinologists often
5 recommend dosing more frequently than the label, every
6 2 to 4 weeks. I often instruct my patients, as do many
7 other experts, to dose every 1 to 2 weeks. This means
8 that the patients may have to receive up to 52
9 injections per year.
10 In addition, short-acting injections carry
11 the risk of POME and anaphylaxis also. Published
12 literature indicates that POME can occur. As a result,
13 we inform our patients receiving testosterone injection
14 that there is a risk of cough that begins immediately
15 after injection and might last up to 20 minutes. The
16 labels for injectables also list a risk for
17 anaphylaxis.
18 In conclusion, hypogonadism is a serious
19 chronic condition which deserves treatment with
20 testosterone. Although there are a number of approved
21 therapies, none is ideal for all patients. The single
22 biggest problem that we have in delivering chronic

1 therapy is that patients don't stay on their therapy.
2 In addition, swings in testosterone concentration when
3 the short- acting injectables are dosed as labeled can
4 cause mood fluctuations. Transference from the patient
5 to his contacts is a concern for many patients if they
6 use the topical gels and solutions. Patients need
7 options that fit their individual needs and preference
8 and give those seeking longer term treatment a chance
9 to stay on therapy. AVEED, as a long-acting
10 injectable, could help address some of these needs.
11 Thank you very much for allowing me to speak
12 to you. I will now invite Dr. Danoff to the lectern.
13 10-Week Dosing & Exposures
14 DR. DANOFF: Thank you, Dr. Swerdloff. I am
15 Dr. Theodore Danoff, Vice President of Clinical
16 Development at Endo Pharmaceuticals. As you heard,
17 hypogonadism is a chronic condition. For testosterone
18 replacement therapy to be effective, patients need to
19 remain on therapy. I would like to present some data
20 regarding patients' persistence on testosterone
21 therapy, and in particular on Nebido.
22 Here we show prescription refill data from

1 Germany, which is the largest TRT market in Europe.
2 This analysis was conducted using IMS Health's
3 prescription data from Germany between January 2008 and
4 September 2012. IMS is a prescription information
5 source that is commonly used by health care companies
6 to understand prescribing behavior. At least in
7 Germany, only 26 percent of patients remain on therapy
8 at 6 months with the gels and only 5 percent with the
9 short-acting injectables. The persistency worsens at
10 12 and 24 months.
11 Now let's look at the persistence with
12 Nebido, which is the AVEED formulation in Germany.
13 Nebido has been available in Germany for more than 9
14 years. We see better persistence with long-duration
15 Nebido compared with the gels or the short-acting
16 injectables, with 56 percent of patients remaining on
17 therapy at 6 months. Persistence remains better with
18 Nebido even at 2 years, with persistence almost
19 threefold better than gels. Although this is far from
20 perfect, it is better than the alternatives. This
21 aligns with what has been observed with therapeutics
22 for other chronic conditions where lengthening the

1 dosing interval improves persistence.
2 So what allows AVEED's 10-week dosing
3 interval? AVEED, like other injectable depo-
4 testosterone formulations, contains a testosterone
5 ester is an oil- based solution. AVEED contains
6 refined castor oil and benzyl benzoate. Both are
7 necessary to allow prolonged release by holding the
8 ester at the site of injection and thereby allow for
9 10-week dosing, which is a key benefit of AVEED. Benzyl
10 benzoate also acts as a co-solvent and reduces the
11 viscosity of the mixture to facilitate injectability of
12 the formulation.
13 The use of an oil-based depo formulation to
14 extend the dosing interval is found in other products
15 marketed in the United States. These products are
16 presented in the briefing books. Some of these
17 products also contain benzyl benzoate.
18 I will now briefly review the PK criteria
19 accepted by the FDA for testosterone replacement
20 therapies and the AVEED results.
21 AVEED met the PK requirements accepted by FDA
22 for approval of testosterone replacement products. The

1 criteria, as shown here, are based on average
2 testosterone blood levels over the dosing cycle as well
3 as peak blood levels. Shown are results from our
4 pivotal open-label clinical trial designed to
5 demonstrate normalization of testosterone levels. The
6 PK population included 117 patients dosed with AVEED
7 every 10 weeks. Testosterone levels were normalized in
8 94 percent of patients with C average within the
9 eugonadal target range of 300 to 1,000 nanograms per
10 deciliter. This is well above the 75 percent
11 requirement of the FDA.
12 The criteria also require that 85 percent or
13 more of patients have a Cmax less than or equal to
14 1,500 nanograms per deciliter. With AVEED, more than
15 92 percent of patients met this criteria. No patient
16 had a Cmax concentration greater than 1,800 nanograms
17 per deciliter or the highest threshold of greater than
18 2,500 nanograms per deciliter. These results support
19 that most patients treated with AVEED achieved
20 normalized testosterone levels.
21 So what does this suggest that AVEED offers?
22 AVEED effectively replaces testosterone levels with a C

1 average rate meeting the FDA criteria for success.
2 Unlike short-acting depo-testosterones, no patients
3 have a Cmax above the FDA threshold of 1,800 or 2,500
4 nanograms per deciliter. Importantly, the IMS data
5 show patients don't stay on testosterone replacement
6 therapy. Conversely, an extended dosing interval helps
7 patients that need long-term testosterone replacement
8 to remain on therapy.
9 With that background, let's move to the key
10 issue for the Advisory Committee, namely, the post-
11 injection reactions of POME and anaphylaxis. Before we
12 start discussing the case adjudication, let me first
13 introduce the two independent experts who identified
14 and adjudicated the cases. Drs. Meyer and Mann are
15 both trained in pulmonology and have worked for the
16 FDA. Dr. Meyer was an office level director as well as
17 a director in the Division of Pulmonary and Allergy
18 Drug Products. And Dr. Mann was a deputy director.
19 These physicians have extensive experience in
20 evaluating drug safety.
21 Before they present their results, let me put
22 the adjudication into context with a high level view of

1 how the cases that Endo presents in our briefing book
2 relate to the 137 cases discussed in the FDA briefing
3 book.
4 The independent adjudicators will present the
5 results of the 225 cases that they adjudicated as POME
6 and anaphylaxis. These cases come from post-marketing
7 reports received through November 24th, 2011. This was
8 the cutoff date for our NDA resubmission. In the FDA
9 briefing book, they present a list of 137 cases that
10 they call severe. None of these cases came from the
11 clinical trials. All 137 cases came from post-
12 marketing reports, including cases from an interim
13 safety report that Endo submitted with a cutoff date of
14 April 30th, 2012. The FDA's review was based on 5
15 extra months of time during which about 500,000 doses
16 of Nebido were sold. We asked our independent experts
17 to also adjudicate the post- marketing cases from this
18 same time period. This resulted in 22 more cases
19 adjudicated as POME or anaphylaxis for our total of 247
20 cases.
21 The experts adjudicated 124 of the FDA's 137
22 cases as POME or anaphylaxis. Thirteen of the cases on

1 the FDA's list were reviewed by our adjudicators but
2 were not considered POME or anaphylaxis.
3 Let me now invite Dr. Meyer to the podium to
4 describe POME and present the POME adjudication
5 results. Pulmonary Oil Microembolism (POME)
6 Adjudication
7 DR. MEYER: Good morning. I'm Dr. Bob Meyer,
8 from the University of Virginia. And I would like to
9 describe for you the process that Dr. Mann and I used
10 to adjudicate the post-injection reactions. But first
11 I think it would be helpful for me to describe POME for
12 you.
13 Dr. Mann and I reviewed the literature
14 related to pulmonary oil microembolism, or POME, to
15 define the clinical features of the syndrome. The
16 first reports were found in the radiology literature.
17 There are a number of reports from the 1950s on cough
18 associated with the use of Pantopaque, which is an oily
19 contrast agent used for myelography, or imaging of the
20 spinal cord. The cases presented when the Pantopaque
21 accidently gained access to the venous system. These
22 cases presented with a cough which resolved

1 spontaneously.

2 POME associated with intramuscular injection

3 of oil-based depo drugs might be attributed to the oily

4 vehicle gaining access to the venous system, but the

5 exact mechanism by which the oil causes the symptoms is

6 not known. The literature, which is scant, suggests

7 the syndrome called POME is generally self-limited, and

8 there is no evidence to suggest there is long-term lung

9 injury.

10 Let me show you our case definition that Dr.

11 Mann and I used after review of the literature. The

12 case definition was based on the presence of the major

13 criterion of cough during or immediately following

14 injection. POME could be also diagnosed based on minor

15 criteria including the urge to cough, dyspnea,

16 bronchospasm or other non-respiratory symptoms, shown

17 here.

18 We adjudicated the cases into three different

19 categories. For a case to be adjudicated as POME, it

20 must have the major criteria of cough or two minor

21 criteria, including one which is from the respiratory

22 system. A case was adjudicated non-POME when the

1 events definitively did not meet the case definition
2 for POME and/or did not occur in temporal association
3 with an injection.
4 A case was adjudicated as indeterminate if it
5 lacked information or features to be categorized
6 definitively as either POME or definitely not POME. For
7 the post-marketing cases, Endo chose to combine the
8 indeterminate cases with the cases adjudicated as POME.
9 Now, let me show you how we use this case
10 definition to review the clinical and post-marketing
11 cases. We used a systematic three-step process for the
12 identification and adjudication of POME cases. As a
13 starting point, Dr. Mann and I referenced a list of
14 preferred terms developed by Bayer Pharmaceuticals to
15 identify cases of post-injection reactions. Bayer is
16 the maker of Nebido as well as a number of other oil-
17 based depo injectables, and Bayer developed this list
18 for their use to screen for potential cases consistent
19 with POME. Dr. Mann and I then removed some terms that
20 were not relevant to the adult male population and also
21 added some terms. In the end, we ended up with a list
22 of 481 preferred terms to do the initial screen of the

1 databases. This broad list was used to be inclusive
2 and sensitive with the understanding that irrelevant
3 cases would be identified.
4 The list terms was used to search the
5 database for potential cases of POME. Now, to add
6 specificity to the preferred term search, Dr. Mann and
7 I each separately adjudicated the cases against our
8 case definition of POME. When our separate
9 adjudications were complete, we compared the results,
10 and if our case adjudication did not agree, we then
11 discussed the case. After the discussion, if we were
12 still not in agreement, which was not very common, then
13 the most conservative adjudication was taken by the
14 sponsor.
15 Let me next review our results. First, of
16 the 3,556 patients in the clinical trial database who
17 received over 20,000 injections, 110 cases were
18 identified which had adverse event terms with at least
19 one of the preferred terms we identified to screen for
20 POME cases. We reviewed these 110 potential cases. We
21 found three cases that met the POME criteria and
22 another 23 we called indeterminate.

1 Three cases were adjudicated as POME. None
2 of these patients discontinued from the studies due to
3 the event. One patient had his POME event on the last
4 injection of the study, and two continued to receive
5 therapy following their events. One case was
6 considered an SAE, or serious adverse event, because
7 the patient had an episode that was deemed medically
8 important by the investigator, who also considered the
9 case mild. The patient reported cough and did not
10 receive any specific treatment and continued in the
11 study. There were 23 indeterminate cases; 14 of these
12 received further injections and continued with no
13 further events, but one had a second event adjudicated
14 as indeterminate for POME. Four patients discontinued
15 the study due to the event. Five cases had incomplete
16 adverse event date, so it was unclear whether they had
17 subsequent injections, but they did not have further
18 POME or anaphylaxis events. Importantly, none of these
19 events were serious and none required intervention for
20 the event.
21 And let me give you some context for some of
22 these indeterminate events. Since none of these were

1 listed as serious adverse events, we only have line
2 listings with preferred terms. Twelve patients were
3 reporting terms of hyperhidrosis, or hot flush, of
4 which 10 occurred in the male contraception trials, and
5 these patients were also getting progestational agents,
6 which can cause these symptoms. We also had three
7 cases of cough, but they did not have a clear temporal
8 relationship in the line listings. This gives you a
9 flavor for why some of these cases were considered
10 indeterminate.
11 We also reviewed cases from the post
12 marketing database. The preferred term search
13 identified 547 cases, which Dr. Mann and I reviewed. We
14 identified 141 cases as meeting our POME definition and
15 82 as indeterminate. Because it was recognized that
16 some of the indeterminate cases might have been
17 adjudicated as POME if more details had been available,
18 the sponsor chose to combine the yes and indeterminate
19 events. This means that Endo considers that there were
20 223 cases of POME reported during 9 years of marketing
21 outside the U.S. based on our adjudication. 110 of
22 these 223 cases were also identified by the FDA on

1 their list of 137 post-injection cases.
2 I will next present the reported
3 interventions from an assessment conducted by Endo of
4 these 223 cases in order to give you a feel for what a
5 person taking care of the patient thought was
6 appropriate management.
7 First off, the outcome in all 223 cases
8 adjudicated as POME or indeterminate was recovery. 173,
9 or 78 percent, of these patients, or cases, did not
10 report a medical intervention in their response, so
11 this includes cases that clearly indicated no treatment
12 was given and cases where there were no details. Fifty
13 cases reported treatment, which may indicate that these
14 cases were considered more worrisome. Antihistamines
15 and/or steroids, but not epinephrine, was administered
16 to 27 patients, which represents 12 percent of the
17 cases. Thirteen, or six percent, of the cases cited
18 treatment with epinephrine as well as these other
19 therapies. Another 10 did receive treatment of some
20 sort but not an antihistamine, steroid, or epinephrine.
21 Most of these reported POME cases did not
22 indicate that the patient went to the hospital or

1 emergency room. Eleven percent of the 223 cases
2 reported having hospital admission or ER visits. More
3 specifically, 19 events led to a hospital admission and
4 6 were managed in the ER without admission. Again, all
5 cases were reported as having recovered and it is
6 important to note that there were no deaths reported in
7 any of these cases.
8 Evaluation of the 223 post-marketing
9 surveillance cases of POME found that 125 reports
10 included definitive information on the time of onset.
11 In 124 of the 125 cases the event occurred within 30
12 minutes of the injection of AVEED, and most often this
13 occurred with the injection or immediately thereafter.
14 Only one case that we saw started about an hour after
15 the injection. Thus, the report suggests an acute
16 onset of the symptoms when they occur. Based on the
17 cases that Dr. Mann and I adjudicated, Endo then
18 calculated rates for POME. Since POME is related to
19 injections, the rates they calculated were reported
20 based on 10,000 injections. In all the clinical trials,
21 only three cases were definitively adjudicated as POME,
22 yielding a rate of 1.5 cases per 10,000 injections with

1 an upper bound of the 95 percent confidence interval of
2 3.2. If one were to include the three indeterminate
3 cases that were listed as cough but where no timing was
4 available, this rate would only double. In the
5 spontaneous post-marketing data, there is known
6 underreporting, and, therefore, one cannot be precise
7 about the numerator for the true rate. However, with
8 that caveat, the calculated rate for cases adjudicated
9 as POME is .7 per 10,000 doses sold.
10 So in summary, POME is an infrequent post-
11 injection adverse event associated with oil-based depo
12 products. When the event does occur, the symptoms
13 start during or shortly after the time of injection.
14 The classical primary symptom is cough, which is self-
15 limited. There have been no reports of deaths
16 associated with these events seen in the clinical
17 trials or reported in the post-marketing surveillance,
18 and Dr. Mann's and my review of these cases in the
19 literature of POME do not indicate any long-term
20 sequelae.
21 Now let's turn to anaphylaxis. I will invite
22 Dr. Larry Borish, a recognized allergy expert and

1 previous member of the Pulmonary and Allergy Drug
2 Advisory Committee, to the podium. Anaphylaxis/Overview
3 DR. BORISH: Hello. I'm Dr. Larry Borish and
4 I am a professor of medicine in the Division of Allergy
5 and Clinical Immunology at the University of Virginia.
6 Thank you for giving me the opportunity to present on
7 anaphylactic reactions and the spectrum of severity of
8 the reactions. A large part of my clinical research
9 and bench research activities focuses on immune
10 responses to allergens, and I have published
11 extensively on this topic.
12 Anaphylaxis is a systemic allergic reaction
13 that is usually rapid in onset, often within minutes of
14 exposure to the allergen. This defining rapidity is
15 especially true when the allergen is administered
16 parenterally. While foods are one of the most common
17 allergens, insect stings and medications are also
18 common causes of systemic allergic reactions. Many of
19 the over- the-counter and prescription drugs in fact
20 carry warnings about the risk of anaphylactic
21 reactions.
22 Anaphylaxis is a multisystem disorder and

1 presents with a constellation of symptoms. Regardless
2 of the allergen, a patient presents with symptoms that
3 can affect the skin, respiratory, GI tract, or the
4 cardiovascular system. Many people think all
5 anaphylactic reactions are potentially life-
6 threatening. Although life-threatening reactions can
7 occur, life- threatening reactions are not the typical
8 presentation of anaphylaxis. In fact, most anaphylaxis
9 episodes are sufficiently mild that the patient does
10 not require medical care.
11 The term "anaphylaxis" is used to embrace a
12 broad spectrum of symptoms. Most cases that are
13 reported are mild events that typically require no
14 intervention. Mild cases typically exhibit symptoms of
15 flushing, urticarial rash, and/or mild angioedema.
16 These symptoms may progress to include respiratory
17 complaints, such as cough, rhinorrhea, conjunctivitis
18 and/or bronchospasm, particularly in allergic
19 individuals. Severe anaphylaxis is life-threatening.
20 Deaths from anaphylaxis have been associated with
21 severe bronchospasm with respiratory compromise,
22 laryngeal edema with airway closure, or with

1 cardiovascular collapse. Anaphylaxis represents this
2 entire spectrum of symptoms, although only rarely are
3 the symptoms severe. With severe anaphylaxis,
4 epinephrine is used to reverse the attack if used in a
5 timely fashion.
6 The biggest challenge in considering the
7 correct approach to anaphylaxis is in making the
8 correct diagnosis. This is true in all presentations
9 but in particular in a drug injection setting. This is
10 a problem I often face in my clinic where patients are
11 referred to me and I am asked whether a particular
12 event was an anaphylactic reaction.
13 With mild or atypical symptoms, it may be
14 very difficult to determine whether a given
15 complication of drug administration is truly an
16 anaphylactic type reaction. For example, many drugs
17 can cause flushing with or without associated itching.
18 Also, many patients have reflex flushing reactions that
19 can occur independently of the agent, but in both cases
20 the result is a cutaneous symptom suggestive of
21 anaphylaxis.
22 Patients can have coincidental flares of an

1 underlying disease such as asthma or COPD. This can
2 present with dyspnea, which can be mistaken for an
3 anaphylactic reaction. Such coincidental variations
4 and the natural history of these diseases can be very
5 difficult to distinguish from an injection-related
6 reaction. It is not at all uncommon for patients who
7 receive a potentially painful injection to develop
8 vasodepressor syncope, which can present with many of
9 the symptoms of anaphylaxis, including diaphoresis,
10 flushing, nausea, abdominal pain, and collapse.
11 Similarly, patients may have anxiety or full-blown
12 panic attacks with an injection, which can present with
13 many of the symptoms of anaphylaxis, including
14 diaphoresis, nausea, light-headedness, severe shortness
15 of breath, globus sensation, or even collapse. A
16 globus sensation is widely reported after injection
17 therapies and is routinely but inappropriately ascribed
18 to laryngeal angioedema by both the patient and the
19 physician.
20 Finally, for a drug such as AVEED, which is
21 in an oily vehicle, the patient can have POME, which,
22 as you have just heard, is characterized by cough,

1 dyspnea, and other symptoms that can be misconstrued as
2 an anaphylactic reaction.
3 There is no universally accepted definition
4 of anaphylaxis, as the condition is a clinical
5 constellation of signs and symptoms for which there is
6 a broad differential diagnosis and for which there is
7 no pathognomonic finding. For these reasons, clinical
8 criteria have been developed to help characterize
9 reactions. The working definition favored by the FDA
10 was developed at meetings convened by the NIAID and the
11 Food, Allergy, and Anaphylaxis Network and is
12 frequently referred to as the Sampson Criteria, named
13 after the summary consensus document published in 2006,
14 on which the senior author was Hugh Sampson. However,
15 it must be emphasized that the Sampson Criteria are not
16 specific.
17 In a case such as AVEED, where POME reactions
18 are known to occur and have many of the features of
19 anaphylaxis, the false positive rate is almost
20 certainly higher. A summary of the Sampson Criteria is
21 provided in your briefing book.
22 For an injectable agent like AVEED, where the

1 preexisting allergic status of the patient is unknown,
2 the diagnosis is based on acute onset, involvement of
3 skin with or without hives, pruritis, or flushing, and
4 swollen lips, tongue, or uvula. In addition, the
5 diagnosis requires at least one other symptom including
6 either respiratory compromise or measured reduced blood
7 pressure or associated symptoms of end organ
8 dysfunction, but these features have a broad
9 differential diagnosis, including many of the features
10 of a POME reaction. Cases of anaphylaxis that
11 represent the entire spectrum of severity are
12 identified by this definition.
13 Importantly, the Sampson Criteria are not
14 based on severity, so a patient who manifests mild
15 symptoms can correctly be diagnosed as having
16 anaphylaxis but not be at risk for serious morbidity or
17 death. In fact, anaphylaxis is a spectrum of severity,
18 and most cases of anaphylaxis are not severe. The
19 statement in the FDA briefing book that all
20 anaphylactic reactions are severe and potentially life-
21 threatening is not an accurate representation.
22 Likewise, in the post-injection reactions I have

1 reviewed for AVEED, while there are some clinically
2 significant reactions, including some that may have
3 actually been anaphylaxis, very few were severe even
4 though they met the Sampson Criteria.
5 Let me now turn the podium over to Dr. Mann,
6 who will review the adjudication of anaphylaxis.
7 Anaphylaxis Adjudication
8 DR. MANN: Thank you, Dr. Borish. I would
9 like to now review Dr. Meyer and my adjudication of the
10 cases for anaphylaxis.
11 Anaphylaxis is a clinically recognized
12 syndrome, and I think clinical investigators know how
13 to report anaphylaxis, and I would like to note that
14 none of the investigators in the clinical trials
15 reported a case of anaphylaxis. Nonetheless, to be
16 comprehensive, Dr. Meyer and I reviewed the clinical
17 trial database for cases of possible anaphylaxis. We
18 also reviewed and adjudicated the post-marketing
19 adverse event reports.
20 I am going to clarify for you now our
21 processes and findings in my presentation. We used a
22 process similar to that which we used for POME. To

1 search for potential cases, we used a well-accepted
2 broad search strategy for anaphylaxis cases that has
3 already been developed by MedDRA. The preferred terms
4 came from two standardized MedDRA queries, anaphylactic
5 reactions and anaphylactic shock reactions. Using
6 those search terms, we identified cases which we then
7 carefully reviewed against the Sampson 1 criteria.
8 Let me show you our results. Among the 3,556
9 patients in clinical trials, there were 25 cases that
10 occurred on the day of injection and that matched a
11 preferred search term. Here is what our clinical
12 review of those cases showed. Of these 25 cases, none
13 met the Sampson Criteria. Eight cases were identified
14 that were considered indeterminate. Of note, these
15 eight cases also include the two cases of anaphylaxis
16 that are noted in the Endo NDA submission. These eight
17 indeterminate cases are also described in your briefing
18 booklet. The remaining 17 of the 25 possible cases
19 were adjudicated as neither meeting the Sampson
20 Criteria or being considered indeterminate.
21 On further review of those eight
22 indeterminate cases, we see that one of these events

1 was considered an SAE. This was a patient with
2 syncope. This patient is described in your briefing
3 booklet, and, of note, he received an additional dose
4 of AVEED without further complication. Indeed, a total
5 of five patients received additional doses of AVEED
6 without any evidence of anaphylactic reactions. This
7 makes it less likely that any of these cases are true
8 anaphylaxis.
9 A search of the post-marketing database
10 yielded 331 potential cases, which we carefully
11 reviewed. Of these 331 potential cases, 19 met Sampson
12 Criteria and 26 were considered indeterminate, for a
13 total of 45 cases. These 45 cases are presented with
14 full patient narratives in your briefing booklet in the
15 appendices. It is important to note that among these
16 45 cases, there was a spectrum of severity. Forty of
17 our 45 cases were also identified by the FDA on their
18 list of post-injection reactions.
19 So let's again try to gain some perspective
20 on the relative severity of these anaphylaxis cases,
21 and I'm going to do that using an assessment conducted
22 by the sponsor. Endo was looking for patients that

1 received relevant medical intervention or who were
2 hospitalized or who went to the emergency room. Of the
3 45 anaphylaxis cases, the outcome in all of these cases
4 was recovery and there were no long-term sequelae.
5 Twenty-one, or 47 percent, either did not cite a
6 treatment intervention or they recorded that no
7 intervention was given on the case report form. Twenty-
8 four of the cases did report receiving treatment, so I
9 would like to tell you more about that.
10 Thirteen of the cases cited treatment with
11 steroids and/or antihistamines; eight of the cases
12 received an epinephrine injection; and, finally, three
13 cases received treatment intervention, but not
14 treatment typical for anaphylaxis.
15 As with POME, most of these post-market
16 anaphylaxis cases did not report hospitalization or ER
17 care, 10 of the 45, or 22 percent, of the cases
18 adjudicated as anaphylaxis reported hospital admission
19 or a visit to the ER. In the remainder of cases, this
20 information was either not reported or it did not
21 occur. While these reports are incomplete and
22 inconclusive, it seems unlikely that the reporting

1 person would report an event of anaphylaxis but not a
2 hospitalization if one had occurred.
3 Evaluation of the 45 post-marketing
4 surveillance cases of anaphylaxis found that 31 reports
5 included information as to the time of onset. In all
6 31 cases, the event occurred immediately or within 30
7 minutes following the injection of AVEED. Thus, the
8 reports support an acute onset of symptoms.
9 Endo also performed a rate of anaphylaxis
10 calculation. I'm going to show you that next.
11 Anaphylaxis is a reaction dependent on the
12 immune system of the patient, so it is most
13 appropriately reported as a per-patient rate. This is
14 unlike POME, which is more of an injection-based
15 reaction. The best opportunity to identify cases of
16 anaphylactic reactions comes from the clinical trial
17 database, as these were conducted under good clinical
18 practice. In the clinical trial database, there were
19 no cases adjudicated as anaphylaxis. That would be a
20 rate of zero per 10,000 patients with an upper bound
21 confidence interval of 10.4 cases per 10,000 patients
22 based on the clinical trial experience. In the post-

1 marketing database, 45 cases were adjudicated as
2 anaphylaxis or indeterminate. Endo estimated that 1.2
3 million patients had been dosed. This yields an
4 estimated reporting rate of 0.4 cases per 10,000
5 patients. Overall, the clinical trial database and the
6 post-market database suggest that the rate of
7 anaphylaxis is small, and there were no events that
8 resulted in death or long-term sequelae.
9 Now, not surprisingly, because the clinical
10 presentations of POME and anaphylaxis do overlap, there
11 was overlap between the cases adjudicated as POME and
12 those that Dr. Meyer and I adjudicated as anaphylaxis.
13 I would like to show that here. Forty-three of the 45
14 cases adjudicated as anaphylaxis were also adjudicated
15 as POME. Just two cases were adjudicated as
16 anaphylaxis only, and 180 cases were adjudicated as
17 POME only. So overall, in our adjudication process, we
18 found a total of 225 cases of POME or anaphylaxis in
19 our review. For these overall 225 cases, 13 patients
20 were reported to have been treated with epinephrine and
21 25 patients were either hospitalized or seen in an
22 emergency room.

1 I would now like to invite Dr. Danoff back to
2 the podium to discuss the 137 cases identified in the
3 FDA's briefing booklet. Review of 137 Cases Identified
4 by FDA
5 DR. DANOFF: Thank you, Dr. Mann.
6 Up to this point, we have been discussing
7 cases based on an adjudicated diagnosis. Drs. Mann and
8 Meyer have adjudicated all of the cases we are
9 discussing. Dr. Mann just presented the 225 cases of
10 POME or anaphylaxis, which were in our briefing book.
11 The FDA presents cases through April 30th, 2012, in
12 their briefing book. This added 22 more cases
13 adjudicated as POME or anaphylaxis. The FDA briefing
14 book presents a list of 137 post- marketing cases,
15 which they entitle as "severe." They did not identify
16 any clinical trial cases with this monitor. The
17 implication of the word "severe" is that the cases are
18 especially clinically worrisome. All 137 of the FDA
19 cases were adjudicated, although 13 were not POME or
20 anaphylaxis.
21 So let's first review how the FDA chose these
22 cases. The FDA gave seven criteria that were used to

1 identify the 137 post-injection reactions that they
2 characterized as severe, yet these criteria may not
3 tell the entire story. Therefore, I would like to
4 provide you with the clinical characteristics of these
5 cases so that you can better understand them.
6 First, let me share with you some of the
7 concomitant treatments that were reported. Previously,
8 Drs. Mann and Meyer outlined these for POME and
9 anaphylaxis cases, but now I would like to present the
10 treatment in the context of the 137 cases that the FDA
11 listed. Of the 137 cases, 83 did not report receiving
12 any medical treatment. Therapy reported for the other
13 54 cases included 33, which reported receiving steroids
14 or antihistamines but not epinephrine, and 13 which
15 received epinephrine. Another eight patients did
16 receive treatment but not epinephrine, antihistamines,
17 or steroids. Twenty-nine of the 137 cases that the FDA
18 listed reported receiving hospital or ER care.
19 Hospitalization is considered a criteria for a serious
20 adverse event. Twenty-two of the cases reported
21 hospitalization. Endo would also consider the seven
22 cases that were seen in the ER as potentially

1 clinically concerning.
2 There were no deaths reported in any of the
3 137 cases. In fact, there were no deaths reported or
4 long- term sequelae reported in any case that Endo
5 adjudicated as anaphylaxis or POME. What makes this
6 compelling is that we have over 9 years of clinical
7 experience. As of the April 2012 cutoff used in the
8 FDA briefing book, more than 3.6 million doses have
9 been sold. I have previously showed you how the 137
10 cases reported by the FDA overlap with the cases
11 adjudicated by our independent experts as POME or
12 anaphylaxis.
13 The FDA did not grade the 137 cases using any
14 severity scale. We examined all 137 case reports.
15 Fifty-nine reported hospitalization or ER care or
16 treatment with epinephrine, steroids, or
17 antihistamines. Our interpretation is that
18 hospitalization and ER care are indicative of
19 seriousness. In addition, the administration of
20 epinephrine, steroids, or antihistamines could signify
21 that the health care provider thought the case was
22 medically concerning. Finally, there were no deaths or

1 long-term sequelae reported in any of these cases.
2 Endo takes patient safety seriously and wants
3 to be sure that when a post-injection reaction does
4 occur, it is identified and managed appropriately. Let
5 me now ask Dr. Shusterman to describe the proposed risk
6 management plan. Risk Management Plan
7 DR. SHUSTERMAN: Thank you, Dr. Danoff.
8 I am Dr. Neil Shusterman, Vice President of
9 Pharmacovigilance and Risk Management at Endo
10 Pharmaceuticals. Endo has been engaged with the FDA in
11 risk management discussions since the first review of
12 the AVEED NDA. We are presenting today our proposed
13 plan designed to mitigate the risks associated with
14 post- injection reactions. This includes, but goes
15 beyond, statements in labeling regarding injection
16 technique and the post-injection wait. We used
17 evidence-based risk assessment methodology to design
18 the risk management program in order to enhance patient
19 safety. The goals of the risk management plan focus on
20 awareness, preparedness, and management of acute post-
21 injection reactions, which are infrequent, detectable,
22 and manageable.

1 The first goal of the risk management plan is
2 for health care providers and patients to understand
3 the risks of these reactions. The second goal is to
4 have patients remain in the health care facility for 30
5 minutes post-injection to allow for early recognition
6 and management of an injection-based reaction following
7 AVEED administration. The third goal is to ensure that
8 AVEED is only distributed to health care provider
9 offices and not available at retail pharmacies.
10 The risk management plan consists of a REMS,
11 a Risk Evaluation and Mitigation Strategy, and
12 additional risk management interventions. The REMS
13 will consist of a medication guide, a communication
14 plan, and periodic assessments. The additional risk
15 management interventions are controlled distribution of
16 AVEED, educational materials, patient wait adherence
17 tools, and enhanced pharmacovigilance.
18 I will now discuss each of these in more
19 detail.
20 The medication guide will be included in each
21 product carton and will also be made available via
22 several other means. Examples of the types of

1 statements that could be included in the medication
2 guide are shown here and on the next slide. The
3 purpose of the medication guide is twofold. The first
4 is to provide patients with important information about
5 the risk of post-injection reactions and what to do if
6 they may be experiencing one. The second is to
7 emphasize the importance of receiving the injection
8 only in a health care provider's office and remaining
9 30 minutes after each injection.
10 The 30-minute wait period is similar to what
11 is done with other parenterally administered
12 medications including allergy shots, which are
13 administrated as often as weekly compared to five times
14 a year for AVEED and have a theoretical risk of
15 provoking a serious reaction because of the direct
16 administration of allergen to an allergic patient.
17 The communication plan will consist of a
18 "Dear Health Care Provider" letter describing the risks
19 of post-injection reactions and the importance of the
20 30- minute wait. It will also inform health care
21 providers of the availability of three types of
22 educational materials that will reinforce proper

1 injection technique, assist the health care provider to
2 recognize and treat a post-injection reaction and aid
3 offices with patient adhere to the 30-minute wait.
4 The final component of the "Dear Health Care
5 Provider" letter is an emphasis on the importance of
6 adverse event reporting, especially of post-injection
7 reactions. The "Dear Health Care Provider" letter is
8 an important component of a risk management plan and
9 will be provided to likely prescribers at launch, 6
10 months after launch, and will be included with every
11 vial of AVEED along with a package insert and the
12 medication guide.
13 To measure the effectiveness of the REMS, we
14 will conduct periodic assessments. First, we will
15 survey health care providers to measure the receipt of
16 the "Dear Health Care Provider" letter, their knowledge
17 of the key risks, their level of compliance with the
18 30-minute in- office wait, and their knowledge of
19 appropriate management of the post-injection reaction.
20 Second, we will survey patients who have
21 received AVEED to measure their receipt of the
22 medication guide, their knowledge of the key risk

1 messages, and their level of compliance with the 30-
2 minute wait.
3 These assessments will be provided to the FDA
4 at 12 months, 3 years, and 7 years.
5 I would now like to discuss our additional
6 risk management interventions. The controlled
7 distribution system will ensure that AVEED will only be
8 available through specialty distributors and
9 pharmacies. This is a distribution model that Endo
10 uses for its other specialty pharmaceutical products.
11 This system will ensure that the drug will be shipped
12 to a health care provider for administration in a
13 health care setting. It will not be available through
14 retail pharmacies, and patients will not be able to go
15 to their local pharmacy to fill a prescription for
16 AVEED. The value of this distribution system for AVEED
17 is that the potential for administration outside of the
18 health care setting is reduced while enhancing the
19 proper administration in a health care setting where
20 the 30-minute wait can be enforced.
21 We will provide educational materials that
22 will reinforce the use of proper injection technique

1 and provide assistance in helping physicians recognize
2 and manage post-injection reactions. The video will
3 remind health care providers to check for a past
4 history of hypersensitivity and instruct in proper
5 intramuscular technique for oily drugs.
6 As stated by the Division of Pulmonary,
7 Allergy and Rheumatologic Products in their review,
8 POME may be less likely when oil-based products are
9 injected carefully and slowly. There are at least
10 three oily products currently on the market which have
11 labeling statements about slow injection.
12 The patient management algorithm is designed
13 to assist health care providers to understand the types
14 of post-injection reactions that might occur, to
15 recognize the signs and symptoms of these reactions,
16 and to manage these reactions should they occur.
17 We will also make available materials or
18 provide suggestions to assist health care providers in
19 having patients remain in the office. These could
20 include reminder signage around the office, a patient
21 post-care instruction sheet noting the injection time
22 and the departure time, and timers that could be useful

1 tools for measuring the 30-minute wait period. In
2 addition, we believe the wait time is a good
3 opportunity for educational efforts either with written
4 materials or by other media.
5 Monitoring reactions when the drug is
6 marketed is important, and Endo proposes to use two
7 approaches to post-marketing surveillance. The first
8 is enhanced passive surveillance of post-marketing
9 reactions. These are reactions reported spontaneously
10 by consumers or health care providers.
11 Surveillance will be enhanced in three ways.
12 First, Endo will encourage reporting of all post-
13 injection reactions in the "Dear Health Care Provider"
14 letter. Second, Endo will enhance intake of
15 information by utilizing a standardized questionnaire
16 to obtain as much information as possible through a
17 uniform comprehensive tool. Third, Endo will increase
18 attempts to obtain missing follow-up information.
19 The second approach would use an active
20 surveillance methodology through utilization of
21 electronic health records, or EHR, information from
22 multiple databases behind HIPAA-compliant firewalls

1 that protect privacy. As an example, one source is an
2 EHR of specialty and primary care practices that
3 captures information on 110,000 men with hypogonadism.
4 Through these sources, it is possible to account for
5 the AVEED injections administered in the outpatient
6 environment.
7 From this information, the incidence of
8 significant post-injection reactions can be calculated
9 because you know the numerator, number and type of
10 reactions, and the denominator, the number of
11 injections given over a period of time.
12 In order to determine the feasibility of this
13 approach, we tested the ability of the EHR I described
14 above to detect post-injection reactions by conducting
15 a retrospective analysis of the incidence of
16 anaphylaxis with short-acting TRT injections. Cases
17 were successfully identified by searching appropriate
18 fields of the EHR among men who received TRT. We were
19 then able to calculate a rate based on the total number
20 of men exposed. This demonstrated that this type of
21 surveillance is practical and useful. This ability to
22 calculate an incidence rate of post-injection reactions

1 such as anaphylaxis will allow us to monitor any
2 deviation from baseline.
3 In summary, Endo has designed a risk
4 management plan that goes beyond labeling to provide a
5 comprehensive approach to support the safe use of
6 AVEED. The specific elements are summarized here.
7 First, prior to gaining access to AVEED,
8 health care providers will be prepared to understand
9 the risks of the drug, discuss those risks with
10 patients, and understand how to respond to post-
11 injection reactions. AVEED will only be distributed to
12 health care provider offices.
13 Second, at the time of drug administration,
14 the plan provides that AVEED injections are
15 administered under the safest conditions possible by
16 utilizing proper injection technique in the health care
17 provider's office followed by a 30-minute wait.
18 Third, the plan prepares health care
19 providers to recognize and manage a post-injection
20 reaction that might occur during the wait.
21 And, fourth, all of this will be monitored
22 with enhanced pharmacovigilance and periodic REMS

1 assessments to understand the impact of the REMS and
2 the risk management plan and react accordingly. As you
3 can see, this provides a comprehensive plan to address
4 potential risks and to give patients access to a new
5 option for long-term testosterone therapy.
6 I will now invite Dr. Casty to provide
7 concluding remarks. Benefit-Risk
8 DR. CASTY: Thank you, Dr. Shusterman.
9 This morning you heard that hypogonadism is a
10 serious medical condition with risks if not treated
11 chronically. Therefore, long-term testosterone
12 replacement therapy is needed. There are many
13 testosterone replacement products available, including
14 topical and short-acting injectable products; however,
15 each of these has limitations in their ability to
16 provide long-term testosterone replacement or have
17 unique safety risks.
18 Unfortunately, many patients do not remain on
19 long-term therapy. There is a need for an alternative
20 testosterone replacement product that can provide long-
21 term testosterone replacement for hypogonadal men.
22 Today, we described AVEED's key benefits: 94

1 percent of patients in the eugonadal range using
2 extended dosing interval of 10 weeks; no risk of
3 transference; and improved likelihood that patients
4 will stay on long-term therapy so they can realize the
5 long-term benefits of testosterone replacement.
6 We also reviewed the AVEED safety database
7 from a total of 18 clinical and post-marketing trials.
8 In addition to the clinical trials, we have over 9
9 years experience from more than 3.6 million doses sold,
10 offering extensive safety experience.
11 With the assistance of independent experts,
12 we have characterized the immediate post-injection
13 reactions of POME and anaphylaxis. Clinical
14 assessments of each case have led to the conclusion
15 that while some clinically concerning cases do occur,
16 the majority of cases occur during or shortly after
17 injection, are mild, self-limiting, and required no
18 treatment. And while they do occur, there have been no
19 associated reports of long- term sequelae or death.
20 The FDA has asked you to vote on the
21 question: Do you believe testosterone undecanoate is
22 safe for the proposed indication? This is a question

1 that cannot be answered in isolation because all
2 medications carry some risk. I hope that after hearing
3 the data we presented today, you will take into
4 consideration the clinical characteristics as well as
5 the low number of these events, which come from a large
6 database.
7 Please consider safety in the proper benefit-
8 risk context by asking yourself, is testosterone
9 undecanoate adequately safe for its proposed
10 indication?
11 You've also been asked to vote on whether
12 instructions for a slow injection and a 30-minute post-
13 injection wait would be sufficient to ameliorate the
14 severe post-injection reactions. The reactions we
15 described are intrinsic to any IM oil-based injection,
16 and the proposed instructions for use in product
17 labeling are consistent with those of other products
18 already in use. The 30-minute wait is commonly used in
19 health care practices and is supported by our clinical
20 and post- marketing data. In your discussions, please
21 consider that these two elements are part of a more
22 comprehensive risk management plan designed to

1 ameliorate the potential for adverse outcomes of these
2 reactions. In fact, this plan also includes other
3 elements, such as controlled distribution, which
4 ensures administration of AVEED in the health care
5 provider's office as well as enhanced surveillance. And
6 so we ask that you consider the totality of the risk
7 management plan we presented today as you evaluate the
8 benefit-risk profile of AVEED.
9 In summary, AVEED provides a unique
10 therapeutic option for hypogonadal men to provide long-
11 term testosterone replacement. Post-injection
12 reactions do occur with AVEED. They are infrequent and
13 detectable and lend themselves to a risk management
14 plan because they occur while patients are present in
15 the health care provider's office where they can be
16 detected and managed appropriately.
17 The analyses we presented today and the
18 totality of the data support a favorable benefit-risk
19 profile for AVEED. Endo has proposed a comprehensive
20 risk management plan designed to mitigate the known
21 risks in the immediate post-injection period.
22 We welcome the input from the Advisory

1 Committee on these data. I thank you for your time,
2 and we welcome any questions you may have. Clarifying
3 Questions to the Presenters
4 DR. JOHNSON: Thank you to the sponsor for
5 the information provided. We will now proceed with
6 clarifying questions. I would ask the Committee
7 members to raise their hand and let Ms. Bhatt know if
8 you have a question.
9 I want the opportunity to go ahead and start
10 with a question. This is a new drug application
11 resubmission with a 750 milligram dose of the agent in
12 3 mls. And not to precede the FDA in any comments they
13 may decide to make, but if you look at the December
14 2nd, 2009, response to your application, the letter
15 from the FDA stated subsequent reformulation of this
16 product, and to show reactions are reduced or mitigated
17 was critical in reapplication. So can you provide us
18 any information that says that the new dosage has less
19 of a reaction or is any way different from the original
20 application that was not accepted in 2009?
21 DR. CASTY: The reformulation was one of the
22 options that the FDA offered Endo at the time of that

1 filing. The components of castor oil and benzyl
2 benzoate are both responsible for the 10-week dosing
3 period necessary for performance of the product. We
4 also looked and recognize that there are three other
5 marketed products with castor oil and benzyl benzoate
6 in them. Those products are Mekana,
7 hydroxyprogesterone, indicated for pre-term labor;
8 Faslodex, for advanced breast cancer; and estradiol
9 valerate, which is indicated for vasomotor symptoms in
10 postmenopausal women. And so we looked and considered
11 that because we felt that these were reactions
12 consistent with other IM-based oil injections, that
13 reformulation was not necessarily necessary.
14 Now, you did allude to the dosing issue. I
15 do want to point out that in our dose ranging studies
16 we did study a 1,000 milligram dose, and that dose
17 demonstrated excessively high Cmax levels, and so the
18 dose that you're seeing today is a dose that's been
19 recognized by the FDA as having met the PK criteria as
20 an acceptable testosterone replacement product.
21 DR. JOHNSON: Do you have any evidence of
22 less of an adverse reaction with this formulation than

1 the previous?

2 DR. CASTY: Dr. Danoff, would you like to

3 take that question, please?

4 DR. DANOFF: One of the important things

5 that's happened over the period from the initial

6 complete response to now is that we have a much larger

7 safety database. So the formulation has not changed,

8 and in part by having the same formulation, we are

9 actually able to draw upon that large safety database.

10 We have looked at 750 and 1,000, but these reactions we

11 don't feel are dose related.

12 So to answer your question, what we've done

13 is we've been able to confirm the safety by analyzing

14 the entirety, which is now up to over 20,000

15 injections, more than 3,500 patients, and as of the FDA

16 briefing book, 3.6 million doses sold in the post-

17 marketing.

18 DR. JOHNSON: Thank you.

19 Dr. Cooper.

20 DR. COOPER: Dr. Casty, this question is for

21 you. In your introductory remarks on I believe it was

22 Slide CO4 on Page 2, you sort of note that there is

1 agreement between the FDA and the sponsor on the fact
2 that immediate -- so there is some rate of immediate
3 post-reaction events, and obviously the rate is one of
4 the reasons we're here today. So that's going to be
5 further discussion.
6 But actually I have a question for you about
7 the second statement on the slide, and that the general
8 safety profile is consistent for this testosterone
9 replacement therapy, and if you could clarify for us
10 what you mean by that, what data led to that
11 conclusion. Because, as you say, we can't make these
12 decisions about safety in isolation, and so we need to
13 understand what's the relative safety or the relative
14 rate of these events compared to other TRT products.
15 Can you tell us what data were used to lead you to this
16 conclusion and potentially share those with us so we
17 can have that?
18 DR. CASTY: Yes, I can. What's meant by that
19 statement is the safety profile with respect to the
20 testosterone-related side effects, and, of course,
21 because testosterone replacement is based upon
22 achieving, getting patients into, a eugonadal range,

1 one would expect that once in a eugonadal range, the
2 testosterone- related side effects would be similar.
3 And so leading up to this meeting today, in our
4 discussions with the FDA, we did agree that
5 testosterone-related side effects per se would be
6 consistent with class labeling for other testosterone
7 replacement products.
8 DR. COOPER: Okay. Thank you. So that
9 clarification is helpful.
10 Then are there safety data on the rates of
11 immediate post-reaction events for other shorter acting
12 testosterone that you could help us understand?
13 DR. CASTY: Yes. Actually, and as Dr.
14 Shusterman alluded to in his discussion, part of our
15 risk management plan is looking at this electronic
16 health record system as a means for us to get an even
17 better understanding of this.
18 Dr. Shusterman, I'm going to ask you if you
19 could please present the data that we obtained on
20 short- acting testosterone agents.
21 DR. SHUSTERMAN: Thank you, Dr. Casty.
22 As part of our workup of an active

1 surveillance system, we were able to use an electronic
2 health record to actually measure the rate of reactions
3 with short- acting TRTs, and it appears to be roughly
4 in the same range as AVEED. And let me take you
5 through that analysis.
6 The database we used was the GE Centricity
7 EMR. It is the largest ambulatory database in the
8 United States. It covers both primary and specialty
9 care, and there are now data in the database from
10 approximately 37.4 million American patients. Quintiles
11 has been given the rights to look at the identified
12 data, and we worked with Quintiles on this analysis.
13 So what did we look at? First we defined the
14 population. We limited it to males through the years
15 1997 through 2012, which are the years that the
16 Centricity database has been in operation, and that
17 provided a search of 14.7 million records. We when
18 looked for exposure of any IM testosterone product, and
19 that yielded 56,427 unique patients. And then we used
20 those parts of the EHR where problems with drugs are
21 recorded, and in this system, that's considered the
22 problem table and the allergy table, and we looked for

1 specific information in this analysis for anaphylaxis
2 to IM testosterone or what reporters called high grade
3 critical allergy. And based on a probabilistic
4 approach, we classified the cases as, yes, this was
5 anaphylaxis probable, possible, or unlikely. Let me
6 say that the unlikely cases had a really low likelihood
7 of being a significant reaction, so we are not
8 including them in any summary measure.
9 What we did was add up the yes, probable and
10 possibles, and came up with 19 cases in over 56,000 men
11 to give the incidence of 3.4 per 10,000 patients. If
12 you limit it to just cases that were considered yes and
13 probably together, it's 10 in 56,000 or so, which is
14 1.8 per 10,000 patients. And if you remember the AVEED
15 data from the clinical trials, which we consider to be
16 the best source for actually deriving an incidence,
17 it's somewhere between zero and 10 per 10,000 patients,
18 using the upper bound of the 95 percent confidence
19 interval.
20 So one of the things we also did, as the FDA
21 did, was look in the FDA's AERS database, and there
22 it's hard to find cases, but we know from the Weber

1 effect and other things about long-term drugs -- short-
2 acting drugs have been on the market for 60 years,
3 since the 1950s -- that reporting rates to
4 pharmacosurveillance databases drop over that period of
5 time. So we think the EHR approach gives us more
6 accurate rates and it's also the reason why we want to
7 use it as part of our active surveillance.
8 DR. JOHNSON: Dr. Kittelson.
9 DR. KITTELSON: Thank you. I would like to
10 understand a little bit more about the persistence
11 question, and perhaps this question is probably best
12 addressed to Dr. Swerdloff. So it's kind of presumed
13 that persistence on therapy is a good thing, but in a
14 lot of clinical trials, we worry that people who are
15 taking the drugs are exactly the ones who are going to
16 have adverse effects later.
17 So we've looked at this has met FDA criteria,
18 which is primarily pharmacokinetic properties, but
19 there are other potential adverse effects from long-
20 term exposure to TRT. And is there anything, is there
21 any evidence, that the limiting you would get with gels
22 or something would prevent longer term consequences,

1 whereas that's not an option really if you're injecting
2 every 10 weeks? You can't decide, "Well, today I'm not
3 going to use it because I don't feel good." Do you
4 understand?
5 DR. CASTY: Yep. Actually, I want to ask Dr.
6 Cunningham if he would discuss that question.
7 DR. CUNNINGHAM: Good morning. I'm Glenn
8 Cunningham. I'm a clinical endocrinologist from
9 Baylor, in Houston. I, like Dr. Swerdloff, who is a
10 member of the Androgen Deficiency Panel that wrote the
11 endocrine guidelines.
12 So I think your question has to do with
13 whether intermittent therapy might be less likely to
14 cause side effects than continuous therapy, and to
15 answer that directly, I don't know of good data to
16 address that issue. Okay? I think that one can
17 speculate that long- term therapy will likely have more
18 beneficial effects on bone, on muscle mass, on
19 strength, and issues like that. There is the
20 possibility that there could be increased adverse
21 effects in terms of hematocrit, so you would have to
22 manage that. So if a patient has erythrocytosis or

1 excessive increase in hematocrit, you would have to
2 address that. That's more likely to be seen in the
3 data that we have with short-acting injectables where
4 you have sort of super high levels intermittently.
5 So I don't think that we have good
6 comparative data like you might like to see. I think
7 we can infer some of the answer with some of the
8 information that we do have.
9 DR. KITTELSON: And how about urologic
10 effects or prostate cancer risk or anything like that?
11 DR. CUNNINGHAM: So prostate cancer risk, I
12 think that, as we all know, men's testosterone levels
13 go down as we age, and the incidence of both benign
14 prostatic hyperplasia with LUTS, lower urinary tract
15 symptoms, along with clinical prostate cancer, goes up
16 with age. So to begin with, these are not directly
17 related to testosterone. In the data, testosterone
18 treatment trials that we have we have not seen a clear
19 increase in prostate cancer, but a decade ago, we
20 estimated that it would take a clinical trial of 6,000
21 men being treated with androgen or placebo and studied
22 for 5 years to be able to address that. So, again, we

1 don't have long-term data to address the issue of
2 prostate cancer.
3 DR. JOHNSON: Dr. Orza.
4 DR. ORZA: I have two clarifications that go
5 to better understanding the safety side, and then one
6 to help me better understand the risk-benefit tradeoff.
7 Is there any reason to think about or be concerned
8 about these oil microembolisms in other organ systems
9 besides the lungs, where we don't have something to
10 show us what's happening like the reactions that people
11 are having? That's the first one. And the second one,
12 I understand why you present the POME risk in terms of
13 numbers of injections, but do you have anything that
14 converts that to the risk for an individual? So if
15 you're going to be on this for 10 or 20 years and
16 you're going to be having five or six injections per
17 year, what does that mean your risk as an individual is
18 of having one of these reactions?
19 And then in terms of better understanding the
20 risk-benefit tradeoff, I understand that the regulatory
21 requirement is simply a PK value, and we were given no
22 information about the extent to which people get

1 symptom relief from this. So do you have anything that
2 summarizes -- there is a lot of information in the
3 Endocrine Society Guideline that actually suggests that
4 a lot of the data about symptom relief is inconclusive
5 at best. Do you have anything that summarizes the
6 benefit side more than just in terms of a PK value?
7 DR. CASTY: Okay. Let me start with the
8 first question, which was with respect to oil emboli
9 potentially being in other organ symptoms. I would ask
10 Dr. Meyer, who has reviewed the cases in literature, to
11 best discuss that question first.
12 DR. MEYER: Hi. Bob Meyer. So as I referred
13 to earlier, the literature is actually pretty scant on
14 what this phenomenon actually even is, and while it
15 carries the name "pulmonary oil microemboli,"
16 personally, after reviewing the literature and
17 reviewing the cases, I'm not even comfortable with that
18 term, but we're using it because that's the term of art
19 because I don't know what it is. I don't think it
20 equates to fat, endogenous fat, embolism, which is an
21 entirely different phenomenon.
22 The classic symptom is cough and sort of an

1 oily taste or a medicinal taste and maybe a little bit
2 of throat irritation, which suggests it is in some ways
3 perhaps reaching the pulmonary circulation and becoming
4 volatile and leading to irritant cough. I don't think
5 there is any evidence that it gets to other organ
6 systems either from the literature or from what we've
7 seen. Most of the cases where there is, say, erythema
8 reported, it sounds very much like what you would
9 expect with somebody vigorously coughing, that they get
10 quite red in the face. But the best answer I suppose to
11 your question is we don't have any evidence of that,
12 but in terms of really good pathophysiology and
13 understanding of this, I think it's a poorly understood
14 phenomenon.
15 If you go back to the Pantopaque data, which
16 I think you could argue informs us some -- I'm not sure
17 it's synonymous either, but it informs it some -- there
18 was description of some of the radiographic dye being
19 in the pulmonary bed, pulmonary circulation. It was
20 not described that it had gone elsewhere.
21 DR. CASTY: Now, your next question I think
22 was related to the injection-based risk for POME versus

1 an individual-based risk.

2 DR. MEYER: Yeah. So I'll answer that as

3 best I can again with the caveat that there is not a

4 lot of good data out there, but from a review of the

5 cases, it appears like this is a sporadic phenomenon

6 where individual patients do not seem to have a

7 particular propensity. Some cases are reported where

8 there are multiple occurrences. On the other hand,

9 presumably many of those are getting their injections

10 from the same operators and so on. It does not, from

11 what I've seen -- and I think Mr. Mann would agree with

12 this -- appear to be a truly allergic phenomenon. There

13 are some cases, admittedly, that you look at and you

14 can't really tell whether it's classic POME or allergy,

15 but it doesn't appear to be an allergic phenomenon.

16 So I think the best I can answer is we don't

17 know, but it looks like your risk over time is no

18 different if you're a new patient or whether you're

19 continuing on whether you've had a case or not. It's a

20 defined risk of the injection over time, and if you

21 look, these are infrequent; they occur, but they're

22 infrequent.

1 DR. CASTY: Thank you, Dr. Meyer. The last
2 question you asked was regarding symptom relief. And
3 I'm presuming you're mostly interested in the clinical
4 trial results from that or are you talk -- okay. So
5 I'll ask Dr. Danoff to comment on that in terms of our
6 clinical trial.
7 DR. DANOFF: So symptom relief, AVEED
8 effectively replaces testosterone, as we showed, is an
9 effective testosterone replacement. So its ability to
10 relieve symptoms is really no different than that you
11 might see with the gels or the short-acting injectables
12 separate from the fact that we have the improved
13 persistence, so any long-term benefits of the
14 testosterone replacement you're more likely to get.
15 So as you said, really the benefits are what
16 the Endocrine Society Guidelines points out, that there
17 are benefits associated, and what Dr. Swerdloff talked
18 about were about the muscle and adiposity.
19 Dr. Zitzmann, who has experience treating
20 patients for periods of time maybe could speak to the
21 benefits that he's seen in his patients with AVEED, or
22 Nebido, as it's called.

1 DR. ZITZMANN: Yes. Thank you very much for
2 inviting me. I am Professor Zitzmann, for
3 endocrinology and andrology from Germany, and I have
4 been treating patients with intramuscular testosterone
5 undecanoate, which is now named Nebido, for about 14
6 years, and we have extensive experience with the
7 efficacy of that drug compared also to the gel, which I
8 propose to the patients, and they choose themselves
9 what they want, the gel or injectables, and they
10 usually prefer gel or long- acting injectables, not the
11 short-acting injectables, because these cause mood
12 swings.
13 So we have, apart from our clinical
14 experience, which is tremendous, that the patients
15 really improve. We have clinical trials. We have
16 placebo controlled trials from many countries which
17 demonstrate that the endpoints, especially concerning
18 libido, well-being, but also metabolism, are changed
19 significantly with the formulation of Nebido compared
20 to placebo.
21 And concerning POME, I have seen cases of
22 that when I inject testosterone undecanoate. All these

1 cases that I have seen, which were very few, resolved
2 within a few minutes. They occurred after 60 seconds
3 on average after the injection was finished, and it was
4 a dry unproductive cough and resolved without sequelae
5 within 3 or 4 minutes. The patients remained in the
6 room for about 30 minutes without any cardiovascular
7 problems.
8 Thank you.
9 DR. CASTY: Thank you, Doctor.
10 DR. ORZA: Do you have any slides that show
11 the efficacy data?
12 DR. CASTY: I'm sorry. Efficacy data from
13 our clinical trials?
14 DR. ORZA: From the placebo controlled?
15 DR. DANOFF: I think there is a publication
16 that shows weight loss data. And maybe Dr. Zitzmann
17 can speak to it.
18 DR. ZITZMANN: Concerning the use of Nebido
19 in comparison to placebo, there have been trials within
20 Germany, there are trials which are placebo controlled
21 from Norway and also from Russia and from Australia,
22 and these are data which are very new, which are

1 observational, and which have one arm. This is just
2 showing weight loss over years, not compared to
3 placebo, but this is consistent with the shorter
4 trials, which lasted about 1 year, compared to placebo
5 arms to Nebido, and what we have see there was
6 depression scales going down significantly in
7 comparison to placebo, and also markers of metabolism
8 especially instant resistance going down, obesity going
9 down, and especially waist circumference. So this is
10 what you expect from Nebido. There are also data
11 concerning bone density that increases over time and
12 it's even better than the short- acting formulation
13 that has been published in 2004 in the JCM. Thank you.
14 DR. CASTY: And I think we might have a slide
15 that shows the bone mineral density data. So this is a
16 small study which looked at bone mineral density in men
17 treated for 36 months with Nebido, and what they looked
18 at was bone mineral density, both in the lumbar and
19 femoral spine. The yellow bars are patients who were
20 on placebo or untreated, and you can see the
21 differences in the bone mineral density. It is a small
22 study, but this is the data that is available.

1 DR. CASTY: Thank you.
2 DR. JOHNSON: Dr. Bockman.
3 DR. BOCKMAN: Thank you. I have two
4 questions, and they're somewhat unrelated, so I'll ask
5 them separately. The first question has to do with I
6 understand the focus on POME and anaphylaxis,
7 obviously, these are serious reactions, but a 3 or 4
8 milliliter oil injection is a rather large injection,
9 it's a large depo injection, and I wondered if you have
10 any information about site irritation or even myolysis
11 that might occur with repetitive dosing of such large
12 oily doses.
13 DR. CASTY: Dr. Danoff, would you like to
14 review that information?
15 DR. DANOFF: So we have the adverse event
16 reporting from the clinical trials, and this shows the
17 results. So first when you talk about repetitive, of
18 course, the injections are only every 10 weeks, so you
19 only get five injections per year, but this shows the
20 adverse events that are reported at the injection site.
21 They're relatively pretty low and they did not result
22 in a significant number of discontinuations. And there

1 does not appear to be a large difference between the 3
2 and 4 ml dose. And as Dr. Zitzmann was saying,
3 patients tend to tolerate and in fact choose to remain
4 on their Nebido, which is the 4 ml dose.
5 DR. BOCKMAN: Thank you. My second question
6 has to do with I wondered if you had done, based on the
7 reactions that have been reported and the fact that
8 patients are taken to the emergency rooms and patients
9 are admitted, did you make any estimate of the
10 additional medical costs of these reactions?
11 DR. CASTY: Medical costs would be difficult
12 to, particularly from post-marketing cases, so we
13 wouldn't have adequate information to really
14 extrapolate what a medical cost would be for that, and
15 that's not information that we would routinely gather
16 for post- marketing trial data, so we don't have that
17 kind of data.
18 DR. BOCKMAN: Just a comment on that. I
19 mean, based on Steve Brill's recent reportage in the
20 TIME Magazine, and you see what the average cost of an
21 emergency room visit is, it's quite high, and certainly
22 several days in the hospital is quite costly as well.

1 So these add to the medical costs overall, and just
2 based on the number of cases you have and the ER
3 visits, I think that would be an easy estimate to make.
4 DR. CASTY: I think it's important to keep in
5 context that these data are occurring over 9 years and
6 3.6 million doses have been delivered. So while we may
7 be talking about 137 or the 247 and we take them
8 seriously, we have to keep in context that this has
9 occurred over a 9-year period, and as Dr. Shusterman
10 showed, the post-injection reaction rate is not
11 atypical from other testosterone injection reactions,
12 and so I think what we are trying to do with our
13 analyses here is to characterize the post-injection
14 reactions as best we can.
15 DR. BOCKMAN: Just a quick follow-up on costs
16 and issues since I'm also a clinical endocrinologist,
17 I'm impressed that your risk management program
18 involves primarily the treating doctor. I mean, it's
19 going to fall primarily on his shoulders or her
20 shoulders to deal with this issue, and as you know,
21 reimbursement for an injection is X amount of money,
22 and any consequences that come from that, and all the

1 extra learning that has to be done is all going to fall
2 on the practicing physicians' shoulders. So I just
3 wondered, do you feel that that's a fair
4 characterization of the plan that you put forward?
5 DR. CASTY: Well, let me have Dr. Shusterman
6 run us through exactly what would be involved in terms
7 of the educational part and the actual execution of the
8 risk management plan.
9 DR. SHUSTERMAN: Let me make two comments.
10 The first is that the reactions that we are talking
11 about occur with drugs that are on the market right
12 now, so we're not discussing a new, novel reaction that
13 a physician would have to learn about. For those who
14 haven't administered oily injections, I think that the
15 POME reaction would be the one that a physician or
16 health care provider would need to learn more about.
17 And as Dr. Meyer has indicated, the amount of
18 information actually would be contained in the proposed
19 labeling that we've discussed with the FDA in addition
20 to the material that we provide.
21 Mostly what we think the risk management plan
22 does is gives physicians the tools to practice good

1 medicine since they're already giving injections and
2 since anybody who gets an injection has a risk of some
3 kind of reaction, including up to anaphylaxis. So we
4 think that this awareness aspect of the plan that just
5 ensures that physicians know what might happen and
6 therefore they can be prepared and therefore they can
7 manage it through this.
8 That's our goals here.
9 DR. JOHNSON: Dr. Morrato?
10 DR. MORRATO: Thank you. I have three
11 questions, one clarifying around the benefit, one
12 around the risk assessment, and one around the risk
13 management.
14 So to start with the benefit, I'll build off
15 of what Dr. Kittelson was talking about in terms of
16 persistence or adherence, and I would like to get a
17 little bit better understanding in terms of how you
18 were evaluating persistence and defining it in the
19 study that was quoted on Slide CO23 as that's the
20 argument for the perceived benefit of this, it's long-
21 acting and it would be better adherence.
22 So, A, how did you define persistence in this

1 study? And, B, did you take into account that
2 different types of patients would be using these
3 different types of dose forms such that there would be
4 likely confounding by that type of indication? I could
5 imagine that a patient with a congenital deficiency
6 might choose a different type of product for long-term
7 use than a patient that has acquired deficiency and
8 might be trying this out, and that might be accounting
9 for some of the differences. So I didn't know if you
10 adjusted for that in your analyses.
11 DR. CASTY: Let me ask Dr. Steve Camper, from
12 our Health Economics Department to answer those
13 questions.
14 DR. CAMPER: Good morning. Dr. Stephen
15 Camper, from Endo's Outcomes Research Department. To
16 answer your question about the definition, if I
17 understand you correctly?
18 DR. MORRATO: Right.
19 DR. CAMPER: We used the International
20 Society of Pharmacoeconomics and Outcomes Research
21 definition of "persistence," which is in essence a
22 duration of therapy before discontinuing. Our

1 definition of "discontinuation" was a gap of greater
2 than 60 days between the end of a day's supply of one
3 script and then the beginning of another script. So
4 patients could have a gap of up to 60 days and we still
5 considered them as persistent.
6 DR. MORRATO: Right. So how did you account
7 for differences between an oral, a topical, and a long-
8 acting? So by definition, are you giving the long-
9 acting 12 weeks?
10 DR. CAMPER: We defined the long-acting, as
11 based on what the data were in the database, as 90
12 days, as the typical day's supply. We went with a
13 specific day's supply for the orals and did not make an
14 adjustment. We allowed 60 days gap for whatever the
15 formulation was.
16 DR. MORRATO: Right. I've been studying this
17 in another category, this is why I know it's a very
18 challenging question.
19 DR. CAMPER: Yes, it is.
20 DR. MORRATO: So if I'm looking at the data
21 and we're quoting 70 percent persistence for your
22 product, is that the second fill is essentially over a

1 3-month period if you're using a 90-day? So they've
2 only really had one or two fills versus the orals or
3 the -- excuse me, the gels are monthly prescription
4 refills, so they -- you know -- do you know what I'm
5 saying?
6 DR. CAMPER: Yes. We did -- it would account
7 for more -- if we use a 30-day supply, for example, for
8 the --
9 DR. MORRATO: Gels?
10 DR. CAMPER: -- for the gels, then they could
11 have had three --
12 DR. MORRATO: Right, so --
13 DR. CAMPER: -- refills prior to that time,
14 and that's one of the issues about the long --
15 DR. MORRATO: Right. So one thing to
16 consider in interpreting this is that by the time you
17 get to the third blue bar in 12 months for your
18 product, a patient has made the decision to come back
19 three times to refill. That's about equivalent to a
20 patient using a monthly refill cycle for a gel, and
21 it's interesting in looking at that that the 35 percent
22 for the long-acting is not that dissimilar from a gel,

1 right. So I understand that, because it's long-acting,
2 there are more days there, but in terms of the decay
3 curve itself, it's probably -- if you look at it in
4 terms of number of decisions a patient is having to
5 make in order to come back or refill, et cetera, it may
6 not be that dissimilar, it's just the fact that we're
7 loading them up with a bunch of drug, right?
8 DR. CAMPER: Exactly, and that's, I think,
9 one of the things that we're presenting, is the mere
10 fact that there are -- and we didn't evaluate this, but
11 the mere fact that there are fewer opportunities to
12 make a decision on whether you will go back and get a
13 refill versus not going back may contribute to the
14 persistence that we see --
15 DR. MORRATO: Right. For year one; right?
16 DR. CAMPER: Yeah, absolutely.
17 DR. MORRATO: And then over time it decays.
18 DR. CAMPER: Absolutely.
19 DR. MORRATO: So did you look at differences
20 in the type of patient that, you know --
21 DR. CAMPER: We did not.
22 DR. MORRATO: -- that might account for also

1 differences in adherence besides just the formulation?
2 DR. CAMPER: With the database that we used,
3 we couldn't do that.
4 DR. MORRATO: Okay. It's nice to see some
5 data, though, so thank you.
6 So my second question was related to the
7 post- marketing database and the much, as I heard, much
8 larger safety database. Could you comment or describe
9 more the actual reporting process for the post-
10 marketing data? Was this an active or passive
11 surveillance? I wasn't quite sure how these studies
12 were conducted and therefore how the case reporting was
13 occurring. And the reason why I'm asking this is when
14 I looked at the FDA briefing materials and they discuss
15 -- you know, they're reporting out the med returns, et
16 cetera, and when they looked at in Table 14 of their
17 briefing materials the U.S. and European clinical
18 trials, on average, there was about 15 percent of
19 patients had at least one serious adverse event.
20 However, when you look at Table 15, which is quoting
21 the post-marketing studies that have been conducted,
22 that rate is more like 1 percent. So that would

1 suggest a very different surveillance reporting scheme
2 going on in these two data.
3 DR. CASTY: Yes, we can explain that. There
4 is an explanation for that.
5 Dr. Shusterman, could you discuss that
6 answer?
7 DR. SHUSTERMAN: Let me break that into two
8 parts. So first we're going to talk about studies,
9 formal studies, sponsored by either Endo in the United
10 States or by Bayer on a worldwide basis.
11 So when we talk about the U.S. and EU
12 studies, there is the category of studies related to
13 hypogonadism and male contraception, and then there are
14 studies that were formally done by Bayer after the drug
15 was approved. The important difference between those
16 two categories is that in the hypogonadism and the male
17 contraception, all adverse events were ascertained
18 during the trial, so they were all collected by the
19 investigators. As is often the case in post-marketing
20 studies, it's often coned down to a narrower set of
21 adverse reactions, so in those studies, the
22 investigators were asked to capture adverse drug

1 reactions, which means the investigator had to feel
2 there was a relationship of the reaction to the
3 medication in order to capture it, and that's a common
4 methodology in post-marketing studies, which explains
5 why you saw those different rates.
6 DR. MORRATO: Right. So then in terms of the
7 cases that were adjudicated, they're coming from both
8 sources; correct?
9 DR. SHUSTERMAN: The database that includes
10 clinical studies is the set of 3,556 patients, and that
11 is coming from both sources. However, it is important
12 to remember that for the purposes of the post-injection
13 reactions, all of the patients were under observation
14 in the office setting when that was given. So we
15 believe there capture was very good and contributes to
16 the ascertainment under that setting.
17 DR. MORRATO: All right. And then my last
18 question relates to the risk management and the point
19 that you're raising in terms of having the injections
20 occur in office. And I was reading some of the
21 materials that we received from the public, they make
22 submissions, et cetera, and one of them struck my

1 attention, it was written by a Dr. Kim, who is a
2 professor of surgery, urology, at the University of
3 Tennessee, and he is giving testament to the product,
4 et cetera, but then he says, "As common in clinical
5 practice, I instruct my patients on home self-
6 injections with testosterone injections, given their
7 very favorable safety profile and my clinical
8 experience."
9 So what assurance do we have that if a
10 product is shipped to the doctor's office, it will
11 actually be administered in the doctor's office?
12 DR. SHUSTERMAN: Yes, that's a good question.
13 A fair amount of the short-acting testosterone use in
14 the United States is self-injection at home, and as Dr.
15 Swerdloff mentioned, the interval may be every 1 to 2
16 weeks, so it would be highly inconvenient, obviously,
17 for a patient to come back on that frequency, and
18 they're often taught to give it to themselves. The
19 difference with AVEED is that the interval is much,
20 much longer, so obviously the amount of times a patient
21 would have to come and the impact on the health care
22 provider's office is completely different than the

1 short-acting injections.
2 And furthermore, what we're really asking is
3 a 30-minute wait and patients come back, for example,
4 for allergy shots often on a weekly basis and wait 30
5 minutes there. So both from an office standpoint as
6 well as from a patient standpoint, there is precedent
7 for this. And, furthermore, the controlled
8 distribution system -- and I think this is important --
9 it's typical that for short- acting injections, a
10 patient gets a prescription, goes to their local
11 pharmacy, can bring the drug home. We want to make
12 sure that does not happen with AVEED so that it is
13 given in the office. Now, can I give you 100 percent
14 assurance that some physician will hand the vial to an
15 individual who takes it home? I can't, but the
16 labeling, the "Dear Health Care Provider," the
17 medication guide all instruct both the patient and the
18 physician that this should given in the office.
19 There is also the matter that it has to be
20 given in the buttocks and that's a little more
21 different than somebody giving an injection in the
22 thigh, and that should be done by a professional.

1 DR. MORRATO: So my just one last point on
2 that since you raise, have you talked with the type of
3 practices that are going to be adopting or using this
4 to see whether or not these offices are ready in terms
5 of waiting space? So I had allergy shots. They're set
6 up and prepared for this, there is waiting space, et
7 cetera, so it's part of the workflow. I mean, this may
8 not be part of the workflow, or is it current workflow,
9 for the type of practice that would be doing these
10 injections? You know, I think also of vaccines are also
11 suggested that there is a waiting period on that, for
12 instance, HPV vaccinations, and in a pediatrician's
13 office, there is not really consideration of space or
14 where you sit or how you observe, et cetera.
15 So to what degree are the type of practices
16 that would be adopting this be ready for this kind of
17 change? How consistent is it with current workflow?
18 DR. SHUSTERMAN: Sure. Let me invite Dr.
19 Dowling to the microphone. Dr. Dowling is a practicing
20 urologist, has experience with managing a large group,
21 and I think he can give a good flavor because
22 urologists are going to be key prescribers of this

1 medication.

2 DR. DOWLING: Thank you. Robert Dowling. I'm

3 a board certified urologist and have been a medical

4 director for a large single specialty group. And to

5 answer your question directly, urologists are prepared

6 to have patients wait after invasive procedures and

7 medications that are already administered in our

8 office. Examples would include leuprolide for prostate

9 cancer, intravesical BCG for bladder cancer, and we

10 also perform prostate biopsies and vasectomies where

11 this is part of the normal workflow, to simply have the

12 patient wait and be sure there are no complications.

13 DR. MORRATO: So what proportion of

14 injections will be performed in urologists' offices

15 versus other kinds of practices? Do you know or

16 anticipate?

17 DR. DOWLING: I can answer based on personal

18 experience that I consider this to be part of the

19 routine care that's delivered in a urology practice.

20 I've learned that it's delivered in endocrinologists

21 and other offices as well. I don't have any

22 information about what the proportions are, but we have

1 patients coming to our office directly and through
2 referrals to support that this is just what we do in
3 urology.
4 DR. JOHNSON: So I'm going to offer my
5 apologies to the Committees. We have still about nine
6 more questions to ask, but we will have time after the
7 FDA presents and again this afternoon. We have time
8 now for one more question, but please save your
9 questions. We will get to them for the sponsors.
10 Dr. Erstad?
11 DR. ERSTAD: I had a question for Dr.
12 Swerdloff, but while he's getting to the mic, I have a
13 quick one for Dr. Casty, and that's, other than the
14 extended dosing interval, do you perceive any
15 clinically important benefits, increased benefits, or
16 decreased risk of AVEED versus the other injectable
17 products?
18 DR. CASTY: I think the key benefits for
19 AVEED that we've outlined earlier is highly predictable
20 PK, which means that 94 percent of the patients can
21 have their eugonadal testosterone levels achieved. It's
22 a 10- week dosing period. We talked about how there is

1 no risk, so in terms of having an option should they
2 have a concern about a risk of transference. And --
3 DR. ERSTAD: Right. Yeah, I said versus the
4 other injectable products, so the kinetic issue and
5 then in terms of other important benefits --
6 DR. CASTY: Yeah. And in terms of the risk
7 is we've shown earlier the risk profile in terms of
8 post- injection reactions appears to be about
9 comparable, and so in total, we think that there is a
10 positive benefit- risk profile.
11 DR. ERSTAD: This is for Dr. Swerdloff.
12 Dr. Swerdloff, for you, the first question is
13 I assume from the patient perspective that this is
14 primarily a quality of life issue. In other words,
15 it's not like hypertension, where there is going -- you
16 know, we counsel the patients on decreased mortality,
17 et cetera, and assuming you agree with that, that
18 that's the case, would you agree that how the adverse
19 effect profile is presented to the patient would really
20 influence the desire to get less frequent injections?
21 In other words, if you presented this simply as a 2-
22 versus a 10-week issue, that there might be a natural

1 inclination to take the longer interval? But again how
2 you present that adverse effect profile could be
3 critically important as to how a patient might choose
4 one product versus another.
5 DR. CASTY: Dr. Swerdloff?
6 DR. SWERDLOFF: Thank you. I'm not certain I
7 understood the context of your question, but I think
8 that the question was related to whether or not the
9 interval between treatments and the persistence of the
10 testosterone levels would have an impact on the adverse
11 effects. Did I understand --
12 DR. ERSTAD: No, no. Let me reword it. You
13 know, we're discussing some potentially pretty serious
14 adverse effects, and the idea being that, again, if you
15 simply present this as one injectable product versus
16 another and only being a dose frequency issue, that
17 there might be this inclination to take the longer
18 interval, but obviously if you would present it as with
19 one product there is this very serious but potentially
20 rare risk versus this other one where that doesn't
21 occur, that that could clearly influence a patient's
22 decision to have a 2- versus a 10-week injection. I'm

1 just simply saying that these -- how it's presented in
2 terms of the adverse event profile would definitely
3 influence the patient's desire to have more versus less
4 frequent dosing interval.
5 DR. SWERDLOFF: Yeah. So I think in terms of
6 the individual patients, that there are considerable
7 differences in terms of their preference based upon
8 their own personal experiences. So from a physician's
9 standpoint, we have those individuals who, for
10 instance, are good medication takers and they're quite
11 satisfied with taking the medication on a once-a-day
12 basis. There are other individuals who are willing to
13 have injections on an every 2-week basis, but many who
14 do not like injectables because of the frequency of the
15 injection, and many of those individuals may be
16 candidates for less frequent intervals.
17 In terms of the presentation of the adverse
18 effects, it really depends upon what adverse effect
19 that you're referring to. So there are certain adverse
20 effects which might be considered injection based or
21 short-term based and others which represent the
22 considerations for long-term treatment. For instance,

1 Dr. Cunningham spoke about erythrocytosis, which is the
2 most common adverse effect that we see with
3 testosterone administration, increased hematocrit and
4 hemoglobin with the assumption that that somehow
5 increases the risk, for instance, for thickening of the
6 blood and may have some effects on ischemic effects,
7 but there is really no evidence for that.
8 The issue of prostate cancer is usually the
9 issue that's raised when we talk about drugs that will
10 last longer in the blood and whether or not there is an
11 increased risk of that. There are two aspects to that.
12 One is that there really is no evidence at the present
13 time that testosterone either causes prostate cancer or
14 converts preclinical prostate cancer into clinical
15 prostate cancer, and most of the urologists who deal
16 with prostate cancer feel that the interval of time
17 between an injection every 3 months or 10 weeks, if you
18 would, and an injection that would have increased
19 testosterone for a shorter period of time will have a
20 huge impact upon the long-term deleterious effects. The
21 whole issue of cardiovascular disease and testosterone
22 is a controversial area and we're presently trying to

1 work out the details of that, but most of the
2 epidemiologic data favor that low testosterone is a
3 risk factor for cardiovascular disease, but there is
4 some data that doesn't conform to that concept.
5 DR. ERSTAD: Thank you, Dr. Swerdloff.
6 DR. JOHNSON: Well, thank you very much. We
7 will now take a 12-minute break, 11-minute break.
8 Committee members, please remember that there will be
9 no discussion of the meeting topic during the break
10 amongst ourselves or any members of the audience. And
11 we will be back at 10:30. Thank you.
12 (Whereupon, there was a break from 10:14 a.m.
13 to 10:30 a.m.) FDA Presentation
14 DR. JOHNSON: Let us now return to our
15 seats. And now we are ready to proceed with our
16 presentations from the FDA. Regulatory History and
17 Major Clinical Issue
18 DR. HIRSCH: Good morning. My name is Mark
19 Hirsch, and I am Medical Team Leader in Urology in the
20 Division of Reproductive and Urologic Products. I will
21 be presenting a brief overview of the regulatory
22 history of this application and a brief overview of its

1 main clinical review issue. In my talk, I will show a
2 series of numbers that relate to post-injection adverse
3 reactions. Unless otherwise specified, these numbers
4 are based on FDA's adjudication of cases.
5 In addition, I would like to point out that
6 my talk is intended as an overview of the FDA
7 perspective. Our presentation will include more
8 detailed talks by Dr. Stacy Chin, Dr. Cynthia Kornegay,
9 and Dr. Suzanne Robottom.
10 The original application was submitted in
11 August 2007. The application received an approvable
12 action based in large part on reports of immediate
13 post- injection adverse events posing a safety concern.
14 In our action letter, we noted that while the exact
15 etiology of these events was yet to be determined, the
16 reports were consistent with pulmonary oil
17 microembolism, POME, and anaphylaxis.
18 The information in the application that
19 generated this concern is shown in this slide. There
20 were eight cases of concern in clinical trials,
21 including two cases of post-injection sudden urge to
22 cough and dyspnea -- I would like to note that only one

1 of those cases was in a U.S. trial -- and six
2 additional cases from trials outside the U.S. where
3 other adverse event terms were listed, including
4 convulsions, syncope, and cardiovascular collapse.
5 In addition, we identified 66 post-injection
6 reaction cases that were reported in 33 months of post-
7 marketing experience outside the United States. Of
8 these 66 post-marketing cases, 28 were serious adverse
9 events, as identified by the reporter, and 12 patients
10 were hospitalized. Several of the cases appeared to
11 reflect anaphylaxis.
12 In its action letter, FDA asked the sponsor
13 to characterize the etiology of these post-injection
14 reactions and to determine their incidence.
15 Subsequently, the sponsor submitted a complete response
16 in March 2009. In response, the Agency issued a
17 complete response action stating again that the post-
18 injection reactions continued to pose a safety concern
19 that precluded approval. In addition, the sponsor's
20 proposed Risk Evaluation and Mitigation Strategy, or
21 REMS, did not assure that the benefits of the products
22 outweighed its risks.

1 The information and the complete response
2 that led to this concern is shown in this slide. There
3 were five cases of POME identified in clinical trials,
4 including one serious adverse event per regulatory
5 definition. There were no cases of anaphylaxis. There
6 were three additional clinical trial cases of concern,
7 again, convulsions, syncope, and circulatory collapse.
8 In addition, the Agency identified at that time a total
9 of 116 post-injection reaction cases from 54 months of
10 post-marketing experience outside the United States.
11 After further adjudication, FDA finally identified a
12 total of 106 post-marketing cases, including 68 that
13 appeared to reflect POME and 38 anaphylaxis.
14 In our action letter, FDA asked the sponsor
15 to identify the component or components of the product
16 that were contributing to these post-injection
17 reactions and to reformulate the product or to identify
18 a population in whom the identified risks would be
19 acceptable.
20 Subsequently, FDA met with the sponsor to
21 discuss a potential path forward. The sponsor proposed
22 a narrow target population and a program to restrict

1 distribution of the product. The Agency responded that
2 the proposed target population was too narrow and that
3 that population was not clinically viable. In
4 addition, the proposed restricted distribution program
5 required clarification.
6 Subsequently, the FDA met with the sponsor
7 again to discuss a potential path forward. At this
8 time, the sponsor proposed a standard hypogonadal
9 target population and a REMS with ETASU, or Element to
10 Assure Safe Use. The proposed ETASU consisted of a more
11 detailed restricted distribution program. The Agency
12 responded that after further consideration, a REMS with
13 ETASU was considered not appropriate in this situation.
14 Dr. Robottom will provide further comments on a REMS
15 with ETASU in her talk later in our presentation.
16 Subsequently, in a submission that preceded
17 the most complete response from the sponsor, the
18 sponsor informed us that they had identified a total of
19 400 post- injection reaction cases in the post-
20 marketing period, including 160 cases of POME, and 240
21 cases of anaphylaxis. The sponsor noted that all POME
22 cases would be counted in their analysis of these

1 events, but only 23 cases of anaphylaxis would be
2 counted. The Agency responded that the sponsor's
3 MedDRA search terms were reasonable, that FDA would
4 continue to use the NIH-based clinical definition of
5 anaphylaxis in its evaluation of cases and that the
6 sponsor should provide detailed reports for each case.
7 The most recent submission was received
8 November 2012, and again the FDA's focus were cases of
9 severe post-injection reactions in clinical trials and
10 in post- marketing experience outside the United
11 States. Few post-injection reactions were identified
12 in clinical trials, and these will be discussed by Dr.
13 Kornegay in her talk.
14 In the post-marketing experience, the sponsor
15 identified a total of 228 cases of POME and 45 cases of
16 anaphylaxis. The FDA identified a total of 137 severe
17 post-injection reaction cases. Severe post-injection
18 reactions were defined by FDA as any anaphylaxis, any
19 serious adverse event by regulatory definition, any
20 case requiring treatment, any case involving syncope or
21 lowering of the blood pressure, or any case reported as
22 serious or medically important by the reporter.

1 In her talk, Dr. Stacy Chin will provide
2 details of the post-marketing cases. Herein, I will
3 provide a brief overview of these events.
4 Signs and symptoms that manifested in the 137
5 severe post-injection reaction cases included impaired
6 breathing, coughing, and choking sensation, including
7 several cases of cyanosis and loss of consciousness,
8 throat-related symptoms, including throat swelling,
9 throat irritation, and throat tightness,
10 gastrointestinal symptoms, including nausea and
11 vomiting, constitutional symptoms, including sweating,
12 dizziness, anxiety, and muscular weakness,
13 cardiovascular changes, including both hypotension or
14 hypertension, and cases of chest discomfort, and in a
15 small number of cases, EKG changes. In addition,
16 allergic type phenomena were reported, including
17 urticaria, rash, face edema, and itching.
18 Of the 137 severe post-injection reactions
19 that we identified, the majority occurred during or
20 soon after the injection. 68.6 percent occurred either
21 during or immediately after the injection, and another
22 8.8 percent occurred within 60 minutes. While all 137

1 cases were reported to have occurred on the same day as
2 dosing, you will note that 25 cases did not report a
3 specific time following the injection.
4 Of the 137 severe post-injection reactions,
5 we found that 23 percent were either hospitalized or
6 visited the emergency room, 7 percent reported by the
7 reporter as life-threatening events, 93 percent were
8 reported as, quote, medically significant by the
9 reporter, and 14 percent reported syncope or sudden
10 lowering of the blood pressure.
11 Of the 137 cases we identified, 60 percent we
12 found received treatment. In many cases, the patient
13 was treated as if he was experiencing anaphylaxis. Ten
14 percent of our cases received epinephrine, 28 percent
15 received corticosteroids, 22 percent received
16 antihistamines, and 13 percent received other
17 therapies.
18 Finally, the FDA conducted a search of its
19 Adverse Event Reporting System, or AERS, to identify
20 severe post-injection reaction cases for other
21 injectable testosterone products. This search employed
22 the same criteria as was used to search for

1 testosterone undecanoate cases. FDA identified a total
2 of 33 severe post-injection reactions in 44 years of
3 experience for the other injectable testosterone
4 products. Of these 33 cases, 14 appeared to reflect
5 severe POME and 19 anaphylaxis.
6 I will now turn the podium over to Dr. Chin,
7 from the Division of Pulmonary, Allergy, and
8 Rheumatology Products. Dr. Chin will provide a more
9 detailed clinical analysis of the 137 post-marketing
10 cases. Testosterone Undecanoate Severe Post-Injection
11 Reactions in the Post-Marketing Setting
12 DR. CHIN: Good morning. My name is Stacy
13 Chin. I am an allergist/immunologist and clinical
14 reviewer in the Division of Pulmonary, Allergy, and
15 Rheumatology Products, known as DPARP. My presentation
16 today will focus on a review of anaphylaxis and
17 pulmonary oil microembolism-related post-injection
18 adverse reactions in the post-marketing setting.
19 This is an overview of my presentation. First
20 I will provide some background for the role that DPARP
21 has played in the review of this NDA. Next, I will
22 discuss the two types of post-injection reactions that

1 constitute the main safety concern. For anaphylaxis, I
2 will describe the diagnostic criteria used to identify
3 cases and results of our case review. I will also share
4 with you several examples of anaphylaxis cases, and
5 finally discuss potential etiologies of anaphylaxis in
6 patients receiving TU.
7 For pulmonary oil microembolism, or POME, I
8 will describe the case definition used to identify
9 cases and go over the proposed pathophysiology. I will
10 then present the results from our case review and again
11 present several examples of severe adverse reactions
12 related to POME. Finally, I will close with our
13 overall findings and conclusions.
14 The Division of Reproductive and Urologic
15 Projects initially consulted our division, DPARP, to
16 review post-marketing adverse event reports from
17 countries where TU is approved that were included in
18 the original U.S. NDA submitted in 2007. At this time,
19 all of the events were considered by the applicant to
20 be POME, and we were asked to determine if any of the
21 immediate reactions might be consistent with
22 anaphylaxis. Since then, our division has continued to

1 be involved in the review of additional reports of
2 post-injection reactions on several occasions. For
3 this current NDA submission, we were specifically asked
4 to review over 500 cases of potential anaphylaxis and
5 potential POME reports that had been culled by the
6 applicant using agreed-upon search terms from their
7 spontaneous post-marketing surveillance database, which
8 spanned an 8-year period from 2003 through 2011.
9 Now I will move on to discuss anaphylaxis.
10 Anaphylaxis is an acute, potentially life-threatening,
11 immediate hypersensitivity reaction. Since their
12 publication in 2006, the FDA has relied on the
13 anaphylaxis clinical diagnostic criteria outlined by
14 the Joint National Institute of Allergy and Infectious
15 Diseases and the Food Allergy and Anaphylaxis Network's
16 Second Symposium on Anaphylaxis to identify cases of
17 anaphylaxis from adverse event reports in all drug
18 programs.
19 The specifics of these criteria are presented
20 in this slide. I will not read through these criteria,
21 but I would like to call your attention to a few key
22 points.

1 First of all, I would like to emphasize that
2 the criteria do not make the distinction based on the
3 presumed underlying mechanism and do not grade the
4 severity of the reactions, since all anaphylactic
5 reactions are considered potentially life-threatening
6 by nature.
7 Secondly, as you can see, there are three
8 criteria that can be met to identify anaphylaxis. These
9 criteria require multisystem organ involvement and are
10 not simply hives. Thus, meeting any of these criteria
11 would constitute a severe reaction.
12 Criterion 1 is the most conservative of the
13 diagnostic criteria, as it requires skin or mucosal
14 involvement, such as hives or angioedema. Many of the
15 cardiopulmonary symptoms associated with POME overlap
16 with those observed in anaphylaxis, but POME in general
17 does not result in skin or mucosal manifestations such
18 as hives or angioedema. Therefore, use of Criterion 1
19 above to identify anaphylaxis ensures that these cases
20 are indeed anaphylaxis but risk underreporting. On the
21 other hand, including Criterion 2, in which skin
22 symptoms are not required to identify anaphylaxis runs

1 the risk of including some severe POME cases as
2 anaphylaxis. Tables within my presentation will
3 display the anaphylaxis case determination using
4 Criterion 1 only, which gives the most conservative
5 estimate of anaphylaxis in the post- marketing reports.
6 However, in my summary, I will also present
7 the impact of including Criterion 2 in identifying
8 cases of anaphylaxis from the post-marketing reports.
9 The next slide presents the results of our case review.
10 Using search terms for anaphylaxis, which are
11 listed as an appendix in the FDA background package,
12 the applicant searched their ex-U.S. post-marketing
13 surveillance database, which included spontaneous
14 adverse event reports over an 8-year period from
15 November 25th, 2003, to November 24th, 2011. This
16 revealed 330 potential cases of anaphylaxis. Using
17 only NIAID Criterion 1 and including cases that
18 reported the adverse reaction as either anaphylaxis or
19 anaphylactoid reaction, we identified 47 cases of
20 anaphylaxis.
21 Additional safety data submitted in a
22 periodic safety update report covering November 25th,

1 2011, through April 30th, 2012, revealed an additional
2 six cases of anaphylaxis, bringing the total number to
3 53 when using the most conservative application of the
4 NIAID criteria, Criterion 1 only.
5 I will now present several examples of
6 adverse reactions determined to meet anaphylaxis
7 Criterion 1. More detailed narratives of the case
8 examples can be found in the DPARP consult within the
9 FDA background package.
10 Patient 1 was a 39-year-old male reported to
11 have anaphylactic shock. Onset of symptoms occurred
12 during injection of the approved TU product, Nebido,
13 and included throat closing, coughing, difficulty
14 breathing, as well as facial and tongue swelling. He
15 was treated with epinephrine twice as well as oxygen
16 and then hospitalized.
17 Patient 2 was a 54-year-old male reported to
18 experience an anaphylactic reaction occurring halfway
19 through the injection of his second dose of Nebido.
20 Symptoms included cough, difficulty breathing,
21 laryngeal edema, diaphoresis, and near respiratory
22 arrest. He was treated with epinephrine twice as well

1 as supplemental oxygen and transferred to the hospital.
2 At this time, I will present an overview of
3 the steps one can undertake to further investigate the
4 cause of anaphylaxis once it occurs followed by what we
5 believe may be possible etiologies of anaphylaxis for
6 the TU drug product. A typical assessment for
7 anaphylaxis can involve three main steps: one,
8 obtaining a good clinical history, especially if the
9 evaluation takes place after the acute episode; two,
10 checking routine, widely available laboratory tests
11 during the acute episode itself -- these tests are
12 easily obtained in the office setting -- and, three,
13 confirming the trigger for anaphylaxis either by means
14 of allergy testing or challenge by reexposing the
15 patient to the suspected allergen in a controlled
16 setting.
17 For the TU program, no substantial
18 investigations have occurred in an attempt to discern
19 the underlying cause of anaphylaxis. While the
20 applicant initiated one study in 2010, Study IP157-003,
21 to skin- test and rechallenge patients with previous
22 hypersensitivity reactions to TU, only one patient has

1 been enrolled.

2 For the TU drug product, we assessed the

3 potential for each of the individual components to

4 trigger clinical symptoms consistent with anaphylaxis.

5 The TU drug product contains the active ingredient

6 testosterone undecanoate and two excipients, castor oil

7 and benzyl benzoate. Without a systematic study of the

8 potential triggers for anaphylaxis to rely on, we

9 looked to evidence from both the literature and

10 individual adverse reaction case reports to support the

11 notion that several components of the TU drug product,

12 including excipients, may be responsible for the cases

13 of anaphylaxis observed.

14 Testosterone undecanoate, the drug substance

15 and active ingredient, is a testosterone ester which

16 forms active testosterone by cleavage of the ester side

17 chain. From review of the literature, we are not aware

18 of reports that testosterone undecanoate specifically

19 is associated with immediate hypersensitivity

20 reactions. However, the following case suggests that

21 testosterone undecanoate itself may be capable of

22 eliciting anaphylaxis.

1 A 46-year-old male was reported to have
2 anaphylaxis, including symptoms of cough, rash, and
3 closing of airways with onset immediately after Nebido
4 injection. He reported previously discontinuing both
5 Testogel and Andropatch due to allergic skin reactions.
6 The fact that testosterone is the only common
7 ingredient among Nebido, Testogel, and Andropatch
8 raises the possibility that the testosterone drug
9 substance was the cause of this anaphylactic reaction.
10 Castor oil is one of the excipients in the TU
11 product. It is derived from the castor seed Ricinus
12 communis. Castor oil is frequently used in the
13 cosmetic and food industry for a variety of purposes.
14 It is also used as a laxative when taken internally.
15 Depending on its purity, it may contain the potent
16 allergens Ric c 1, Ric c 2, and allergen 3. In the TU
17 product, castor oil is used to increase storage in
18 fatty tissues of the body and thus prolong drug half-
19 life.
20 Ricinoleic acid is the principal fatty acid
21 in castor oil. It has been implicated as a cause of
22 allergic contact dermatitis. In addition, ricinoleic

1 acid shares structural similarity with salicylic acid
2 since both are hydroxy acids, and ricinoleic acid has
3 been demonstrated to act on the prostate system as
4 well. In addition, a castor oil derivative,
5 polyethoxylated castor oil, is used as an excipient and
6 has been implicated in anaphylaxis observed following
7 administration of the drugs cyclosporin and paclitaxel.
8 Given the structural and functional relation
9 between ricinoleic acid and salicylic acid, the
10 following report of a patient with an immediate adverse
11 reaction to TU who subsequently was found to have
12 salicylate hypersensitivity may support the concept of
13 castor oil and salicylate cross-reactivity.
14 A 38-year-old male experienced an immediate
15 adverse reaction during his first Nebido injection. He
16 was treated with prednisolone and cetirizine, an
17 antihistamine. He was subsequently the only patient
18 enrolled in the applicant-sponsored clinical trial
19 Study IP157-003 designed to assess immediate
20 hypersensitivity reactions in a controlled manner. On
21 evaluation, he had no reaction to skin prick testing
22 with either diluted or undiluted Nebido. When

1 subsequently exposed to one-tenth the dose of Nebido,
2 0.4 milliliters, he developed symptoms, including
3 flushing, hypertension, and dyspnea. He was treated
4 with corticosteroids and antihistamines. He reported
5 having similar hypersensitivity reactions to aspirin in
6 the past, leading the allergist involved in the case to
7 believe the reaction was related to salicylate
8 hypersensitivity.
9 Benzyl benzoate is the other excipient in the
10 TU product. It is a colorless liquid widely used as a
11 preservative, flavoring agent, and a component of
12 topical insecticides. As a class, benzoates are
13 recognized to produce immediate reactions, including
14 contact urticaria. The following published report of
15 anaphylaxis in an adolescent patient directly
16 implicates benzyl benzoate as the cause after receiving
17 the approved TU product Reandron.
18 A 16-year-old boy experienced an anaphylactic
19 reaction less than 3 minutes after the third dose
20 administration of Reandron. Symptoms involved
21 generalized urticaria, throat tightening, angioedema of
22 the lips and face, dyspnea, and hypotension, among

1 others. He was treated with epinephrine,
2 antihistamines, steroids, oxygen, and intravenous
3 fluids. Upon further evaluation, skin prick testing
4 revealed a 10-by-8 millimeter wheel to the Reandron
5 product and a 10-by-10 millimeter wheel to benzyl
6 benzoate, but no reaction to either castor oil or
7 testosterone undecanoate alone.
8 To summarize, anaphylaxis cases were
9 identified using NIAID Criterion 1. This is the most
10 stringent application of the criteria and thus results
11 in a conservative estimate with the potential for
12 underreporting cases of anaphylaxis. In our case
13 review, we identified 47 cases of anaphylaxis over an
14 8-year period from 2003 through 2011 and six additional
15 cases from a safety update report from November 2011
16 through
17 April 2012. The TU drug product contains
18 three components: testosterone undecanoate, castor
19 oil, and benzyl benzoate. While there has been little
20 investigation regarding the cause of anaphylaxis,
21 literature and case reports suggest that any of the
22 three components may cause anaphylaxis.

1 I will now move on to discuss pulmonary oil
2 microembolism, or POME.
3 POME is a phenomenon that likely results from
4 direct vascular or lymphovascular embolization of oil-
5 based preparations to the pulmonary microvasculature.
6 POME was initially described following procedures which
7 involved large injection volumes of oil, such as during
8 lymphangiography and hysterosalpingography. However,
9 POME has also been noted to occur during or immediately
10 after IM injections of smaller amounts of oil-based
11 depo drugs such as TU. Both the presenting symptoms
12 and severity can be variable, but cough and some degree
13 of dyspnea are virtually always present. POME can be
14 quite severe, and in these cases, symptoms such as
15 chest pain, dizziness, profuse sweating, paresthesias,
16 syncope, and circulatory collapse have been noted.
17 The pathophysiology underlying POME is likely
18 similar to that which occurs with the more widely
19 recognized fat embolism. Some portion of the oil from
20 the injected drug product makes its way through the
21 venous circulation back to the right side of the heart
22 with subsequent embolization into the lungs. This can

1 result in mechanical vascular occlusion leading to
2 transient acute pulmonary hypertension with immediate
3 respiratory symptoms such as cough and dyspnea, and if
4 severe, decreased cardiac output resulting in syncope
5 and circulatory collapse.
6 In addition to the acute vascular occlusion
7 phenomenon, the action of pulmonary lipases may release
8 toxic free fatty acids resulting in a pulmonary
9 inflammatory response, as occurs with fat embolism.
10 This may explain prolongation of symptoms and prominent
11 chest x-ray changes observed in severe POME and fat
12 embolism.
13 The case definition we used to identify POME
14 cases was the same as that used by the applicant in the
15 initial NDA adjudication except for the timing of the
16 event. In our case definition, the event must have
17 occurred within 24 hours of injection unless timing was
18 unspecified or unclear, in which case it was included.
19 The rationale for using a 24-hour window is that for
20 spontaneous post-marketing reports, the default time is
21 the day of the event unless the timing was specifically
22 provided. However, for most cases included, the

1 reaction occurred immediately after or during
2 injection. Symptoms involved must have included cough
3 or dyspnea or two or more symptoms suggestive of POME,
4 such as those listed here.
5 As previously mentioned, the severity of POME
6 can be quite variable. Because our primary focus was
7 review of severe immediate adverse reactions, we
8 assessed cases of POME for severity as well. To be
9 categorized as severe, the reaction must have met the
10 case definition for POME and must have met at least one
11 of the following criteria listed on this slide. Of
12 note, nearly all cases categorized as severe fulfilled
13 more than one of these criteria.
14 Using search terms for POME, which are
15 available as an appendix in the FDA background package,
16 the applicant searched their ex-U.S. post-marketing
17 surveillance database, which included spontaneous
18 adverse event reports over an 8-year period from
19 November 25th, 2003, to November 24th, 2011. This
20 revealed 533 potential cases of POME. Applying the
21 POME case definition, we identified 191 cases of POME
22 from the post-marketing surveillance database and an

1 additional eight cases from the bridging periodic
2 safety update report, bringing the total number of POME
3 cases from November 2003 to April 2012 up to 199. Of
4 the 199 cases of POME, we determined that 84 cases were
5 severe using the severity grading criteria.
6 Following are several examples of what we
7 believe to be severe POME events.
8 Patient 3 was a 52-year-old male who
9 experienced a heat sensation in his neck, tickle in his
10 throat, and 20-second loss of consciousness following
11 Nebido injection. He was placed in shock positioning
12 and given intravenous fluid resuscitation. He was
13 hospitalized in the intensive care unit for further
14 clarification, where he underwent radiographic imaging
15 of his head. A head CT revealed no evidence of
16 bleeding or infarction. He was retrospectively
17 diagnosed with a micro-fat embolism possibly related to
18 Nebido.
19 Patient 4 was a male of unknown age who
20 experienced circulatory collapse with several minutes
21 of unconsciousness, nausea, cough, and encopresis, or
22 defecation, 15 seconds following Nebido injection. It

1 was unclear if any treatment was given, but he
2 recovered over an unknown period.
3 Patient 5 was also a male of unknown age who
4 experienced difficulty breathing, dizziness, vertigo,
5 darkened vision, weakness, pallor, profuse sweating,
6 and total absence of autonomy. Onset of symptoms
7 occurred 1 to 2 minutes after Nebido injection. The
8 patient thought he would die as a result of these
9 events. It is unclear if treatment was given, but he
10 recovered after an unspecified duration.
11 In sum, we identified a total of 199 cases of
12 POME, 84 of which were determined to be severe per the
13 severity grading criteria. Severe cases often involved
14 severe dyspnea, loss of consciousness, circulatory
15 collapse, and/or loss of bowel function. While the
16 applicant asserts that POME is a self-limited
17 phenomenon that can be prevented by reducing the
18 injection volume and using proper injection technique,
19 there is scant clinical evidence to support these
20 claims. The applicant has proposed a lower volume of 3
21 milliliters in the U.S. NDA at least in part to reduce
22 the incidence of and alleviate concern over POME

1 events.

2 However, because the 4 milliliter dose is

3 that approved around the world, and there is little

4 data from the use of the 3 milliliter volume, we do not

5 know if the lower volume might be associated with

6 reduced POME events. Furthermore, the fact that many

7 of the immediate reactions have been reported to occur

8 mid-injection argues against that possibility.

9 Please note that severe POME events account

10 for less than half of total POME cases. However,

11 because the reports of POME events in the literature

12 are sparse and only describe the acute event, the long-

13 term consequences of severe POME or even multiple

14 episodes of less severe POME are largely unknown.

15 While some patients may discontinue treatment

16 after a severe event, others may continue treatment

17 despite repeated milder POME events. The harmless

18 nature of these milder cases of POME is largely

19 speculative since there is no data to suggest what the

20 long-term cardiopulmonary consequences might be of

21 repeated POME over time.

22 In conclusion, there is clear evidence of

1 substantial numbers of severe post-injection adverse
2 reactions including both anaphylaxis and POME occurring
3 in the post-marketing setting. We identified 53 cases
4 of anaphylaxis using the most conservative definition,
5 199 cases of POME with 84 of those judged to be severe.
6 This results in a total of 137 severe post-injection
7 reactions, which include all cases of anaphylaxis and
8 severe POME.
9 As mentioned previously during my overview of
10 the NIAID criteria, use of the most conservative
11 diagnostic criteria for anaphylaxis likely results in
12 underdiagnosis of anaphylaxis cases. However, it is
13 notable that when Criteria 1 and 2 are used, the number
14 of anaphylaxis cases increases by 23 to a total of 76
15 with a corresponding reduction in the number of severe
16 POME cases. Anaphylaxis and POME share many of the
17 same clinical symptoms, making it sometimes difficult
18 to distinguish between the two phenomena. Nonetheless,
19 we consider these cases severe regardless of etiology
20 or categorization.
21 Finally, although the applicant maintains
22 that POME is self-limited and harmless in nature, we

1 have concern for the long-term consequences of POME.
2 Given that TU is intended for chronic use, the unknown
3 effects of both severe and repeated mild events on
4 future cardiopulmonary function must be taken into
5 consideration when weighing the potential risks and
6 benefits of this product.
7 This concludes my presentation of the
8 anaphylaxis and POME-related adverse reactions in the
9 post-marketing setting. I will now turn the podium
10 over to Dr. Cynthia Kornegay, who will present
11 reporting and incidence rates for POME and anaphylaxis.
12 Reporting and Incidence Rates for Pulmonary Oil
13 Microembolism (POME) and Anaphylaxis
14 DR. KORNEGAY: Good morning. My name is
15 Cynthia Kornegay, and I am going to spend the next few
16 minutes describing FDA's assessment of the pulmonary
17 oil microembolism, or POME, and anaphylaxis reporting
18 and incidence rates associated with testosterone
19 undecanoate, or TU.
20 I will briefly describe the prevalence of
21 hypogonadism and touch on the sales and use of
22 testosterone products in the United States. Then I

1 will touch on issues with the use of reporting rates to
2 evaluate potential TU safety signals.
3 Finally, I will discuss the incidence rates
4 submitted by the applicant and summarize my findings.
5 Briefly, there are two classifications of
6 hypogonadism: primary and secondary. Primary
7 hypogonadism is the result of disorders of the testes,
8 while secondary, or hypogonadotropic hypogonadism,
9 derives from pituitary gland conditions. Secondary
10 hypogonadism, in particular, can be idiopathic or
11 caused by tumors, trauma, or radiation.
12 The prevalence of hypogonadism is not known,
13 but an estimated 30 percent of men have some form of
14 the condition, and between 6 and 12 percent are
15 symptomatic. An Institute of Medicine report estimated
16 that between 4 and 5 million men in the U.S. have
17 hypogonadism and approximately 5 percent are treated.
18 In other parts of the world, about 1 percent receive
19 treatment.
20 This graph displays the number of
21 testosterone packages sold by manufacturers to U.S.
22 channels of distribution between 2008 and

1 2012. Note that these data do not include TU. Topical
2 testosterone products dominated the U.S. market during
3 this entire period. Sales of injectable testosterone
4 products increased from 2 percent of the market in 2008
5 to 6 percent in 2012.
6 This graph shows the number of patients who
7 had a prescription claim for testosterone between 2009
8 and 2012. The data in this graph are from outpatient
9 retail pharmacies and account for between 45 and 55
10 percent of injectable testosterone sales. The
11 remainder was shipped to non-retail sources such as
12 clinics, federal facilities, HMOs, and mail order.
13 Slightly more patients 50 years of age and older used
14 testosterone injections as compared to patients who
15 were less than 50 years old.
16 Next, I will discuss the post-marketing
17 reporting rates for TU. To assess risk, post-marketing
18 reports need to be placed in the context of drug use.
19 In many cases, this is done by comparing the post-
20 marketing cases to the number of patients who took the
21 drug. The resulting metric is called the reporting
22 rate. In the case of TU, however, information on the

1 actual patient exposure is not available. The next
2 section will briefly review why this and other
3 limitations render the reporting rate a less than ideal
4 measure for risk of TU and why the incidence rates from
5 the clinical and post- marketing trials provide a more
6 accurate assessment of the POME and anaphylaxis
7 signals.
8 The applicant and FDA had similar POME and
9 anaphylaxis reporting rates. Determining what these
10 rates actually mean, however, is not an easy task.
11 Reporting rates are often used because at first glance
12 they appear to have several advantages. They are
13 simple to construct, use readily available information,
14 and are seemingly intuitive to understand. In some
15 situations, they are compared to population incidence
16 rates to provide context. However, there are several
17 conditions that must be met for reporting rates to be a
18 valid and interpretable metric.
19 The biggest challenges are first to
20 accurately identify the population at risk, and,
21 second, to ensure that the cases, or the numerator, and
22 the population at risk, or the denominator, are from

1 the same base population. This is an essential part of
2 calculating any rate. If these conditions are not met,
3 then the resulting ratio describes a correlation but
4 does not provide any information about a direct
5 relationship. This is the case for the TU reporting
6 rates. The cases are from a spontaneous reporting
7 system, while the denominator represents sales, not
8 actual patients. This means that for TU, the
9 population at risk is estimated but cannot be measured
10 or verified directly. An added complication here is
11 that if a specific drug was not mentioned in the case
12 report, for example, testosterone instead of Nebido,
13 the European brand name of TU, then either the case
14 must be excluded from the numerator or all
15 testosterone-containing products must be included in
16 the denominator rather than only Nebido. This may
17 unduly minimize the reporting rate.
18 A third hurdle is identifying cases of
19 interest.
20 There can be any number of reasons that a
21 potential case may not be reported by a health care
22 provider or patient:

1 the event is not recognized or is not
2 associated with the drug; not knowing where, how, or
3 what to report; or, since reporting is largely
4 optional, simply choosing not to report an event. Even
5 if a potential case is reported, there may not be
6 sufficient information to make a determination, and
7 there is no guarantee that records of the event are
8 still available and accessible.
9 As Dr. Chin described, the similarity and
10 symptoms between POME and anaphylaxis may also
11 contribute to the misidentification of cases. The
12 result of any and all of this is likely
13 underascertainment and underreporting of potential
14 cases of interest.
15 Because the TU reporting rates do not meet
16 the definition of a rate, they cannot be compared to
17 incidence rates. The main reason for this is the use
18 of sales data as a denominator. The number of patients
19 exposed is actually an estimate based on sales, and
20 there is no way to verify the accuracy of that
21 assessment. In addition, there is a possibility of
22 abuse or diversion, as is the case for injectable

1 testosterone products, such as TU, there is no way to
2 ascertain how much of the product was used for the
3 labeled indications.
4 Given all of these issues, reporting rates
5 should be calculated with caution and considered a
6 crude measure of risk. If more reliable metrics are
7 available, particularly incidence rates, they should be
8 used instead. Incidence rates are preferable here
9 because the exposure and cases both arise from the same
10 base population of patients.
11 Fortunately, the applicants also provided
12 incidence rate information for TU. The information I
13 will be using for this section of my talk are from the
14 applicant's summary of clinical safety. Incidence
15 rates were calculated using data from both clinical and
16 post- marketing studies. These investigations included
17 a total of 3,556 men; 725 participated in clinical
18 trials, while 2,424 participated in post-marketing
19 hypogonadal studies. An additional 407 men were from
20 clinical contraceptive studies. 272 U.S. study
21 participants received the 750 milligram dose. All
22 other participants received the 1,000 milligram dose

1 regimen.
2 This table shows the POME incidence rate from
3 the clinical studies and from two post-marketing TU
4 studies. Note that since both POME and anaphylaxis
5 occur at the time of injection, it is more appropriate
6 to measure these incidence rates with respect to
7 injections rather than person time.
8 The red box highlights the incidence rates
9 for each of these studies. The overall clinical trial
10 incidence rate is 4.5 cases per 10,000 injections,
11 similar to the rates in the post-marketing trials of
12 4.8 and 5.1 cases per 10,000 injections respectively.
13 Of note, the incidence study participants are also
14 included in the overall clinical estimate; however, the
15 incidence rate in the clinical trials when this study
16 is excluded is 4.6 cases per 10,000 injections, so it
17 did not unduly influence the results.
18 The red box here highlights the clinical
19 trial anaphylaxis incidence rate, which was 1.2 cases
20 per 10,000 injections, or 5.5 cases per 10,000 person-
21 years. Person-years were used in this instance to
22 enable comparison with published incidence rates for

1 anaphylaxis. The background rates for drug-induced
2 anaphylaxis vary widely for a number of reasons,
3 including the use of multiple definitions and
4 difficulty in finding and identifying cases through the
5 various health care settings. Nevertheless, a
6 generally accepted range is between 0.8 and 5 cases per
7 10,000 person-years, putting the TU rates at the upper
8 end.
9 There were a number of limitations associated
10 with this analysis. The applicant's evolving
11 methodology for classifying POME cases, and the
12 applicant's use of multiple definitions to determine
13 anaphylaxis have led to different numbers of cases in
14 successive applicant adjudications. Since only study
15 summaries were provided for most of the clinical
16 investigations, it was not possible to assess study
17 quality. Finally, some cases were difficult to
18 categorize due to minimal descriptions being provided,
19 and the lack of supplementary or additional data
20 available.
21 To summarize, the POME incidence rate
22 remained constant throughout the clinical and post-

1 marketing studies. Although reporting and incidence
2 rates cannot be compared, we note that cases of POME
3 occurred in the ideal administration setting of the
4 clinical and post- marketing trials. The presence of
5 post-marketing POME cases indicates that this event
6 continues to occur outside of the controlled study
7 setting and likely at a greater rate than indicated
8 since post-marketing estimates are assumed to be
9 underreported.
10 The anaphylaxis incidence rate was on the
11 higher end of the published range for drug-induced
12 anaphylaxis, although the actual number of cases was
13 low. As with the POME information, the continued post-
14 marketing reports of anaphylaxis that Dr. Chin reviewed
15 indicate that this event also continues to occur in
16 less controlled and ideal circumstances. Finally, the
17 combined clinical trial incidence rate, including both
18 POME and anaphylaxis, was 6.4 cases per 10,000
19 injections.
20 In conclusion, regardless of how it is
21 categorized, this can be a severe and life-threatening
22 event. The risk of POME or anaphylaxis should be

1 carefully weighed against the benefits for injectable
2 TU particularly since multiple alternatives both in the
3 same and other dose forms and regimens are already
4 available.
5 Thank you.
6 In the next presentation, Dr. Robottom will
7 discuss risk management considerations for TU. Risk
8 Management Considerations
9 DR. ROBOTTOM: Good morning. I am Suzanne
10 Robottom, and I'm a risk management analyst in the
11 Division of Risk Management in the Office of
12 Surveillance and Epidemiology. I have the distinct
13 honor of being the 13th and final presentation of the
14 morning. So lunch is on its way and hopefully that's
15 not the most important thing I just told you.
16 Once a risk of serious concern is identified
17 with a product, and in this case testosterone
18 undecanoate, we ask ourselves, can this risk be
19 mitigated to improve the risk-benefit profile? And if
20 so, how?
21 The following slides will provide a brief
22 overview of our process for evaluating that question

1 for testosterone undecanoate beginning with a brief
2 overview of FDA's authority with regard to risk
3 management. I will highlight some of the risk-benefit
4 considerations we have taken into account for TU,
5 provide comment on Endo's risk management plan, and
6 discuss some of the other risk management approaches
7 that FDA has identified.
8 The Food and Drug Administration Amendments
9 Act of 2007 authorizes the Food and Drug Administration
10 to require a Risk Evaluation and Mitigation Strategy,
11 or REMS, to ensure that the benefits of a drug product
12 outweigh its risks. A Risk Evaluation and Mitigation
13 Strategy, or REMS, is really just a risk management
14 plan that utilizes strategies beyond the product's
15 package insert to ensure that the benefits of the drug
16 outweigh the risks. It's designed to achieve specific
17 goals, to mitigate the serious risks associated with
18 the use of that drug product, and FDA has the authority
19 to require these types of programs before or after
20 approval.
21 The elements of a REMS may include a
22 medication guide or patient package insert which are

1 both directed at patients, a communication plan for
2 outreach to health care providers, and measures or
3 elements to safe use, or some sort of restricted
4 distribution program. It can also include an
5 implementation plan to address how those elements to
6 assure safe use are implemented. A REMS must also
7 include a timetable to assess the program.
8 The next few slides summarize some key
9 considerations FDA takes into account when assessing
10 the benefit-risk for a product.
11 Looking at the condition, as you've heard
12 earlier today, hypogonadism is a condition resulting
13 from insufficient endogenous secretion of testosterone.
14 Drug utilization data estimates that the use of
15 testosterone replacement products has been growing, and
16 given this condition and the growing product use, it's
17 appropriate to ask ourselves, what is an acceptable
18 treatment risk for this patient population?
19 Another consideration is the availability of
20 other treatment options. Currently, there are a
21 variety of testosterone replacement formulations
22 available in the U.S., and as we have discussed

1 earlier, there are approved and marketed intramuscular
2 injectable formulations available as well.
3 With regard to the benefit, the Food and Drug
4 Administration and Endo agree that testosterone
5 undecanoate replaces serum testosterone to the normal
6 range in adult men. Testosterone undecanoate has an
7 extended dosing interval resulting in fewer injections
8 per year compared to the approved intramuscular
9 injections.
10 From benefit, we turn to the risk of POME and
11 anaphylaxis. The clinical trial data indicate the
12 incidence of these adverse reactions is small but
13 consistent. Post-marketing experience in Europe
14 indicates that the events continue to occur, and the
15 magnitude of those risks under the real world
16 conditions remains unknown. These reactions can be
17 severe, requiring hospitalization as well as
18 resuscitation, and reactions can occur during or after
19 any dose with cases of reactions reported during the
20 first dose and after more than 4 years of treatment. To
21 date, no deaths have been reported. And as Dr. Chin
22 stated, the long-term cardiopulmonary consequences of

1 repeated POME events is unknown.

2 Given these characteristics, there is no way

3 to predict who will experience these post-injection

4 reactions or when. None of the risk management

5 approaches can prevent post-injection reactions with

6 the current formulation. Therefore, risk management is

7 limited to informing and minimizing serious sequelae.

8 We come back to the question, given these

9 considerations, how can severe post-injection reactions

10 associated with testosterone undecanoate be mitigated

11 to improve the risk-benefit profile?

12 Endo has proposed the following measures:

13 they have reduced the injection volume from 4

14 milliliters to 3; their proposed product label

15 recommends slow administration and to observe the

16 patient for 30 minutes post-injection. Endo plans to

17 ship testosterone undecanoate directly to prescribers,

18 and they have proposed a REMS, which includes a

19 communication plan consisting of a "Dear Health Care

20 Provider" letter. They have also proposed other

21 educational materials to both patients as well as

22 prescribers.

1 There are a few points that I would like to
2 make. The impact of reducing the injection volume is
3 unknown, and we note that many reactions occurred
4 during the injection. We agree that distributing
5 directly to prescribers for administration is
6 appropriate. However, reactions continue to occur in
7 Europe despite reports of proper injection technique,
8 including slow administration. With regard to
9 distribution of educational materials, we would like to
10 point out that there is little incentive for
11 prescribers to review materials that are not required
12 given the demands on their time and other competing
13 priorities.
14 Other risk management approaches that FDA has
15 considered include reformulation. If these reactions
16 are indeed due to the excipients, the most effective
17 mechanism to prevent these events is product
18 reformulation. However, this would require
19 testosterone undecanoate to be redeveloped beginning
20 with Phase I trials.
21 Moving forward with testosterone undecanoate
22 in its current form, additional risk mitigation

1 measures could include communication efforts similar to
2 or more robust than what you've heard earlier this
3 morning. Again, these materials are not useful if they
4 are not read, understood, and the recommended safe use
5 measures are implemented.
6 More restrictive measures can be used to
7 better ensure the safe use messages are received and
8 appropriate actions are implemented. This would
9 require certification of the pharmacy or distributors
10 to ensure only certified prescribers receive
11 testosterone undecanoate. To become certified,
12 prescribers would need to complete training before
13 ordering and administering testosterone undecanoate and
14 possibly enrolling the patient to document that the
15 risk was discussed before he receives treatment.
16 A program such as this one that I just
17 described requires significant resources to develop,
18 implement, participate in, maintain, and monitor.
19 Therefore, the burdens of a program like this one
20 creates particularly for prescribers, pharmacists, and
21 the health care system must be considered.
22 In summary, testosterone undecanoate is

1 associated with severe post-injection reactions. There
2 is no way to predict who will experience post-injection
3 reactions or when it will happen. None of the risk
4 management approaches can prevent the post-injection
5 reactions with the current formulation. Measures could
6 mitigate serious outcomes associated with event through
7 education and access to appropriate supportive measures
8 and treatment. However, requiring safe use
9 restrictions to attempt to ensure these measures are
10 implemented would pose substantial burden on
11 prescribers.
12 FDA is working to strike a balance
13 considering the benefits that TU offers, the
14 seriousness of the condition, the availability of other
15 treatment options, and the severity of the risk in
16 light of the burden these safe use measures can place
17 on health care providers and patients. The Agency is
18 very concerned that implementing any one of these
19 restrictive measures or some combination of them for TU
20 imposes excessive burden for the affected health care
21 providers for a drug with limited additional benefit.
22 Clarifying Questions to the Presenters

1 DR. JOHNSON: Thank you to the FDA for your
2 presentations. We will now proceed with clarifying
3 questions. These will go specifically to materials
4 presented by the FDA. We have approximately 45
5 minutes, so if time allows, we will return back to the
6 questions to the sponsor if that has time; if it does
7 not, we will readdress those in the afternoon. Remember
8 to raise your hands when you have questions that you
9 wish to bring forward.
10 I am going to take the prerogative again of
11 being able to ask a question to start.
12 Going back to 2009, similar to the question
13 that I asked of the sponsor, the Division gave remedial
14 actions, one of which was to identify which components
15 were causing the reaction and possibly to reformulate.
16 So does the FDA believe that the reformulation with a
17 decreased dosage meets that criteria? And I would
18 assume, just from what I've heard, perhaps not, but I
19 just want to hear that said.
20 The second is you were asked to identify men
21 for whom the additional risk could be acceptable
22 because they were particular candidates for this

1 medication. Do you feel that that issue has been
2 addressed? And again this comes from your 2009
3 recommendations to the sponsor.
4 Dr. Hirsch?
5 DR. HIRSCH: Yes. In response to the first
6 question, we agree with the sponsor's earlier response
7 to you for the same question, that they did consider
8 reformulating the product. However, the product is
9 fairly simple in its components, and reformulating
10 would change the product significantly, requiring
11 perhaps an entire new development program from Phase I
12 studies up. So that was a very difficult thing for them
13 to achieve. We do agree with them.
14 In regard to whether the 3 ml dose is less
15 dangerous or less problematic than a 4 ml dose, I don't
16 think there is data to inform that question, we don't.
17 We have no evidence that that is true.
18 In regard to the second question, the sponsor
19 did propose a target population that was fairly narrow;
20 for example, men in whom a child was in the house, but
21 the patient, the man himself, was unable to avoid
22 contact with the child under any circumstance or could

1 not in any way avoid that sort of contact or would not
2 follow the directions in the current package inserts
3 for those products, that was one of the populations.
4 Others were those who could not tolerate other forms of
5 drugs that are available, and we thought that this was
6 a very, very narrow group of patients that was not
7 really a clinically viable target population or
8 indication given the very finite numbers of patients
9 that we could think of in these categories.
10 DR. JOHNSON: Thank you.
11 Dr. Cooper.
12 DR. COOPER: My question is for Dr. Chin and
13 refers to Slide 23 in Dr. Chin's slide set.
14 Dr. Chin, I think that as we look at the data
15 and we try to bridge between the sponsor's
16 interpretation of the severity data and the FDA's
17 interpretation, we are struck with trying to sort of
18 figure out how we determine the safety profile based on
19 the severity. And so the sponsor presented, both from
20 the adjudicators and from clinicians who have cared for
21 patients with POME, a brief self-limited episode of
22 coughing lasting 3 to 4 minutes. In their data, they

1 present that 22 percent required a medical
2 intervention. When I look at this slide, you say that
3 84 of the 199 cases, which is 42 percent roughly, had
4 severe dyspnea, loss of consciousness, circulatory
5 collapse, et cetera. The only difference I can see
6 between your definition of severity and the sponsor's
7 definition of severity is that someone labeled it as a
8 severe adverse event or they considered it to be life-
9 threatening. Otherwise, if it required medical
10 intervention, hospitalization, or emergency department
11 care.
12 So of the 84 severe cases, can you tell us
13 how many of those had this constellation of symptoms or
14 any of these symptoms and how that fell out? Because
15 it's hard for us to know how to interpret that. Again,
16 we're thinking of 22 percent of a pretty rare event
17 versus 42 percent. So it's a small number, but I think
18 it's important for us to understand how you reached
19 this conclusion on this slide.
20 DR. CHIN: Stacy Chin, FDA. So all of these
21 84 cases met the severity grading criteria that I
22 outlined earlier, and the number of cases that required

1 medical intervention or hospitalization were as listed
2 by Dr. Hirsch and the applicant. The description
3 listed underneath were just examples. I'm not saying
4 all of these cases had those symptoms exactly. A lot
5 of them were categorized as medically serious, severe,
6 life- threatening, by the reporter, and that
7 constitutes the discrepancy, I believe, between our
8 assessment and applicant's.
9 DR. COOPER: Can you qualify "a lot" for us?
10 DR. CHIN: Just one moment. So out of the
11 POME cases that we identified as severe, I would say
12 that we had 76 that were identified as medically
13 serious or life- threatening by the reporter.
14 DR. HIRSCH: Our analysis of the cohort of
15 137 severe post-injection reactions, in our analysis,
16 we found that 60 patients, 44 percent, required or
17 underwent treatment of some sort. I believe the
18 sponsor has found a slightly lower percentage in their
19 analysis of the data. We found that 93 percent were
20 described as medically significant by the reporter, and
21 7 percent as life-threatening, and 23 percent were
22 either hospitalized or visited the emergency room.

1 I think overall, given the nature of
2 spontaneous adverse event reports and the quality that
3 we usually get, this is actually very good data
4 considering what we usually see in such reports. And I
5 believe it speaks to a certain percentage of severe
6 events among the 500 that we received, and the
7 percentage are those that we stated in our
8 presentation.
9 DR. JOHNSON: Dr. Orza?
10 DR. ORZA: I have three questions for
11 assorted FDA speakers. One relates to the ability to
12 identify and prevent the severe adverse events, and I
13 can understand why that would be true for the POME, but
14 one of the FDA speakers presented data to suggest that
15 in the case of anaphylaxis, you could do allergy
16 testing, and I was wondering if that was something that
17 was considered and something that could be factored
18 into a REMS.
19 And my second question went to the
20 indication, and I was wondering about what the
21 relationship was between hypogonadism, which is the
22 indication under discussion here, and low T, which is

1 the indication that we see advertised constantly on TV
2 and in other places.
3 And then lastly, I was really struck in going
4 through the background materials and listening to the
5 discussion that the sole efficacy criteria for all of
6 these drugs is a PK value, and I was wondering if FDA
7 was considering or discussing raising that bar at all
8 because it seems to me that there is a long space
9 between a PK value and the patient experience of
10 symptoms and symptom relief.
11 DR. DURMOWICZ: This is Tony Durmowicz, and I
12 will try to address the first part of your question
13 with regard to, quote, unquote, allergy testing. Years
14 ago, we discussed with the sponsor applicant with
15 regard to trying to delineate the cause of some of
16 these reactions, for anaphylaxis, if you will, how you
17 might go about doing those, and one way was to try to
18 do subsequent testing, skin testing, with reexposure,
19 and that's what that one patient that you saw that
20 potentially had a reaction maybe from the castor oil
21 was. He had gone into a study, got his exposure on a
22 graded way, and had a reaction with one-tenth the dose.

1 The intent was not and is not for them to develop their
2 own allergy test for Nebido or AVEED, to give it to
3 somebody before they get it. That's a very onerous
4 thing to do, and we have not required anybody to do
5 that. So I hope that addresses it. It's a difference
6 between skin testing to see what the mechanism and what
7 the reaction was due to of the three components versus
8 de novo development of an allergy test, which we're not
9 going to do.
10 DR. ORZA: No, I didn't mean that they would
11 have to develop it, but as onerous as it might be, is
12 that something that could be considered for a REMS, to
13 be able to move forward with it, that skin testing
14 could be an element of safe use?
15 DR. HIRSCH: Tony, we have a person from the
16 Division of Pulmonary, Allergy, and Rheumatology
17 Products that wishes to speak, I believe the Deputy
18 Director, to take the question.
19 MS. BHATT: Please state your name for the
20 record.
21 DR. LIMB: Hi. Susan Limb. I'm a clinical
22 team leader in the Division of Pulmonary, Allergy, and

1 Rheumatology Products. I'm also a practicing allergist
2 and a faculty member at Hopkins. So I do see patients,
3 and I think the idea that you're presenting is very
4 attractive, the idea that you could develop a skin test
5 and potentially screen patients. The issue is that
6 developing a skin test is actually quite difficult. It
7 would require the sponsor to develop validated test
8 reagents and then delineate the characteristics of the
9 test, so sensitivity, specificity, the predicted
10 values.
11 So if the company decided to undertake this
12 and they could actually develop a test, then I think
13 that's something that would be open for consideration,
14 but at this point, there is no such test. So while
15 it's an attractive idea, I don't think it's something
16 that's feasible at the moment.
17 DR. HIRSCH: I will take the second and third
18 questions, which are very similar questions. I believe
19 you asked whether the advertisements of men with low T
20 are the same as men with hypogonadism. In the context
21 of the approval of these products, I believe that is
22 true, but that relates to your second question, which

1 regards the efficacy endpoint of a PK parameter for
2 approval, and it is true the FDA does accept
3 pharmacokinetic efficacy as the prime efficacy endpoint
4 for TRT right now. But, yes, we have had over the
5 years and we continue to have discussions about what
6 other endpoints would be appropriate, would be better.
7 Right now, a patient, to enroll in one of
8 these trials, has to have a low T as well as some
9 symptom that is believed to be associated with that low
10 T, and we therefore accept the normalization of his T
11 as evidence of efficacy. But, yes, we have considered
12 and continue to consider very seriously other endpoints
13 or other designs.
14 DR. JOHNSON: Dr. Suarez-Almazor?
15 DR. SUAREZ-ALMAZOR: Yes, thank you. I am
16 struggling a little bit with the indication for this
17 agent and what the definition of hypogonadism and
18 testosterone deficiency might be. The FDA had a slide
19 that said that 30 percent of men have this disorder, if
20 we want to call it disorder. So that would mean that
21 basically 50 million men in the U.S. would have an
22 indication to receive this, which is a little scary.

1 So I was wondering if the prevalence
2 estimates really match the indication. And also I
3 didn't understand whether the indication that was
4 requested in 2009 changed now or it didn't. I'm not
5 completely clear about that, the population covered
6 there. And I would also like to know whether the
7 indication that has been approved in Europe is exactly
8 the same indication that is being requested here.
9 DR. HIRSCH: I think the numbers are a little
10 confusing because they may reflect low T versus men
11 with a symptom associated with a low T. So clearly the
12 number of men will be lower who are indicated because
13 they need to be symptomatic as a consequence of their
14 low T. So I think the 30 percent of men is a bit
15 exaggerated. I think the FDA wrote that 4 to 5 million
16 men are possibly a target population for this drug, not
17 50 million. I'm sorry.
18 DR. SUAREZ-ALMAZOR: But the indication does
19 not require symptomatic in any way that's clearly
20 defined; correct?
21 DR. HIRSCH: No, the indication is for
22 conditions associated with absence or deficiency of

1 endogenous testosterone. So one must have a condition
2 associated with that low T. That is the specific
3 indication itself. And in regard to whether the
4 indication has changed, no, it has not. The indication
5 is the same indication that it is for all approved
6 products. It has not changed during this development
7 program or for this sponsor in any way.
8 DR. SUAREZ-ALMAZOR: The European indication,
9 is it exactly the same wording?
10 DR. HIRSCH: We have it right here and we can
11 actually read it to you. It is simply, "Testosterone
12 replacement therapy in primary and secondary male
13 hypogonadism." That is the therapeutic indication for
14 Nebido.
15 DR. JOHNSON: Dr. Kittelson?
16 DR. KITTELSON: Yes. So I have a number of
17 questions that have already been raised, but in
18 particular, the life-threatening or hospitalized, why
19 would there be disagreement necessarily between sponsor
20 and FDA classifications of those? And could you just
21 elaborate on that? That's the first question.
22 And then the risk estimates from self-report

1 or from post-market -- well, other reports may be
2 difficult because of either numerator or denominator
3 problems, but do you have any other evidence from --
4 have you done any other kinds of epi studies that might
5 help inform who would be at greater risk? Do we know
6 anything about that or is it largely just a big
7 question mark at this point?
8 And then off-label use and transference have
9 been discussed quite a bit. First of all, do we know
10 the magnitude of the problem, and do we know anything
11 about whether or not this particular form, a long-
12 acting injectable, might help with that?
13 So those three things. What were the
14 criteria for specifically life-threatening that would
15 be different that caused FDA's analysis to be more
16 concerning? And then, second, is there any other epi
17 data from either the AERS database that would say,
18 well, different patient populations or different
19 products are at higher or lower risk for these adverse
20 events? And then off-label use.
21 DR. DURMOWICZ: Tony Durmowicz, I'll try to
22 attack the first part and then hand it off.

1 With regard to the severity and the reporting
2 of the adverse reactions with anaphylaxis and POME, for
3 a set of two adverse reactions, which there is some
4 overlap and for which it's difficult to discern
5 sometimes which is one and which is the other, and I
6 think that's why the FDA labeled them all as severe and
7 put them in a group, just to try to get things out of
8 the weeds, if you look at the case reviews or
9 adjudications between the sponsor's initial in-house
10 assessment, which was submitted at the NDA, the
11 sponsor's consultant analysis, and the FDA's analysis,
12 you come up with extremely similar numbers of
13 anaphylaxis and POME events. So it's not that their
14 numbers are that different. For instance, the FDA says
15 47 anaphylaxis cases, the consultant says 45. The
16 initial anaphylaxis assessment by the company in the
17 NDA said 79. So they're very similar, with the
18 company's being higher for their internal. POME is
19 very similar with those numbers in the 200 range.
20 The issue -- and I think this is what you're
21 asking -- is the interpretation of those. Now, we
22 agree actually and have no question at all with the

1 company's data that says this many percent of patients
2 got treated with epinephrine, this many got treated
3 with this, this many got treated with this. Our
4 definitions of severity, if you look at those NIAID
5 criteria for anaphylaxis, regarding anaphylaxis
6 severity, it was pointed out earlier that anaphylaxis
7 can be not severe, it can be mild, and if you look at
8 the criteria there, we would contest that statement by
9 saying that any anaphylaxis case that met that
10 criteria, Criteria 1, would automatically be considered
11 by any normal person as severe. The less severe cases
12 of anaphylaxis I think would fall into a different kind
13 of category, at least for us, which would be more like
14 immediate hypersensitivity reaction, which might be
15 just urticaria by itself.
16 With regard to POME, again there is no
17 question with regard to questioning the company's data
18 because they're very similar to what we came up with,
19 but it's the reporting mechanism in these post-
20 marketing cases that the Pulmonary Division looked at,
21 and if -- and Dr. Cooper I think brought that up
22 earlier, and Dr. Chin tried to answer -- if the

1 reporter or the investigator, whoever it was, said that
2 this was medically important, this was severe, this was
3 life-threatening, this was whatever, we put it in that
4 severity category. We didn't just go by whether it was
5 treated with epinephrine or whether it was treated with
6 antihistamines. So if you look at our composite
7 definition of severity, that is probably different than
8 the definition of severity for the POME cases that the
9 company is using, and that's probably the discrepancy.
10 But the total numbers of what we call anaphylaxis and
11 what we call POME, for a strange reaction that is from
12 post-marketing reports is remarkably similar.
13 DR. KITTELSON: And so life-threatening in
14 particular, that was because it's mentioned in the case
15 report? Is that how FDA came up with that
16 classification?
17 DR. DURMOWICZ: Yes. FDA wouldn't
18 necessarily put life-threatening in there by itself. We
19 don't do that. But it would say it in the report or it
20 would say in the report "medically important" or
21 "severe."
22 DR. KITTELSON: And so the sponsor has the

1 same classification then. I mean, there is no real
2 disagreement on that one; it's in the case report.
3 DR. DURMOWICZ: I'm not sure I caught what
4 you were saying.
5 DR. KITTELSON: So I guess I didn't pick up
6 as much on life-threatening events in the sponsor's
7 presentation, we would have to go and find them, but
8 they do highlight, they are highlighted here. And so
9 I'm just wondering if there really is any sort of
10 discrepancy or it's just a difference in reporting, on
11 interpretation of the same data.
12 DR. DURMOWICZ: I think I tried to mention
13 that I think it's just a difference in interpretation,
14 almost the exact same data and different conclusions
15 based on it that would inform a different risk-benefit
16 ratio. I think the Division of Epidemiology needs to
17 answer a question?
18 DR. KITTELSON: So I had a question about,
19 the risk is hard to measure, but are there any sort of
20 case control -- any sort of evidence that either
21 differed by product perhaps in the AERS database?
22 Anything that there was a difference in products or a

1 difference in people that were at risk for adverse
2 events?
3 DR. OUELLET-HELLSTROM: Well, the AERS
4 database. The only data that we have in the AERS
5 database, it's for the other testosterone products, and
6 they were approved a long time ago. There is just a
7 handful. Dr. Chin I think reviewed some. She can
8 speak to that. But there is no sales data, whatever,
9 where we could use to calculate reporting rates or
10 incidence rates with those older products.
11 DR. JOHNSON: Dr. Ownby.
12 DR. OWNBY: One of the difficulties I think
13 all of us have had with this is the overlap between the
14 symptoms of POME and anaphylaxis, and one of the
15 questions I have -- I'm not enough of a medicinal
16 chemist, but remembering the old days where paraldehyde
17 was used regularly to treat seizures, and you would
18 detect the odor of the drug on the patient's breath
19 within a minute or two of its administration. Are
20 there any volatile oils contained within the complex
21 organic mixture of castor oil that could be volatilized
22 and come out through the lungs quickly after an

1 inadvertent access to the vascular system?
2 DR. DURMOWICZ: I'm just going to take a wing
3 at this. I don't believe there are, but I think some
4 of the adverse event reports have stated that they had
5 a taste in their mouth, but whether that's due to a
6 volatile oil or something is completely
7 unsubstantiated.
8 DR. OWNBY: I think the importance would be
9 if it was a volatile compound, then it would be
10 relatively -- well, I say relatively easy, at least
11 it's potentially measurable and could be traced and
12 might provide a mechanism for what's going on with
13 these and help sort these out.
14 DR. JOHNSON: Dr. Swenson.
15 DR. SWENSON: Yes. We've been hearing
16 varying rates of POME both from the FDA and Endo, and
17 then there was data given potentially relating older IM
18 preparations of testosterone with side effects. The
19 question I wanted to ask was -- and I can't recall who
20 gave these data, but the look-back on older
21 preparations and the rate of side effects, obviously
22 going back into the 1960s -- was that data of the non-

1 undecanoate preparations also looked at in the same
2 time interval as the present application here, that is,
3 in the last decade? And could we be seeing differences
4 in just why things are being reported and maybe the
5 incidence really isn't much lower because the data
6 suggests that other preparations have a lower reported
7 side effect rate?
8 DR. HIRSCH: Yes. We hesitated to put up
9 comparisons because they're sort of hazardous in that
10 you are correct, many of the POME and anaphylaxis
11 reports that were a total of 33 that we identified in
12 the AERS database, but they were older and our use
13 information was more current. So there is no way to
14 really even provide a crude reporting rate for those.
15 We looked at testosterone cypionate and testosterone
16 enanthate, the two approved non-undecanoate injectables
17 right now, but yet we thought you should at least see
18 what there is in AERS, that that was something you
19 would want to know, and what we found was after
20 adjudication, the way we adjudicated the same
21 testosterone undecanoate cases, we found 33 severe
22 post-injection reactions over a total course of 44

1 years that we used to search AERS. I would ask the
2 epidemiologist -- perhaps Rita would have a comment
3 about this in regard to analysis of such data.
4 DR. OUELLET-HELLSTROM: The reporting rules
5 differ based on how long a product has been on the
6 market. So to compare the older products with the
7 newer products is unfair and has some problems, but to
8 compare the reporting of an older product today with a
9 newer product on the market today is also problematic
10 because with the newer product the providers or
11 prescribers are more likely to report a problem than
12 with the older product saying maybe that everybody
13 knows about this, so there is no point in reporting it.
14 So that is why Dr. Kornegay presented and emphasized
15 that incidence rates, especially coming in from the
16 post-marketing setting where you have a numerator and a
17 denominator is much more informative than to try to
18 compare reporting from one product to another,
19 especially when there are differences over time. Does
20 that answer your question?
21 DR. SWENSON: Well, I guess so. I'm getting
22 the drift that this is possibly just an insurmountable

1 difficulty in comparing. But did you specifically look
2 just at what was being reported in the last decade of
3 all the non-undecanoate preparations?
4 DR. OUELLET-HELLSTROM: We didn't. We did
5 not focus on that, on just the last decade.
6 DR. SWENSON: Because that would at least be
7 the same time period, the same mindset, around that
8 issue of side effects and whether that could be
9 exploratory in any way.
10 DR. OUELLET-HELLSTROM: I think Dr. Chin
11 looked at those reports.
12 DR. HIRSCH: Actually, most of the POME and
13 anaphylaxis reactions for the other products were older
14 and not within the recent timeframe that you are
15 describing, to be direct. We didn't do a specific
16 analysis of that, but most are not from the last 10
17 years. Dr. Chin looked at all of them that we did
18 find.
19 DR. CHIN: I'm sorry, I don't have the exact
20 spreadsheet in front of me with the breakdown of all
21 the dates, but most of them were, as they said, from
22 more than 10 years ago.

1 DR. JOHNSON: Dr. Nelson?

2 DR. NELSON: Thank you. So I have a question
3 I believe for Dr. Robottom, but maybe it's also a
4 little bit more generic, and the first part of this
5 question may not directly be addressed to you, but is
6 there any data -- and I was going to ask the sponsor,
7 but I'll ask you as well -- that would suggest that
8 this slower rate of administration would actually make
9 a difference? You know, I could foresee if we believe
10 that the problem is intravascular administration. It
11 wouldn't seem to me that if you put the needle into the
12 vein and inject it more slowly, it's going to be any
13 different than if you inject it more rapidly. So I'm
14 not really sure I understand how in the REMS or in the
15 suggestions for safe use that simple change is going to
16 make a big difference.

17 And then I guess what I really was directing
18 at Dr. Robottom was the -- you know, we've been talking
19 about these med guides and patient packaging
20 information and other things for years, and I wonder if
21 there is actually data to say that this works because
22 Dr. Erstad asked the question about how it would be

1 worded, and I know you probably can't answer that until
2 the discussions occur post-approval or something, but
3 it would seem to me that, from what I've read and what
4 I know about these patient inserts, package inserts,
5 they're probably not very effective.
6 And the corollary to that is the doctor
7 information. You know, you provided a potential REMS
8 solution that was much more extreme than the sponsors
9 wanted, but maybe there is something in the middle. You
10 know, part of the REMS that you had proposed -- or I'm
11 not sure if you were proposing, but you were modeling
12 it -- would both include this more restricted
13 distribution network, which would probably solve the
14 abuse problem but wouldn't necessarily be directed at
15 the core administration practices, which they were
16 attempting to address with the "Dear Doctor" letter
17 perhaps or a video that wasn't mandatory. Is there a
18 certification process that's much more limited rather
19 than a whole big formal certification process that
20 could be directed at administering it correctly,
21 assuming that we think that that slow administration is
22 going to actually make a difference? Remember, we

1 didn't talk about needle size, type of needles. There
2 are a lot of other things that might affect this as
3 well. So is that too complicated a question?
4 DR. ROBOTTOM: I think I can at least start,
5 and Dr. Chin may want to respond, too, as well with the
6 slow administration, but my understanding is with slow
7 administration that it could affect POME, but it would
8 have no effect on anaphylaxis.
9 DR. NELSON: Right, that I agree with, but
10 how would it actually affect the embolization of the
11 oil? Because it's not clear to me that would matter. I
12 mean, if I put an IV in my hand, just to use the
13 analogy, and I gave it slowly versus quickly, I don't
14 see that that would make a difference.
15 DR. DURMOWICZ: I'm just going to again wing
16 this one, if you will. But if you look at other
17 testosterone products, depo products -- I'm looking at
18 testosterone enanthate's label right now, it also
19 mentions slow deep muscular injection. My feeling is
20 that first we're going to assume that it's not an
21 intravascular injection -- okay? -- we're going to
22 assume that it's given the right way, that the

1 pressure, subcutaneous intramuscular pressure, if you
2 will, generated by a rapid injection would be more
3 likely to cause the drug to go into either the lymph
4 system and therefore the venous system, something along
5 those lines, and that's the reason why there is the
6 precaution to do it slowly. Now, whether that really
7 ameliorates the problem, I don't know, but I think
8 that's the theory behind it, as I understand things in
9 my own little way of thinking.
10 DR. NELSON: Although that's not really the
11 way it was built, you know, I think somebody at one
12 point suggested it's intravenous injection. I don't
13 remember who said that. Maybe I just heard that.
14 DR. DURMOWICZ: No, I think that for the vast
15 majority, if not all, of the cases that we presented, I
16 think we're assuming that it was an intramuscular
17 injection, not an intravenous injection.
18 DR. NELSON: Oh, I'm sorry. I know it was
19 intramuscular, but when you put it in the muscle, you
20 know, you're supposed to draw back --
21 DR. DURMOWICZ: Right.
22 DR. NELSON: -- and we know that's not

1 necessarily preventive of giving an intravascular
2 injection. When you're injecting it, you know, there
3 is a lot of vasculature in there, so you might be very
4 well right, and by giving it more slowly, it would -- I
5 don't know if there is data to actually support that.
6 DR. DURMOWICZ: I don't know if there is data
7 to support it, but I'm just reiterating the theory by
8 which I think that it could potentially be helpful.
9 DR. ROBOTTOM: I believe you had a second
10 part to your question with regard to certification of
11 health care providers, and I think the important thing
12 to remember with risk management is we would love to
13 have our cake and eat it, too, but if we want them to
14 be certified and we don't want the drug shipped to
15 anyone other than someone that's certified, then you
16 have to involve either the pharmacies or the
17 distributors because somebody needs to be checking that
18 that health care provider has that certification in
19 place, and without having that aspect, you don't have a
20 gatekeeper. Otherwise, you have really like a glorified
21 communication plan where the information is out there
22 and health care providers are more than welcome to

1 review it and implement it, but there is really no
2 check as to whether or not they've done so before
3 they're providing it to patients.
4 In the slide that I had in my presentation, I
5 also mentioned about patient enrollment. I think the
6 point there would be whether or not that part would be
7 necessary to enroll patients, but if there is a
8 concern, I think one of the other Committee members
9 raised it early about making sure that the patient
10 understood what the risks were in comparison to his
11 other treatment options, then you would want to
12 consider that as well.
13 So in order to really make a closed system,
14 you really have to have all the parts working together
15 so that it is closed. Does that make sense?
16 DR. JOHNSON: Dr. Cavazzoni?
17 DR. CAVAZZONI: I have a question that
18 actually follows on Dr. Swenson's. Obviously, one of
19 the major challenges in understanding these data is the
20 lack of comparative data that could provide context to
21 what we see, not only clinical trials, but even more
22 importantly in the post-marketing period. So

1 understanding the chronological difficulties with
2 regard to spontaneous reporting, I have two questions.
3 The first one is about AERS per se. So understanding
4 that the majority of the cases may have occurred before
5 2009, did you have an opportunity to look at the total
6 number of cases reported for the injectable
7 testosterones and to see whether there are any major
8 changes, differences in orders of magnitude, the number
9 of cases of interest reported?
10 And then probably a question for Dr. Kornegay
11 is really about opportunities to better characterize
12 incidence rates for other injectable testosterones and
13 potentially for other injectables that contained castor
14 oil or benzyl benzoate using longitudinal databases.
15 So, for instance, by querying Mini-Sentinel, as we have
16 heard, the sponsor has done at least in a preliminary
17 fashion using the GE electronic health records.
18 DR. KORNEGAY: My apologies. Could I ask you
19 to repeat the first question that you had?
20 DR. CAVAZZONI: So the first question was
21 probably more for Dr. Hirsch and really spoke to the 33
22 cases that have been identified in AERS. And we heard

1 earlier that obviously these cases where, the majority
2 of these cases where, reported prior to the past 10
3 years, if we looked at the more recent cases that might
4 coincide with the time span of reporting for the
5 undecanoate cases, do we see any major differences in
6 the total number of reports in AERS? And I'm really
7 talking about proportionate reporting and not,
8 obviously, with the understanding, obviously, that
9 we're talking about different chronologies, are there
10 any major orders of magnitude that would help us
11 understand why there are so few cases for the other
12 injectable testosterones?
13 DR. HIRSCH: I think you are faced with the
14 same difficulty that we are here at FDA, that there are
15 few, if any, of these cases reported for the other
16 injectable testosterones in the recent past, and that's
17 what we have in AERS. How to make sense of that is not
18 -- I don't think it's possible to draw clear
19 comparisons based upon what we have in front of us, and
20 our epidemiologist can expound on that.
21 DR. OUELLET-HELLSTROM: I think Dr. Hirsch
22 mentioned basically that's our dilemma, is we don't

1 have the information on other products, especially a
2 denominator, to even come close to being able to
3 compare what that would be. The only information was
4 presented by the sponsor this morning, and we have had
5 no opportunity to look into that and evaluate the
6 information that was presented.
7 DR. CAVAZZONI: You know, my question may be
8 more simply articulated, is there overall less
9 reporting for the older drugs?
10 DR. OUELLET-HELLSTROM: There is always less
11 reporting with an older product.
12 DR. CAVAZZONI: Okay.
13 DR. OUELLET-HELLSTROM: Almost nothing.
14 DR. KORNEGAY: And to address your second
15 question, if I understood it correctly, you were asking
16 about the possibility of studying POME and/or
17 anaphylaxis in existing epidemiological and claims
18 databases?
19 DR. CAVAZZONI: So my question was more
20 specific, really did not point to a formal
21 epidemiological study, but more whether there is any
22 data from longitudinal databases that could be obtained

1 through a relatively simple query potentially if we're
2 talking about claims databases more for anaphylaxis
3 that might give us a context for the incident rates
4 that are seen with the undecanoate.
5 DR. KORNEGAY: There is very likely data that
6 is in medical record and other databases. The
7 simplicity of obtaining it, on the other hand, is
8 probably what would drive any type of investigation. I
9 am not aware of any studies to date that have looked at
10 the specific type of association. I do know that some
11 of the hurdles or some of the challenges that would
12 have to be met would be defining POME in such a way
13 that it would be detected or that we would be able to
14 detect it and validate it well in these databases, and
15 given that this seems to be a fairly rare occurrence
16 and in a specific setting with injectable drugs, we
17 would also have to figure out how to determine how to
18 associate the specific visit with the drug with the
19 specific reaction.
20 An additional difficulty would happen if, for
21 example, the drug was administered in a doctor's office
22 but the reaction brought the person to an emergency

1 room after they had left the doctor's office or from
2 the doctor's office. Many of the databases, including
3 Mini- Sentinel, have limitations when crossing settings
4 of care. So I think that it could be gotten, but it
5 probably would not be a simple or easy task.
6 DR. JOHNSON: Dr. Woods?
7 DR. WOODS: Thanks. I would like to go back
8 to something that Dr. Bockman started and then Dr.
9 Morrato followed up on, but the distribution network.
10 In many market places, physicians' offices are becoming
11 less and less interested in taking on administering
12 drugs like this and really referring patients to
13 hospital-based infusion centers or infusion centers
14 that are adjacent to their offices. And as I
15 understand the system as it was proposed by the
16 sponsors, that it would only be available through
17 physicians' offices.
18 As I look at Dr. Robottom's Slide 15, it
19 looks like maybe FDA had a little bit different idea or
20 at least some way that pharmacies associated with
21 infusion centers or hospitals or health systems maybe
22 had a little different idea. Is FDA thinking that

1 there might be accommodation for a little bit wider
2 distribution network to accommodate infusion centers so
3 it minimizes the need for the patient to have to go to
4 the physician's office, then brown-bag the drug into
5 the infusion center, which then raises a whole level of
6 issues around integrity in the supply chain?
7 DR. ROBOTTOM: This is Suzanne Robottom. I'm
8 from the Division of Risk Management with FDA. I think
9 the first thing I would like to point out is that for
10 this slide, this was really just to illustrate what
11 some type of restricted distribution program would look
12 like. It was not what we were recommending would need
13 to be done for this product. But I think what you
14 bring up is whether or not it should be available for
15 infusion centers and that sort of thing. If it was a
16 health care setting that was appropriate, we would
17 design a REMS to ensure that the drug was able to be
18 administered in that type of setting. There are always
19 challenges with who is giving it, especially if one
20 physician is ordering it and then the patient has to go
21 to an infusion center to actually get the drug
22 administered. There are always going to be those sorts

1 of challenges, so we would have to work through those
2 if we were going down that road.
3 DR. WOODS: Well, that then sets up the issue
4 of if I have a patient who comes to the infusion
5 center, how do I know they're in the program?
6 DR. ROBOTTOM: Right.
7 DR. JOHNSON: I would like to ask the
8 Committee if it's acceptable, we have two more
9 questions for the FDA, even if we run a little bit
10 after 12:15, is that acceptable?
11 (No audible response.)
12 DR. JOHNSON: Dr. Morrato?
13 DR. MORRATO: So I had the same question as
14 Dr. Nelson, so mine is going to be looking at the other
15 point in product labeling around, is it theory based or
16 evidence based? And I'm wondering if the FDA has been
17 presented any information or in their case review to
18 say, what proportion of the cases occurred within 30
19 minutes such that if you could have observation for 30
20 minutes, that that would be a meaningful mitigation
21 strategy?
22 DR. HIRSCH: Yes. Of the 137 severe post-

1 injection reactions, well, we have 1 hour, we do not
2 have a 30-minute breakout in our information, we have 1
3 hour, and 1 hour would include 78 percent of all cases
4 that we captured in our cohort. During injection or
5 immediately thereafter is approximately 69 percent of
6 cases. So I would assume that 30 minutes is somewhere
7 around 70, 75 percent.
8 DR. MORRATO: Okay, so the majority but not
9 necessarily all, which is the point around they might
10 present in other places. Okay.
11 And then the other, earlier I had asked the
12 sponsor, you know, it gets back to the question of the
13 distribution site, et cetera, and what are the
14 practices and norms that are at those sites and
15 familiarity of injections, et cetera, and having
16 systems set up. And during the break I did a quick lit
17 search and found on FDA's site for briefing information
18 -- this was for the 2009 briefing material for AndroGel
19 as part of their Best Pharmaceuticals for Children's
20 Act Drug Use Review, and I want to see if I use this
21 number as a good approximation or if you, in your other
22 drug use review, have more relevant information to

1 injectables. But that data, if I look at the 2007
2 prescribing data, again I believe it was coming from
3 IMS Health, and the data for AndroGel -- and gels are
4 the most common form, and AndroGel is the market leader
5 -- 33 percent were prescribed by GP/FPs and doctors of
6 osteopathy, 27 percent by internal medicine physicians,
7 16 percent urologists, and 10 percent endocrinologists.
8 So that would say about 60 percent are being prescribed
9 in a more primary care setting, not in a specialist's
10 setting. Do you think that's a good estimation for
11 when we start to deliberate and think about the
12 distribution plans?
13 DR. GREENE: This is Patty Greene. I'm a
14 drug use analyst for FDA. And basically according to
15 office physician survey data, when we look at
16 injectable testosterone products, they were most
17 commonly mentioned with general practice and internal
18 medicine, and that was at about 58 percent.
19 DR. MORRATO: All right. Very small.
20 DR. GREENE: So it's very similar to the
21 gels. And basically with urology, urology was about 26
22 percent of that number.

1 DR. MORRATO: Okay. So maybe a little
2 higher. All right.
3 DR. GREENE: All right?
4 DR. MORRATO: Very good. Thank you.
5 DR. JOHNSON: Dr. Orza.
6 DR. ORZA: So we've been asked to focus in on
7 anaphylaxis and POME because that's the only respect in
8 which the safety profile for this form of testosterone
9 is appreciably different, and I just wanted to confirm
10 that the side effect profile is otherwise similar
11 because I also heard some things about some of the
12 really important side effects, like prostate cancer,
13 are just poorly understood. So is it the case that any
14 impact like that of this drug is also poorly
15 understood?
16 DR. HIRSCH: The list of adverse reactions
17 are qualitatively the same as what we see for AndroGel,
18 for any testosterone replacement therapy that's been
19 approved in the last 10 years, so there is nothing
20 qualitatively different. And the incidence rates are
21 reasonable.
22 In regard to prostate cancer, in all of the

1 NDAs of testosterone replacement therapy there are
2 usually a small number of patients who develop -- who
3 are reported to have prostate cancer diagnosed during
4 the trial or during the development program. How to
5 interpret those is very difficult given the small
6 number of patients studied and the small number of
7 events, and to compare this drug to any other drug for
8 that would be not possible, although I've heard
9 discussion of theoretical differences, but that's
10 really all they would be, given the data that's
11 available, which is very small in number.
12 DR. JOHNSON: Well, I would like to sincerely
13 thank FDA for your excellent presentations and
14 answering of our questions, and also again to the
15 sponsors for providing excellent information and
16 answering our questions. We will have the opportunity
17 after the open public hearing to be able to address
18 more questions. We'll start off with the sponsor and
19 finish those questions and then we can return to FDA if
20 needed.
21 Now it is time for us to break for lunch.
22 We'll reconvene again in about 40 minutes, at 1:00. Do

1 take any personal belongings with you.
2 For Committee members, please remember that
3 there is to be no discussion of the meeting during
4 lunch amongst yourselves, the press, or any member of
5 the audience. Lunch for the Committees will be at the
6 kiosk. You can go back behind the back of it if you
7 would like; that's a little shorter wait time. And
8 then come up to Room 1506. See you in a moment.
9 (Whereupon, a lunch break was taken.) Open
10 Public Hearing
11 DR. JOHNSON: So I would like to welcome
12 everyone back. As we start with the open public
13 hearings, I would like to say that both the FDA and the
14 public do believe in a transparent process for
15 information-gathering and for decision-making. To
16 ensure such transparency, at the beginning of the open
17 public hearing session to the advisory committee, the
18 FDA believes it's important to understand the context
19 of an individual's presentation.
20 For this purpose, the FDA encourages you, the
21 open public speakers, to begin your written or oral
22 statement with advice to the committee regarding any

1 financial relationship you may have with the sponsor,
2 its products, or, if known, its direct competitors. For
3 example, this financial information may include the
4 sponsor's payment for your travel, lodging, or other
5 expenses in connection with your attendance at the
6 meeting.
7 Likewise, the FDA encourages you to begin
8 your statement on the advice to the committee if you do
9 not have any such financial relationships. If you do
10 not wish to address this issue on financial
11 relationships at the beginning of your statement, it
12 will not preclude you from speaking.
13 The FDA, and this committee, place great
14 importance on the open public hearing process. The
15 insights and comments provided can help the agency and
16 this committee in their consideration of the issues
17 before them. This said, in many instances and for many
18 topics, there are a variety of opinions. Our goal
19 today with this open public hearing is that it be
20 conducted in a fair manner that allows each participant
21 to speak clearly and openly and to be treated with
22 dignity, courtesy, and respect.

1 One issue I would say, that please remember
2 to wait to be speaking until recognized by the Chair.
3 We do thank you for your cooperation.
4 Will Speaker Number 1 kindly step up to the
5 podium and introduce yourself? Please state your name
6 and any organization you represent for the record.
7 Thank you.
8 MR. BOLLHORST: My name is Donald Bollhorst.
9 I have no financial disclosure to share. As stated, my
10 name is Donald Bollhorst of Baltimore, Maryland. While
11 participating in the Endo Pharmaceuticals study for
12 AVEED, I was a part of an education -- Health (sic)
13 Body Healthy Mind DVD called Treating Hypogenism (sic).
14 This DVD was done by Adrian Dobs' office at Johns
15 Hopkins Medicine Clinical Trials Unit in conjunction
16 with Endo Pharmaceuticals.
17 After my wife died 11 years ago, I noticed
18 that in addition to depression, I was experiencing
19 fatigue and a poor energy level and a low sex drive.
20 After a series of blood tests, my urologist, Dr.
21 Breschi, diagnosed that I had a low testosterone level,
22 and over the next two years, prescribed for me a number

1 of different therapies, including packs of clear
2 testosterone gel that was applied once a day to my
3 shoulders and arms.
4 AndroGel and a skin patch called Androderm
5 were applied once a day. Both the gels and patches
6 were difficult to apply to my body each day and also
7 were not every effective. I also felt uncomfortable
8 with the gels and patches while working my part-time
9 jobs, because I was fearful of any odors from the gels
10 and patches while attending to my clients' needs and
11 conversation.
12 Each year, I take at least three or four
13 vacations with my female partner and my children. Also,
14 I take large travel groups on cruises and a week's
15 vacation to the Caribbean Islands for beach vacations.
16 When I was using these gels and patches, I felt
17 extremely uncomfortable when family and friends asked
18 me about the patches and gels that I used on my
19 shoulders and arms.
20 Naturally, I was embarrassed when questioned
21 about wearing the patches and gels. Therefore, I was
22 reluctant to tell my family and friends why I was using

1 the patches and gels for testosterone purposes. After
2 seven years, I started to participate -- about seven
3 years ago, I started to participate in testosterone
4 therapy trials at Johns Hopkins Clinical Trials Unit
5 School of Medicine with Dr. Adrian Dobs. One of these
6 trials was for a test-run injection called AVEED, which
7 was given to me once every 90 days by the Hopkins Trial
8 Unit.
9 The injection was absorbed in my bloodstream
10 quickly, and I noticed an increase very soon in my
11 energy level and libido. Compared to all the other
12 testosterone therapies I had tried during my time at
13 Hopkins as well as the many gels I had used in previous
14 years with my urologist, AVEED gave me a greater sense
15 of well-being in my daily moods, which of course became
16 a huge relationship plus with my female partner.
17 In closing, I would like to say that you
18 consider your decision today, I hope you remember my
19 story, the difference a testosterone therapy like AVEED
20 can make. I now have a broader outlook on life, thanks
21 to this testosterone therapy, and the energy and
22 feelings of a man younger than my true age, which

1 allows me to have a part-time job with a large travel
2 agency that I truly enjoy and a rich relationship with
3 my female partner and my children.
4 Thank you for this opportunity to express my
5 experiences.
6 DR. JOHNSON: Thank you very much. Now we're
7 going to move on to Speaker Number 3.
8 MR. SCHWARTZ: Stefan Schwartz. I have no
9 financial disclosures to share. Good afternoon. Again,
10 my name is Stefan Schwartz, and I have Klinefelter
11 syndrome. Klinefelter syndrome is a genetic condition
12 that occurs in 1 in 500 males. There is no cure for
13 Klinefelter syndrome, and testosterone therapy is our
14 best and most effective option.
15 Testosterone therapy is a necessity for those
16 living with Klinefelter syndrome, because it replaces
17 what we are unable to produce naturally. It greatly
18 assists those who are born with this condition to live
19 with its effects.
20 I was diagnosed with Klinefelter syndrome in
21 1996 at the age of 26. Shortly after my diagnosis, I
22 developed and published a website to assist with

1 education and support for those with this condition.
2 The website still exists today, and it can be found at
3 klinefeltersyndrome -- it's all one word. It's K-L-I-
4 N-E-F-E-L-T-E-R syndrome.org.
5 I immediately began on testosterone therapy
6 after my diagnosis occurred, initially using a patch
7 called Androderm, which was not a viable option for me.
8 I then switched to testosterone injections, which I
9 administered myself. I have been self-injecting
10 testosterone by intramuscular injection every 11 days
11 for the past 17 years. That works out to roughly 33
12 injections per year, or 561 injections over 17 years.
13 This number of injections builds up extensive
14 scar tissue. AVEED would significantly decrease that
15 number. I am familiar with AVEED, as there is a
16 product on the market in Europe, Latin America, Asia,
17 Australia, and parts of Africa called Nebido. Nebido
18 has been available outside of the United States for a
19 number of years and works quite well, according to the
20 patients I've been in touch with throughout the world.
21 AVEED is a much better option, in receiving 5
22 injections per year versus 33. As I mentioned earlier,

1 I've been injecting every 11 days. It took time to
2 determine the exact frequency for which I should
3 receive my injection. Those who have this condition
4 are unique, with a unique set of symptoms and to
5 different degrees. We are square pegs for round holes
6 and sometimes need to adjust the frequency for our
7 injections.
8 Those of us who have been on testosterone
9 therapy for many years know what we need to combat the
10 symptoms of low testosterone. Again, this is our
11 hormone replacement therapy. We are not taking this
12 therapy to bulk up or for any other reason other than
13 the necessity to have a normalized testosterone level.
14 My current form of testosterone therapy,
15 testosterone cypionate, significantly improves my
16 quality of life, helps to increase my low libido
17 levels, greatly improves fatigue, increases focus and
18 concentration, and helps to keep my bone density at a
19 normal level. I'm a different person, much better able
20 to handle my life since my diagnosis and since starting
21 on testosterone therapy back in 1996.
22 The only negative about my current form of

1 testosterone therapy are the peaks and values -- the
2 peaks and valleys one has to deal with during the
3 injection cycle. In the beginning, just after the
4 injection, you experience a high, almost a euphoric
5 feeling. During the 11-day cycle, the testosterone in
6 your body decreases, and around the 11th day, I feel
7 the need and that my testosterone level is low and
8 sometimes lower than the normal range.
9 I suspect through my extensive research that
10 with AVEED, after your first few injections, that the
11 peaks and valleys will no longer be an issue. I'm sure
12 for some people who have been on testosterone
13 enanthate, cypionate Delatestryl, and other short-term
14 injectables, there'll be a period of time where we may
15 feel like there are still valleys when we are awaiting
16 our next injection. I suspect over time, those valleys
17 will simply disappear.
18 I hope you will give serious consideration to
19 approving AVEED for use by those needing testosterone
20 replacement here in the United States. This product
21 will be extremely beneficial, as has been proven with
22 Nebido outside of the United States. When approved, I

1 will be one of the first in line to give it a try, as I
2 truly believe this medication will be extremely
3 beneficial for the Klinefelter community as well as
4 anyone who suffers from hypogonadism.
5 Thank you so much for your time and allowing
6 me to present my views on this extremely important
7 subject.
8 DR. JOHNSON: Thank you very much. Speaker
9 Number 4?
10 DR. TAMLER: Good afternoon. I'm Dr. Ronald
11 Tamler. I have slides -- fabulous. The slides are
12 coming up. I'm the Clinical Director of the Mount
13 Sinai Diabetes Center. I'm an Associate Professor of
14 Medicine at the Icahn School of Medicine at Mount
15 Sinai, and today I'm speaking on behalf of the American
16 Association of Clinical Endocrinologists, AACE. I do
17 not have any financial conflicts to disclose today.
18 A little bit about AACE: AACE is the world's
19 largest organization of clinical endocrinologists, and
20 our mission statement is that we are a professional
21 community of physicians specializing in endocrinology,
22 diabetes, and metabolism committed to enhancing the

1 ability of its members to provide the highest quality
2 of petition care, and that's what today is all about.
3 A little bit about male hypogonadism, as you
4 are probably aware, the prevalence depends on how you
5 define hypogonadism and what population you study. It's
6 strongly affected by age and by comorbidities over
7 time. Once men reach the age of 40s, testosterone tends
8 to decline, and certain comorbidities, especially
9 diabetes and obesity, are very strongly associated with
10 male hypogonadism. In one study, obese men with type 2
11 diabetes were found to have greater than 50 percent
12 prevalence of male hypogonadism.
13 We all know about the physiology of
14 testosterone. It acts on the androgen receptor to
15 influence, among others, bone health, erythrocyte
16 production, and lean-to-fat body mass, but also mood,
17 libido, erectile function.
18 Signs and symptoms of hypogonadism may
19 include, therefore, low libido, erectile dysfunction,
20 hot flashes. It's also found frequently in patients
21 using chronic opioid or glucocorticoid treatment, and
22 it's also seen in HIV-associated weight loss.

1 Testosterone supplementation may help improve
2 libido, mood, erectile dysfunction, and bone density,
3 and it's currently being investigated for effects on
4 cognition, CHF, and frailty. It's also being
5 investigated for its effect on diabetes and insulin
6 resistance, which may be related to its effect on lean
7 body mass and fat body mass.
8 Contraindications of testosterone
9 supplementation include any kind of prostate disease or
10 prostate cancer, breast cancer, and relative
11 contraindications are untreated erythrocytosis,
12 polycythemia, bladder problems, and obstructive sleep
13 apnea, if it's untreated.
14 The most relevant adverse event that we
15 encounter in clinical practice with testosterone
16 supplementation is erythrocytosis. Uh-huh. And there
17 you go. There are options available for patients in
18 the United States today for testosterone
19 supplementation. Most of them are transdermal and need
20 to be applied daily. Transdermal formulations are
21 usually well- tolerated, but they do carry the risk of
22 transfer to minors and to females.

1 There are non-transdermal options available,
2 such as, as we just heard, testosterone enanthate,
3 testosterone cypionate injections, which could be
4 injected every one to four weeks, but those carry the
5 disadvantage of requiring frequent injections
6 intramuscularly and seesaw testosterone valleys, and we
7 just heard earlier from the previous speaker how that
8 can affect patients in a negative manner.
9 There's also the option of testosterone
10 pellets, which can be implanted surgically into the
11 buttocks every three to six months. Europe does have a
12 few more treatment options available, and the treatment
13 that we're discussing today is among them.
14 So the challenges for the clinicians that we
15 represent are that, first of all, the algorithm for
16 diagnosis and workup needs to be followed for
17 hypogonadism, because we really don't want patients to
18 be labeled with having hypogonadism when in reality
19 they have a different disease, or, if there's something
20 that's treatable and fixable, for them to have that
21 missed.
22 The other thing is that different patient

1 circumstances, life circumstances, but also adherence
2 and lifestyle, call for a variety of treatment options,
3 and different treatment options then require the
4 physician to know about different monitoring regimens.
5 So, in conclusion, AACE does not advocate for
6 any approval of any specific drug; however, there is a
7 need for new drugs to help manage the increasing burden
8 and prevalence of male hypogonadism, and we need
9 effective medications to improve testosterone
10 supplementation for our patients that will facilitate
11 medication adherence and minimize risk of transfer to
12 family members. Thank you.
13 DR. JOHNSON: Thank you. And Speaker Number
14 5?
15 MR. LEONARD: Good afternoon. My name is
16 Brandon Leonard, and I'm a Program Manager with Men's
17 Health Network. I have no relationship to disclose.
18 Men's Health Network is a national nonprofit
19 organization whose mission is to reach men, boys, and
20 their families, where they live, work, play, and pray,
21 with health prevention messages and tools, screening
22 programs, educational materials, advocacy

1 opportunities, and patient navigation.
2 Recent studies have indicated that
3 approximately 13 million American men may have
4 hypogonadism, often referred to as low testosterone or
5 low T. Hypogonadism is associated with symptoms,
6 including decreased energy and mood, fatigue, loss of
7 muscle mass, decreased libido, and erectile
8 dysfunction.
9 There's also growing evidence of the link
10 between low testosterone and other serious health
11 conditions, including heart disease, diabetes, and
12 metabolic syndrome. Because the symptoms of low
13 testosterone are often similar to those of other
14 medical conditions, over 91 percent of men suffering
15 from this condition go undiagnosed.
16 Low testosterone carries a significant burden
17 for men, both physically and psychologically. During
18 the many community health fairs, screenings, and other
19 events I've attended while on the staff of Men's Health
20 Network, I've heard numerous stories from men and their
21 loved ones about the impact of this condition.
22 In addition to feelings of weakness and

1 fatigue, men suffering from low testosterone often feel
2 they have lost their manhood and that their quality of
3 life has decreased significantly. Depression, anxiety,
4 and stress often accompany low testosterone.
5 While the symptoms may become an impediment
6 to daily life, many men wait months or even years to
7 get treatment for low testosterone, because they assume
8 the symptoms will go away, or they're embarrassed to
9 discuss them. This can be largely attributed to
10 cultural attitudes that have been ingrained in American
11 boys and men for years.
12 Men are taught at an early age to suck it up
13 and that big boys don't cry. When a boy is five years
14 old and falls down and skins his knee, his mother or
15 father tells him to shake it off, and when he's 50 and
16 having chest pain, he may believe it's just
17 indigestion, while it may be -- really be the first
18 sign of a cardiovascular event.
19 Many of those who suffer from low
20 testosterone may be reluctant to seek help and
21 treatment due to stigma and lack of understanding of
22 their condition. Men may also be averse to seeking

1 help because of social norms that teach them to suffer
2 in silence. This dangerous mentality often leads to
3 the exacerbation of medical conditions that only grow
4 more severe and costly if they are not managed and
5 treated early.
6 Men living with low testosterone need to know
7 that they are not alone and that they have a serious
8 health condition that deserves attention. They also
9 need to know that there's a variety of safe and
10 effective treatment options available to help them
11 address low testosterone and the related comorbidities
12 and that new treatments for this condition will provide
13 more options that may be the best match for them.
14 Each patient and his healthcare provider
15 should work closely together to determine the best
16 treatment plan given that patient's individual
17 situation. New and innovative treatments will have a
18 significant impact on the lives of the millions of men
19 living with low testosterone today. Today is an
20 important day for those men and the millions more who
21 will be diagnosed with low testosterone in the coming
22 years as well as their loved ones.

1 Thank you for the opportunity to remark.
2 DR. JOHNSON: Thank you. Now, Speaker Number
3 6.
4 MS. LESTER: Good afternoon. My name is
5 Imani Lester, and I have no financial relationship to
6 disclose today. As stated, I'm Imani Lester, and I'm
7 the Communications Coordinator for the nonprofit
8 organization Women Against Prostate Cancer. We're a
9 national organization working to unite the voices and
10 provide support for the millions of women and families
11 who are affected by prostate cancer. We advocate for
12 prostate cancer education, public awareness screenings,
13 legislation, and treatment options.
14 As you know, low testosterone is a condition
15 that affects many men as they age and can cause a
16 decreased enjoyment of life through uncomfortable and
17 distressing symptoms. There is an estimated 13 million
18 men who are currently living with low testosterone,
19 which I will refer to as low T, and there is growing
20 evidence on the length between male menopause,
21 testosterone, and other men's health issues.
22 Common symptoms of this condition include low

1 sex drive, erectile dysfunction, increased
2 irritability, and much more. However, because the
3 symptoms of low T are similar to other serious medical
4 conditions, over 91 percent of cases go undiagnosed.
5 Although low T is a men's health concern, it carries a
6 significant burden on both the men and the women in
7 their lives.
8 Within my organization, I have come across
9 thousands of women who often express to me their
10 intimacy concerns, which are often connected to low T;
11 women like Selene (ph), for example, who I met in
12 Memphis. Selene is happily married to her husband of
13 27 years, James. Selene shared with me her extreme
14 distraught and frustration with her husband's struggle
15 to find the right treatment option to address his low T
16 as well as the adverse effects his low T had on their
17 relationship and overall lifestyle.
18 It is imperative for women like Selene and
19 the millions like her to have other treatment options
20 available to them. In the male body, testosterone is
21 the most important sex hormone. As you know, low T can
22 cause low decreased sex drive, also known as libido,

1 causing a decreased desire for sex that may lead to
2 reduced sexual activity. This burden, in turn, also
3 affects millions of women and prevents them from having
4 a normal sexual relationship with their significant
5 other.
6 As stated, again, new treatment options to
7 address the absence of testosterone will have a
8 significant impact on these -- the millions of men
9 living with low T as well as the wives and loved ones
10 who are affected by the condition.
11 WAPC is continuing to educate women on men's
12 health issues such as low T and develop campaigns to
13 address this touchy issue in hopes of bringing more
14 awareness on the condition and making it easier for men
15 to discuss it with their loved ones.
16 The detection of low testosterone and the
17 appropriate follow-up treatment can lead to an improved
18 quality of life, healthy relationships, and
19 productivity in the workplace. While this health
20 crisis is of particular concern to men, low T is also a
21 concern for women regarding their fathers, husbands,
22 sons, and brothers.

1 Thank you for this opportunity to disclose my
2 comments.
3 DR. JOHNSON: Thank you. Speaker Number 7?
4 DR. SHABSIGH: Good afternoon. My name is
5 Ridwan Shabsigh. I'm a urologist in New York City for
6 the past 22 years with a urologist practice
7 subspecialized in men's health and andrology. And for
8 purpose of transparency, I disclose to you that over
9 the past 20 years, I have performed consulting services
10 to a number of pharmaceutical and medical device
11 companies, including, but not limited to, Endo
12 Pharmaceuticals, on a fee-for-service basis. However,
13 my travel to you today is completely on my own personal
14 expense.
15 I am speaking to you from the perspective of
16 my practice and my observations of patients' needs.
17 Hypogonadism is a common and important men's health
18 condition that is associated with significant impact,
19 symptoms, morbidity, and mortality. Although currently
20 approved treatment options do provide efficacy and
21 safety, there are significant limitations to their use
22 in clinical practice, resulting in unmet patient needs.

1 In the case of gels and patches, we continue
2 to observe in clinical practice irregular use,
3 noncompliance, failure to take the drug every day,
4 failure to refill the prescription on time. In certain
5 states, such as New York State, where I practice,
6 testosterone products are handled as restricted drugs,
7 making refills very difficult and requiring writing of
8 repeatedly monthly prescriptions.
9 In the case of currently approved short-
10 acting intramuscular injections, the limitations
11 include suboptimal pharmacokinetics with too-high peaks
12 and too- low troughs in addition to the need of
13 frequent injections; therefore, there is an unmet need
14 for a long- acting, efficacious, and safe product.
15 Just to make this point, I can mention that
16 patients in our practice are frequently very happy when
17 converted from daily gels and patches to the long-
18 acting testosterone pellets, attesting to the fact that
19 patients prefer and need a reliable, convenient,
20 infrequent dosing form.
21 The occurrence of anaphylaxis and POME should
22 be acknowledged. However, an effective risk management

1 strategy should be encouraged to make long-acting
2 testosterone undecanoate available, effective, and safe
3 to meet current patient needs.
4 Thank you very much.
5 DR. JOHNSON: Thank you. Speaker Number 8?
6 DR. GLASS: My name is Allan Glass, and I am
7 an endocrinologist. I appear before you today,
8 representing The Endocrine Society, the world's largest
9 professional organization of endocrinologists,
10 comprising over 16,000 members. I have no financial
11 conflicts of interest.
12 The Endocrine Society membership includes
13 numerous clinicians from countries around the world,
14 where injectable testosterone undecanoate has been
15 approved for use for many years. Consequently, The
16 Society is quite familiar with this drug, even though
17 it is not approved for use in the United States.
18 The Society's Clinical Practice Guideline on
19 testosterone therapy in men with androgen deficiency
20 symptoms, which was last updated in 2010 and which is
21 evidence-based, peer-reviewed, and developed without
22 outside funding, indicated that in those countries

1 where injectable testosterone undecanoate has been
2 approved for use, it would be an acceptable option in
3 the treatment of men with androgen deficiency.
4 The Society's Clinical Practice Guideline on
5 testosterone therapy recommends that the choice of
6 testosterone preparation to be used should be based on
7 a patient's preference, while taking into account
8 considerations such as pharmacokinetics, treatment
9 burden, and cost, among others. Many U.S. patients
10 choose injectable testosterone esters as their
11 preferred form of treatment.
12 These clinical practice guidelines also
13 recommend periodic monitoring after initiation of
14 testosterone therapy, the specifics of which will
15 depend in part on the type of testosterone preparation
16 selected. Over a period of several years, the FDA has
17 conducted a very extensive review process for
18 injectable testosterone undecanoate, with special
19 attention to safety issues.
20 In particular, the FDA has expressed concern
21 about post-injection cough and dyspnea. The Society's
22 clinical guidelines make specific reference to post-

1 injection cough, which has been attributed to oil
2 microembolization, and recommends that physicians using
3 injectable testosterone preparations question their
4 patients specifically about this side effect.
5 Clinicians using testosterone preparations
6 are focused on the risk-benefit ratio of the various
7 treatment alternatives. The FDA's extensive analyses
8 of injectable testosterone undecanoate have helped
9 greatly to clarify some of the risks of this drug, but
10 similar safety evaluations of alternative injectable
11 testosterone preparations, one of which was first
12 approved in this country 60 years ago, are woefully
13 lacking.
14 A single published study examining the
15 incidence of cough following injection of testosterone
16 enanthate in a castor oil vehicle reported that the
17 incidence of this side effect was 1.5 percent per
18 injection, nearly two orders of magnitude higher than
19 the values being discussed today for injectable
20 testosterone undecanoate.
21 With regard to anaphylactoid reactions after
22 injection of testosterone esters, there is nothing in

1 the literature related to testosterone enanthate or
2 testosterone cypionate that is even remotely comparable
3 to the detailed analysis of injectable testosterone
4 undecanoate that you are reviewing today.
5 Better understanding of the nature and
6 pathogenesis of these post-injection side effects would
7 facilitate the determination of whether these side
8 effects might be relevant to the entire class of
9 injectable testosterone esters.
10 In addition to the side effects noted,
11 injectable testosterone undecanoate has some potential
12 advantages, including lower frequency of administration
13 compared to the shorter-acting ingestible --injectable
14 testosterone ester preparations as well as a smoother
15 pharmacokinetic profile.
16 It all comes down to risk versus benefit. In
17 that regard, I would close by noting that the charge to
18 the advisory committee states, quote, "In addition to
19 injectable testosterone undecanoate, other approved
20 testosterone injectable products will be referenced,
21 especially in regard to oil microembolism and potential
22 anaphylactic reactions reported for those products,"

1 unquote.

2 The Society encourages the advisory

3 committees to keep in context the risk-benefit

4 information, or lack thereof, for the alternatives to

5 injectable testosterone undecanoate as it finalizes its

6 deliberations. All of us that prescribe this class of

7 medications, and all of the patients to whom they are

8 administered, have a critical stake in obtaining the

9 best comparative information possible. Thank you.

10 DR. JOHNSON: Thank you. Our open public

11 hearing portion of this meeting is now concluded, and

12 we will no longer have comments from our audience. The

13 committee can now turn its attention to addressing the

14 task at hand. Let us do a careful consideration of

15 data before the committee as well as the public hearing

16 comments that we have had delivered.

17 We can now proceed with clarifying

18 questions to the sponsor. Before we do so, however,

19 the sponsor has several clarifying issues they want to

20 bring forward from questions that were introduced this

21 morning. Clarifying Questions to the Presenters (cont.)

22 DR. CASTY: Thank you, Dr. Johnson. We

1 appreciate the committee members' deliberation this
2 morning. We listened carefully, and we have had, as
3 you've seen, some pretty exhaustive analyses that we
4 think we can add to further the discussion that you all
5 had this morning.
6 The topics that I'm going to ask Dr. Danoff
7 to come up and discuss would be cases reported to the
8 life -- in the life-threatening category, cases
9 reported as medically serious, and then data on the
10 onset of action of those 137 cases that we discussed
11 from the FDA. And then, finally, I'll ask Dr.
12 Shusterman to come up and give us some additional
13 information with respect to injection reactions from
14 other short-acting testosterone agents.
15 So, Dr. Danoff, would you like to start?
16 DR. DANOFF: One of the questions that the
17 committee was asking is the number of cases that was
18 life-threatening. We have done such an analysis, and I
19 can show you that -- those results.
20 There were 15 cases that were cited as life -
21 - in which the life-threatening box was indicated.
22 Fourteen of those cases were adjudicated as POME. Nine

1 of the cases were also adjudicated as anaphylaxis. As
2 we talked about before, there's a lot of overlap, and
3 one case was not adjudicated, is either -- I think,
4 actually, even more informative in regards to thinking
5 about the life-threatenings, the treatment that these
6 patients received, which is FA29.
7 So of the 15 cases, 4 had no treatment
8 reported. Of the other 11, 2 of them received steroids
9 or antihistamines, and 9 received epinephrine. And, of
10 course, there was no deaths reported in any of these
11 life-threatening cases.
12 Lastly, our analysis looked at the
13 hospitalization and ER care. Eight of them were seen
14 in either the hospital or the ER. Hospital -- seven of
15 them were the hospital, and one only went to the ER.
16 That's the information you were asking about the life-
17 threatening.
18 I'd also like to talk about the important
19 medical events. And the -- one of the questions that
20 was asked is why there was a discrepancy between the
21 number of severe cases that we, Endo, were identifying,
22 versus the FDA.

1 And as Dr. Chin indicated, one of the
2 criteria that she listed was severe was medically --
3 was whether they were identified as medically important
4 by the -- and so we actually have done -- we looked at
5 the important medical event box, which is also on the
6 data capture form for adverse events.
7 And what that shows is that we found 86 cases
8 that were indicated as important medical events that
9 did not have other boxes checked; for instance, life --
10 so these don't include the ones that contain the life-
11 threatening. Eighty-six had important medical event
12 box checked. But the important thing to note is that
13 78 percent of those cases were checked due to Bayer
14 Pharmaceuticals checking the box, so you need to
15 understand a little bit about that.
16 When a case report comes in to Bayer, they --
17 there are certain preferred terms. Their process is if
18 one of those preferred terms match a list of 7,700
19 cases -- 7,700 preferred terms that are on a list
20 created by the European Medical Agency, then they
21 elevate and check that important medical event box
22 because of the matching of the preferred term, having

1 nothing to do with the severity. This is their general
2 process.
3 So 78 percent were due to Bayer. Now, on
4 that list of 7,700 terms includes POME and anaphylaxis.
5 So it's not unsurprising that the FDA selected a lot of
6 their cases as important medical events because since
7 most of those cases on their 137 were either POME --
8 adjudicated by us as POME or anaphylaxis, and, hence,
9 also adjudicated by Bayer as POME or anaphylaxis, they
10 would have that box checked.
11 But to understand what it sort of means,
12 let's take a look at how these patients were treated.
13 So of the 86 where the important medical event box was
14 checked, 59 received no treatment. There was no
15 treatment reported. Only 27 of them had treatment
16 reported. Just to -- that gives you an idea of maybe
17 the medical severity of the -- of what those important
18 medical events The last thing that needs to -- that
19 might be a little confusing is that in the summaries
20 that the FDA supplied in your briefing book, and I
21 reproduce one here, which is 2010 to 2004, 41 -- can I
22 keep it up on my monitor too, please? They -- if you

1 look at the bottom line, says Box 8 through 12 of the
2 CIOMS Form was checked as other.
3 Okay. So this is an example of where it was
4 checked because of matching the other terms. And this
5 case was -- like many of them, have other details, such
6 as that there were subsequent injections given without
7 adverse events. So I think that -- I hope that helps
8 you understand a little bit about why there might be a
9 discrepancy in the number of severe cases that we
10 identified, because we identified it based on the
11 treatments that the patients received or whether they
12 went -- they were seen in the hospital or the emergency
13 room, rather than a checkbox which matched against a
14 preferred term list, of which POME and anaphylaxis
15 matched.
16 DR. JOHNSON: Thank you for that
17 clarification. Did FDA have any comment?
18 DR. DURMOWICZ: I would -- this is Tony
19 Durmowicz again. I'd just like to reiterate that we
20 used the criteria for severity for the -- especially
21 for the POME cases that we had -- you had seen in our
22 slide set. The box checked -- if you're familiar with

1 the CIOMS Form, the box check thing on the right side
2 can be checked or cannot be checked. We looked at the
3 actual narrative itself, and in some cases, it was --
4 it would say life-threatening, and it was not,
5 potentially, checked in the box. We went beyond
6 checking the box, from that standpoint.
7 You know, I think that it's an interesting
8 discussion whether they got treated or whether they
9 didn't get treated and what's severe and what's not
10 severe, and I think there's a certain amount of
11 subjectivity to it, and I think that what you're seeing
12 is a difference in opinion in some aspects of what's
13 severe, especially for -- you know, in the perfect
14 world, if you give somebody an injection, other than
15 some pain, you wouldn't expect anything to happen.
16 So I think that in that context, just to
17 bring up two cases that -- at least one of the two
18 cases or three cases that Dr. Chin brought up, of the
19 patients that thought they were going to die, quote,
20 unquote, and patients that had passed out or lost
21 consciousness. It's unknown whether they received any
22 treatment at all, so they would be -- they would go in

1 the untreated category. So just to give you the other
2 side of the coin, somebody who is laying on the floor,
3 passed out, we don't know if they got any treatment,
4 and that would go as the untreated section.
5 So slicing and dicing it to determine
6 severity is an academic issue, and you can take it into
7 the risk- benefit, but I think that some of them are
8 very severe regardless, and just because somebody got
9 treated or didn't get treated should not be the main
10 determination of severity. So we can do this all
11 afternoon, but I don't think it's going to be very
12 helpful.
13 DR. JOHNSON: I tend to agree that I think
14 that going over the words utilized is not of great
15 value. I see a slide that you have regarding explicit
16 subjective comments. I'm not sure that's of great
17 value --
18 DR. DANOFF: Okay.
19 DR. JOHNSON: -- in giving to the committee.
20 DR. DANOFF: So maybe I'd have Dr. Meyer, Bob
21 Meyer come up and talk about -- because he's looked at
22 these cases, and maybe he can give you his clinical

1 impression. And while he's getting up, let me also
2 just remind you, as you've heard before, these are 137
3 cases out of the totality of after 3.6 million doses.
4 DR. JOHNSON: Again, I would not put a lot of
5 time into discussing details.
6 DR. MEYER: Yeah, actually, I was going to
7 say that. I mean, I think, in essence, the heart of
8 the matter is that we're in fairly close agreement on
9 the number of cases. You could, indeed, debate back
10 and forth the severity. I think what really needs to
11 be thought about is the number of cases and the overall
12 exposure rates. Thanks.
13 DR. JOHNSON: Well, thank you to both groups
14 for that good discussion, because that topic did come
15 up. And there was one other issue you wanted to
16 clarify?
17 DR. CASTY: Yes. What we could do is have
18 Dr. Shusterman discuss the post-injection reactions in
19 short-acting testosterone agents.
20 DR. SHUSTERMAN: As I described this morning,
21 Endo, in trying to better understand the situation with
22 short-acting TRTs, did an analysis of an electronic

1 medical database and found that these cases are
2 detectable at a measurable rate.
3 We were -- so this is for anaphylaxis. We
4 were so intrigued by this, we wanted to see if we could
5 obtain a corroboration, because we could not find
6 anything like this, either in the AERS database or in
7 the literature.
8 So we had access to a claims database, and,
9 very quickly, this claims database was called
10 MarketScan. It's called MarketScan. It covers 30 to 50
11 million lives between 2007 and 2011. And, very
12 importantly, this is an integrated database, from an
13 epidemiologic standpoint, that includes inpatient care,
14 outpatient care, and emergency care and prescription
15 claims. So to one of the issues that came up in this
16 morning's discussion, this overcomes that limitation.
17 The methodology was the same as I mentioned
18 this morning, so we searched 43 million records, we
19 identified 120,000 men who were exposed to IM TRT, we
20 used the anaphylaxis code of ICD-9 995.0, and it had to
21 be on the same day as exposure, and came up with a
22 probabilistic approach to classifying the cases.

1 And here again what we found is that there
2 are measurable cases. If you use the more liberal
3 definition, yes, probable and possible. Sixteen out of
4 120,000 giving 1.3 per 10,000 patients. We had data
5 here to actually calculate patient years, so that
6 calculates as 2.1 per 10,000. And if you look at yes
7 and probable, that's 12 out of 120,000, or 1 per 10,000
8 patients, 1.5 per 10,000 patient years.
9 So we think this provides corroboration to
10 the previous data as well as showing that we're in the
11 same range with AVEED. Thank you.
12 DR. CASTY: And the final topic was related
13 to the onset question, with respect to the percentage
14 that had an onset in the 137 cases within 30 minutes.
15 DR. JOHNSON: Okay.
16 DR. DANOFF: So the -- we wanted to give you
17 the information about the onset within 30 minutes,
18 because that was the time point that we thought was
19 important, and what we're proposing in our risk
20 management plan, the data cut was not that way as
21 presented earlier.
22 And when we did our analysis, what we found

1 is that 91 percent -- 91 started within 30 minutes.
2 Only one cases started after 30 minutes. These numbers
3 are very similar to the numbers that Dr. Hirsch
4 mentioned, although he didn't mention the fact that
5 there were actually a number of cases that, when he
6 presented the percentage, he didn't mention that there
7 were a number that didn't have onset times reported, so
8 -- but of the 92, 91 were within 30 minutes, and the
9 one that was more than 30 minutes was at the one-hour
10 mark.
11 DR. JOHNSON: Yes, FDA?
12 DR. GASSMAN: This is Dr. Audrey Gassman. I
13 would just like to point out that we -- the FDA has not
14 had the opportunity to review the data that the sponsor
15 has presented on the other testosterone products.
16 DR. JOHNSON: Thank you very much. Now we
17 will proceed with questions. We're going to start with
18 Dr. Curtis.
19 DR. CURTIS: Thank you. I wanted to go back
20 to the risk management plan and the impact that might
21 have on mitigating any risk. And Dr. Shusterman has
22 mentioned two types of surveillance activities, one an

1 assessment of patients and of providers and their level
2 of adherence with the REMS, and particularly that 30-
3 minute waiting period, and the second activity was both
4 passive and active surveillance of post-injection
5 events.
6 So I'm wondering if we could hear a little
7 more about do you have specific plans about how you
8 might do that, and, more importantly, what impact that
9 might have, and, in particular, you know, how would you
10 monitor this? If you find out, for example, patients
11 aren't adhering to 30 minutes, do you have plans to
12 change that, and, in particular, if the rates of
13 injection events are greater than you expect, what
14 would you do?
15 DR. CASTY: Right. Okay. Dr. Shusterman can
16 address that.
17 DR. SHUSTERMAN: Yes. Thank you very much.
18 The -- let me cover the assessments first, and then
19 I'll go to the issue about surveillance. So REMS
20 assessments are commonly done. As the FDA mentioned,
21 they are actually required by the law. We're proposing
22 doing them at 12 months, 3 years, and 7 years.

1 Now, what you do is you survey healthcare
2 providers, and you survey patients, and what you want
3 to survey is that the key messages of your -- for the
4 patients of the medication guide have been conveyed and
5 the key risk messages from the "Dear Healthcare
6 Provider" letter have been conveyed to the
7 practitioners.
8 So there has been a lot of literature since
9 REMS came into effect in 2007 about what to do with
10 this information, but I want to show you that we have
11 given this considerable thought, and we've actually
12 come up with what we consider goalposts to achieve, and
13 I want to show them to you, and I also want to show
14 some historical information about what has been done.
15 So this is in terms of REMS assessment by
16 survey of healthcare providers. We have set a target
17 for receipt of the "Dear Healthcare Provider" letter at
18 95 percent, and we have set a target for knowledge and
19 understanding of our key risk messages, which are the
20 post-injection reactions and the 30-minute wait, at 85
21 percent.
22 And there's historical information from other

1 programs about knowledge and understanding of key risk
2 messages -- not these per se, because these have not
3 been tested per se -- in the 82 percent range. So we
4 think that's a good target. And also compliance with
5 the 30- minute wait period, we have set at 85 percent.
6 We've set the same goals for the patients,
7 and that's shown here; 95 percent for receipt, 85
8 percent for knowledge and understanding, which actually
9 exceeds what historically has been published in the
10 literature, and 85 percent with compliance.
11 It is our intent to -- if we do not hit these
12 targets to take on additional measures to understand
13 why. What's not working? Is it a communication
14 problem? Is it a problem with getting the material to
15 the individuals? Is it a problem with the
16 patient/phylogenetic interaction? And try to improve
17 upon that.
18 On the second topic, we think that the active
19 surveillance system is very important, because we all
20 know from passive surveillance, it's impossible,
21 literally, as we heard this morning, to get incidence
22 information. And since we have a baseline rate, it's

1 actually possible to construct a mathematical function
2 of when you would expect a reaction to occur.
3 So by following this in real time, if
4 reactions were occurring sooner than expected by chance
5 alone or at a greater rate, then we would want to
6 intervene with additional types of investigations. So
7 if we can bring that slide up.
8 For example, one of the first things that
9 you'd want to do is investigate the cases as fully as
10 possible to understand all the circumstances. For
11 example, were the injections being given appropriately?
12 Were they being watched for 30 minutes afterwards? Is
13 there an issue with the quality of the actual material?
14 Have some contaminants slipped in for some reason? So
15 we would do a product quality investigation.
16 Again, our instructions -- for example, are
17 patients accidentally receiving it when they've had a
18 reaction before and should actually be excluded from
19 subsequent injections? And is there a way to improve
20 the technique for actually administering it?
21 So, as I said, we take this seriously, and we
22 think, between the REMS assessments, the goals we've

1 set, and then the active surveillance and being able to
2 have trigger points when levels are exceeded that we
3 can actually react and make improvements. So I hope
4 that addresses your questions.
5 DR. JOHNSON: Dr. Clarke?
6 DR. CLARKE: I had a clarification question
7 for, I think it was Dr. Mann's presentation from
8 earlier. Dr. Danoff may have addressed some of this,
9 but on Slide 52 in Dr. Mann's presentation, there was
10 the discussion about characteristics of the clinical
11 indeterminate anaphylaxis cases and a discussion of one
12 event that was considered serious, but then they still
13 received an additional dose. Five additional patients
14 apparently had multiple injections, actually, with this
15 indeterminate case.
16 So the question that I had was in terms of
17 the anaphylaxis versus POME and the uncertainty
18 sometimes in terms of the diagnosis, do we have any
19 evidence of the cases that were adjudicated by the
20 sponsor to be anaphylaxis who did receive subsequent
21 injections prior to the adjudication having been done?
22 Is there any information on that and what the risk of

1 further anaphylaxis was after that?
2 DR. CASTY: Dr. Danoff would probably be best
3 to answer that.
4 DR. DANOFF: I think your question is were
5 there further -- of these people who got re-exposed,
6 were there further cases of anaphylaxis?
7 DR. CLARKE: Yes.
8 DR. DANOFF: And these five patients did not
9 have any further anaphylaxis, even though some -- one
10 of them received up to 13 more injections.
11 DR. CLARKE: All right. And specifically the
12 ones -- I don't know if these were later adjudicated as
13 being anaphylaxis by the sponsor, but if they or others
14 were adjudicated as being anaphylaxis, were there any
15 of those patients who had gotten further doses that we
16 know about to have any idea about subsequent risk of
17 anaphylaxis?
18 DR. DANOFF: So the ones that were listed as
19 none, we have -- they didn't receive further
20 injections, so we don't have that. And these were in
21 the clinical trials.
22 DR. CLARKE: Thank you.

1 DR. JOHNSON: Dr. Hoeger?
2 DR. HOEGER: Thank you. So I had two
3 separate questions, one related back when Dr. Morrato
4 was going over your preference and continuation of
5 therapy, and if there's a correlation between other
6 forms of hormone therapy we use -- for instance, I
7 treat a lot of women. They change frequently from one
8 formulation to another. And is that kind of information
9 captured on continuation if you're just looking at
10 refills of prescription? And particularly with the
11 transdermal forms, at least in our clinical practice,
12 we see a lot of men taking it temporarily, taking a
13 break from it, and then going back to it.
14 DR. CASTY: So Dr. Camper, would you like to
15 address that question?
16 DR. CAMPER: We did look at switching, as we
17 termed it, behaviors as part of the analysis.
18 Unfortunately, I don't have data on that in slides. I
19 can get that to you after a break. What I can tell you
20 is that, off the top of my head, the switching rate for
21 the -- in the German analysis overall was about 15
22 percent of the population switched one time, and we

1 only followed one switch, because very, very few switch
2 twice.
3 And what we found was about -- the rates were
4 about 21 percent for the short-acting injections and
5 about 15 percent for the -- right on about the norm or
6 the average for the gels and about 7 percent for the
7 patients who were receiving Nebido. And what our data
8 showed was that Nebido -- the long-acting injection was
9 the most switched to and it was the least switched
10 from, if that makes sense.
11 DR. HOEGER: Second question was, then,
12 related -- was a question specifically for the issue of
13 POME in your database. It appears, having heard
14 discussions since I first formulated the question, that
15 there may not be predictive factors, but are there
16 conditions about which one would be more concerned
17 about giving somebody who had a history of pulmonary
18 hypertension or severe asthma? Would this be something
19 that we would need to pay attention to in the labeling?
20 DR. CASTY: Yeah. Well, let me ask Dr.
21 Meyer, who refuted the cases, of course, to comment on
22 that.

1 DR. MEYER: So I think the -- there are
2 certain cases where you'd probably -- or certain
3 patients you'd want to avoid, even with a very low rate
4 of POME, which would be people with very unstable
5 asthma and/or very severe COPD, for instance. I would
6 not particularly -- I'm not sure pulmonary hypertension
7 would be a very likely concomitant disease here anyway,
8 but I have a very different view of the pathophysiology
9 than what I would view as the speculative slides that
10 were put up by FDA. That's based on a very different
11 process.
12 But I do think, considering the cases as we
13 reviewed them, that if you had unstable pulmonary
14 disease or perhaps very unstable cardiac disease, that
15 you would not want a patient going through one of these
16 episodes.
17 DR. JOHNSON: Dr. McCammon?
18 DR. MCCAMMON: May I ask just a very quick
19 question on that point?
20 DR. JOHNSON: Yes.
21 DR. MCCAMMON: Were the trials such that
22 people just as you described were excluded?

1 DR. SWENSON: You had people with severe lung
2 and heart disease who the impact of sudden coughing
3 might be more disastrous than in healthy people?
4 DR. DANOFF: So we did not exclude patients,
5 but I'm not sure we captured, you know, severity. So
6 there were patients who had asthma, and there were
7 patients who had COPD.
8 DR. JOHNSON: Yes, Dr. McCammon?
9 DR. MCCAMMON: When we talk about the
10 anaphylaxis and POME, we looked at -- there's about
11 greater than 40 percent of the patients are receiving
12 some kind of treatment, epinephrine or medications. In
13 your safety and risk management, we don't discuss that;
14 the physician should have that in their office. Is
15 there something that we should do or could do that
16 would guarantee -- because I don't think every
17 urologist keeps epinephrine in their office, and that
18 would be something
19 DR. CASTY: So part of our risk management
20 plan is -- has several components in terms of achieving
21 awareness, preparedness, and management of the issues;
22 awareness that the patient and the healthcare provider

1 would be aware of these potential reactions, and then
2 prepared should management need to be required.
3 We feel that the elements of our risk
4 management plan would properly inform. But let me ask
5 Dr. Dowling to come up and comment in terms of his
6 practice experience in a urology practice.
7 DR. DOWLING: Bob Dowling. The practice that
8 I come from did have emergency equipment and personnel
9 trying to use that equipment in our offices. Reactions
10 to the procedures I mentioned earlier this morning that
11 are done routinely are real, but very rare, and we feel
12 that we need to be able to manage and recognize them.
13 I can't speak for all urologists in the
14 United States. I do network with a number of them, and
15 I believe this is common, that many urology practices
16 are geared to manage emergencies that occur in their
17 office. They're dealing with an elderly population.
18 DR. JOHNSON: Dr. Nelson?
19 DR. NELSON: So I'm going to kind of re-ask
20 my question to you guys this time, but if we assume
21 that anaphylaxis is fairly unpredictable and we assume
22 that the embolic problem is predictable, I think we're

1 basing our entire risk management plan, at least the
2 part that serves to prevent the effects in the first
3 place -- not the 30-minute wait that'll help detect it,
4 but the actual prevention of causing the syndrome in
5 the first place, we're basing that on what it sounds to
6 me like this slow injection. Right?
7 I mean, that's the only -- maybe I'm wrong
8 about this, but it seems like that's the only part of
9 the risk management strategy that will reduce the risk
10 of having an embolic phenomenon. So I just want to
11 know if there's any reason to believe that that's going
12 to be effective. Is there an animal model? Is there
13 pharmacokinetic modeling? Is there something that
14 would suggest that this subgroup of people that gets
15 rapidly injected has a problem? Because the vast
16 majority of people probably get injected the same way.
17 Right? And that only a small number of them get this
18 intravascular or this syndrome that may be related to
19 intravascular injection from rapid -- from this
20 purportedly rapid administration.
21 And I guess the corollary to that is, is
22 there any reason to believe that showing a video to a

1 busy doctor and his nursing staff and others is going
2 to actually effect that change that we want? Because I
3 just -- I'm not sure that that would happen.
4 DR. CASTY: So, first, POME, of course,
5 happens quite infrequently, and so it is difficult to
6 thoroughly study it, but Dr. Zitzmann has been treating
7 patients with Nebido, and I think he can comment on
8 some of those educational points that you've asked as
9 well as the injection technique.
10 DR. ZITZMANN: Yeah. As I have given several
11 thousand injections of Nebido and I have seen the
12 pulmonary oiling microembolism, but no case of
13 anaphylaxis, we have, of course, precautions, as we
14 take care of every patient very carefully. And we
15 observed that -- I haven't seen the POME for a long
16 time now, as we injected it more slowly, as I believe
17 in that theory of increasing pressure within the
18 tissue, pressing the substance into the lymphatic
19 pathway.
20 So -- and also warming the ampule, decreasing
21 viscosity -- that means letting the oil distribute
22 within the muscle more easily -- has led to a much

1 lower rate of POME, as we haven't seen it during last
2 year's. So I think -- this is just personal experience
3 and my opinion concerning the mechanism, but it seems
4 to work.
5 DR. JOHNSON: Dr. Durmowicz?
6 DR. CASTY: And just to let everyone know,
7 they're -- in our pivotal trials, there was a time
8 period of 30 to 60 seconds for a slow injection, and in
9 Europe, there is -- it's also labeled that way as well,
10 as are several other IM, oil-based products in the U.S.
11 DR. JOHNSON: A comment from the FDA?
12 DR. DURMOWICZ: Just to make a quick comment,
13 and I think we touched base on this a little bit
14 earlier, Dr. Nelson, but to clarify, from our
15 standpoint, we don't think that POME is predictable. It
16 can happen on any injection. It's relatively
17 infrequent, as you know. From nine years or eight years
18 of experience, we've got, you know, about 200 cases or
19 so that we've looked at.
20 And there's no real evidence that the slow
21 injection will help. We talked about that as a
22 theoretical thing this morning. So it is what it is,

1 and I think you have to go into establishing a risk
2 mitigation strategy, if you think you can, taking into
3 consideration that it's not going to be predictable and
4 the slow injection, we don't know if it helps.
5 DR. CASTY: But I think the other part of our
6 risk management plan isn't just to prevent POME; it's
7 to be able to manage the reaction, if it does occur,
8 appropriately.
9 DR. NELSON: Right. But that's obviously not
10 preventing, but I understand your point. And I don't
11 think I was suggesting that it's predictable to get the
12 embolization problem. I was suggesting that
13 anaphylaxis, in theory, should be much more
14 unpredictable. I mean, you should -- if you -- you
15 know, I think if you knew something had had
16 anaphylaxis, you presumably wouldn't give it, although
17 I know it's been done in a few patients.
18 What I've not quite understood about
19 anaphylaxis is, you know, these are people who have
20 presumably gotten multiple, multiple doses of it. You
21 know, on your first dose, probably nobody should have
22 anaphylaxis, unless they've been exposed and had this

1 type of chemical before. You know, and I guess at some
2 point, you could develop an allergic response to
3 anything. I mean, I'm sure the allergist could talk to
4 that better than I can. So, I mean, I guess it is
5 pretty unpredictable that anaphylaxis would ever
6 happen, that it would occur.
7 DR. DURMOWICZ: Yeah. I'm not the allergist
8 in the division, but I've worked in the allergy field
9 for the last bunch of years that I've been at the FDA,
10 since we're all one happily family, and I do know that,
11 as you alluded to, that, first of all, there were some
12 anaphylaxis cases after multiple doses, and there were
13 some on the first dose, so you have to -- if you are
14 going by a strict allergic phenomenon, which the NIAID
15 criteria doesn't necessarily go by -- they go by a
16 clinical presentation -- then there would likely be
17 some kind of exposure earlier.
18 But for this particular product, I think
19 everybody in the room has got benzyl benzoate hundreds
20 of times on any kind of cream or anything like that.
21 Castor oil is one of the main ingredients of lipstick.
22 So from an exposure standpoint, I think that if it --

1 it's not surprising that sometimes it would happen,
2 from an allergic phenomenon, the first dose. So that
3 doesn't help us very much, I don't think.
4 DR. JOHNSON: Dr. Ownby?
5 DR. OWNBY: I have two questions about the
6 risk management mitigation efforts. The first is I
7 haven't heard any statement about the risk of trying to
8 manage anaphylaxis when a patient's on a beta-blocking
9 drug, and given the age group that these are likely to
10 be given to, has that been considered?
11 And the second one is whether there's any
12 experience -- because of the -- a 3 ml injection of oil
13 is going to be somewhat painful, I'm sure some
14 physicians have split this into two injections, and I
15 wondered if there's any information the sponsor may
16 have, whether that increases or decreases the risk,
17 especially, of the
18 POME.
19 DR. CASTY: So let me ask Dr. Borish to
20 address your first question, and then we can discuss
21 the other.
22 DR. BORISH: Whether or not the agency or the

1 sponsor wants to recommend withholding beta-blockers in
2 the risk management plan is for them to decide. To me,
3 what's really stunning about this is that we're not
4 meeting after a Phase III study, where they gave it to
5 a thousand perfect people who have no medical problems
6 and then were looking at a rate of anaphylaxis were --
7 and then wondering what's going to happen in the real
8 world when they start giving this to people with
9 coronary artery disease and on beta-blockers, ACE
10 inhibitors, and all the other risk factors that you and
11 I appreciate very much?
12 The real-world study's been done. I mean,
13 they've given over 3 million injections to people who
14 apparently had no screening as to whether they had
15 asthma, severe asthma, hypertension, or on beta-
16 blockers. So they may -- I would actually encourage a
17 recommendation not to give it to people on beta-
18 blockers, but I suspect, out there, a lot of patients
19 on beta- blockers have had it. And your second -- oh,
20 the --
21 DR. CASTY: I can take that one.
22 DR. BORISH: Yeah.

1 DR. CASTY: I think you were asking about
2 splitting the dose.
3 DR. OWNBY: (Inaudible).
4 DR. CASTY: Yeah, we haven't done that. When
5 we did our trials, all the trials, it was a single
6 injection, and there were only three patients who
7 discontinued due to an injection reaction, two of which
8 had pain. One had a local rash.
9 DR. JOHNSON: Dr. Cavazzoni?
10 DR. CAVAZZONI: I have a question with
11 regards to the data from longitudinal databases that we
12 saw earlier, specifically from MarketScan and the IG
13 database, and, obviously, those data are difficult to
14 extrapolate to spontaneously reported data, so we're
15 looking at incidence rates versus reporting rates.
16 So given that the drug has been available in
17 Europe for a number of years, are there any databases
18 in Europe that might be amenable to a direct comparison
19 across the injectable testosterones?
20 DR. SHUSTERMAN: That is exactly the question
21 we asked when we wanted to research this as well in
22 order to do comparative work. And the best available

1 database is the -- well, it's now called the GOLD. I
2 guess that was the GCPR -- the U.K. database.
3 Unfortunately, the U.K. was one of the
4 countries where the use of Nebido was at a much lower
5 level. Even as recently as a year, year and a half
6 ago, when we surveyed that diabetes, there were about
7 2,000 Nebido patients in it, which makes it actually
8 less than our clinical experience.
9 And then there's the thin (ph) database, and
10 there's some databases in Germany, and we looked into
11 them also, but they have some linkage issues as well.
12 For example, there are only outpatient records. They
13 don't link to emergency room or hospital. So we -- and
14 that's pretty much it. We survey all the available
15 databases for epidemiologic work in Europe, and,
16 unfortunately, we're not able to come up with anything.
17 DR. JOHNSON: Dr. Woods? Dr. Orza?
18 DR. ORZA: I'm thinking that there are
19 actually two very different risk-benefit equations here
20 and wondering whether the REMS can help us, especially
21 with the latter one. The first one is, I think, a
22 relatively small group of men who have Klinefelter's

1 syndrome or, you know, true hypogonadism or androgen
2 deficiency, the way that The Endocrine Society
3 guideline defines it, or are trans men, or a group of
4 men who really don't have any choice. They have to
5 take testosterone.
6 And for that group, it would be nice if they
7 had a maximum number of options to choose from. And
8 that group, it seems to me, will also be more likely to
9 be under the care of an endocrinologist or a urologist,
10 and so some of these other concerns we have about the
11 environment in which the injection is taking place
12 would be mitigated by that.
13 But what's lacking there for those men is any
14 direct comparison, any studies that make direct
15 comparisons between these different options that could
16 really help inform their choice and help them make the
17 decision about whether this risk is worth taking,
18 compared to using the patch or the short-term injection
19 or the gel.
20 And then there's this much larger group, to
21 which I think there's a completely different risk-
22 benefit equation. That's, I think we saw in one slide,

1 up to 30 percent of men who have this amorphous
2 condition called low T, and The Endocrine Society
3 guideline actually recommends against offering
4 testosterone therapy to them. It says, "We recommend
5 against a general policy of offering testosterone
6 therapy to all older men with low testosterone levels."
7 And that's a very different equation, in my
8 mind, and it's happening in this context, where, you
9 know, more -- this is being marketed very heavily, and
10 more and more people are looking into it, more and more
11 people will potentially be offered -- they will be
12 offered it in settings where there aren't the kinds of
13 controls we're looking for. And I'm wondering if
14 there's anything -- there's anything that the REMS can
15 do about that. Is there anything a REMS can do around
16 marketing? Is there anything it could do around
17 restricting indications?
18 And in that case, I think -- you know, I have
19 in the back of my mind our experience and the hard
20 lessons we learned with estrogen replacement. I mean,
21 right now we're talking as though you have low
22 testerone (sic); you give them testosterone, and that

1 fixes the problem. And I'm wondering if, down the
2 line, we're going to learn that, in the absence of a
3 large clinical trial that really rigorously studies
4 this, we're going to find some hard lessons like we
5 learned about estrogen.
6 DR. CASTY: So there's a few questions, I
7 think, within your question. Let me ask Dr. Cunningham
8 to first address some of the aspects you mentioned
9 around The Endocrine Society guidelines and who should
10 be treated in those two separate groups that you
11 started off with.
12 DR. CUNNINGHAM: As an endocrinologist, I
13 spend quite a bit of time taking people off of
14 testosterone when I don't think that it's beneficial to
15 them or that it's justified. But in The Endocrine
16 Society guidelines, we tried to define hypogonadism as
17 males who have symptoms that are consistent with low
18 testosterone and also low testosterone levels on at
19 least two occasions.
20 So with that kind of definition, most of the
21 time, if you've got a good assay -- and that's been
22 another issue, but that's being addressed by The

1 Endocrine Society, and in time, I think that will be
2 improved. So I think if one follows those guidelines
3 and then follows the monitoring guidelines, then
4 testosterone can be given safely to men.
5 In the men who are 65 and older, there are
6 two issues. The group that wrote the guidelines felt
7 strongly that one should not, at this point, either
8 screen men, as a routine, for low testosterone, but
9 should only screen people who have symptoms and then
10 find out if they're hypogonadal. And so one should not
11 offer treatment unless people are symptomatic and have
12 low T, so that's where we are now.
13 There is an ongoing trial, and Dr. Swerdloff
14 and I are both co-investigators on this trial, called
15 The Testosterone Trial. Right now, we've essentially
16 recruited 750 men who are 65 and older and treating
17 them for a year and looking at a number of different
18 endpoints. So I think in terms of efficacy issues,
19 that study will be able to address the problem of
20 efficacy of treatment in truly hypogonadal men who are
21 65 and older.
22 As I mentioned earlier this morning, it's

1 going to take a much larger study to address the issue
2 of potential side effects, prostate, or cardiovascular.
3 At this point, we don't think there are problems there,
4 but as you and I know from the Women's Health
5 Initiative, you can be wrong. And so we hopefully will
6 not make that mistake.
7 DR. ORZA: Can I just follow up? Do you have
8 any information about the extent to which your
9 guidelines are followed, either by specialists or in
10 general practice?
11 DR. CUNNINGHAM: I don't have any information
12 on that. I don't believe that we do. Ron, are you
13 aware of anything? I would say that they're heavily
14 quoted, and they're referred to by, you know, lots of
15 societies across the country in the world. But as far
16 as data driven showing the guidelines are followed, I
17 don't know of good data for that.
18 DR. CASTY: I just wanted to -- one other
19 point. I think, within our pivotal studies, we did not
20 have a large number of men over the age of 65, so our
21 proposed product label will indicate that there's
22 insufficient evidence for treatment in men over the age

1 of 65.

2 DR. JOHNSON: Thank you. Dr. Swenson?

3 DR. SWENSON: Yes, thank you. I have two

4 questions, one for the sponsor, and that is in the data

5 that were shown about the follow-up of maintenance of

6 therapy, we found that by two years, at least the

7 European experience suggests only 25 percent of men

8 with what is being regarded as maybe a very, very

9 favorable way of giving this drug still maintain. Do

10 you have any answers as to why the rate of maintenance

11 is so poor?

12 DR. CASTY: Dr. Zitzmann, you might be,

13 perhaps, the best person -- position to answer that.

14 DR. SWENSON: And might it be, to some

15 extent, some of the problems we're worried about? Do

16 patients who have an episode of cough just say, "I

17 don't want to do this again"?

18 DR. ZITZMANN: Actually, I was, myself,

19 surprised seeing adherence number of 20 percent,

20 because in our office, in our center, we see a much

21 higher adherence rate, which is way over 60 percent,

22 because people do not really change.

1 Once they have received these injections,
2 they feel they are being treated well, they see the
3 effect, they see also that they are being taken care of
4 every three months, that we are checking their levels,
5 which is one of the advantages, because if they apply
6 the gel, they might forget, and they don't see the
7 doctor maybe for one or two years, so we don't really
8 know. This is really increasing compliance.
9 And those people who had the cough stayed on
10 the treatment. It was not a reason for them to stop
11 it, because it was actually eight different people
12 having that, and they continued on the treatment for
13 years, and I think most of them are still on it. Thank
14 you.
15 DR. SWENSON: And my other question is to the
16 FDA, and that is around the issue of this incidence in
17 other preparations that are oil-based, whether they be
18 testosterone or otherwise, with reported cough-like
19 syndromes. And we did have mention of a study done
20 about 20 years ago, looking at this incidence in a
21 group of about 25 men and 500 injections, where the
22 frequency of acute, sudden, and severe cough was about

1 1.5 percent.

2 So it may be outside of our remit to even ask

3 about other preparations and this problem, but are we -

4 - but I'm going to ask it anyway. Are we possibly

5 holding Endo to a higher standard than what is out

6 there? And you're surely probably looked at the

7 incidence of this problem in other preparations.

8 DR. HIRSCH: This is Mark Hirsch. The study

9 you referred to, I think, is the Mackey study, and Dr.

10 Handleman (ph) is the final author, is the single

11 publication that I'm aware of that addresses this issue

12 for the competitive products. And it is a unique study

13 in that the investigator was seeking the cough. The

14 study was done for that intent, which is very different

15 than spontaneous reports that we access through AERS or

16 through CIOMS.

17 So, of course, when you proactively have

18 patients in the office and you are actually waiting or

19 asking them whether they're going to -- whether they

20 feel like coughing, your rates will be a little higher,

21 considerably higher than if you have spontaneous

22 reports. This was a very small study, as you mentioned

1 the nature of -- I think 20 per arm, something to that
2 effect. And I don't recall that the cough was very
3 severe in these patients.
4 DR. SWENSON: They described it as sudden
5 onset, nonproductive cough associated with faintness.
6 It's starting to sound like what everyone would
7 consider an adverse effect.
8 DR. HIRSCH: That's not my recollection --
9 DR. SWENSON: And I'm only reading from the
10 abstract because I haven't been able to read the
11 article in depth, and perhaps you have.
12 DR. HIRSCH: That's not my recollection of
13 the paper, and it is the only paper that addresses this
14 that I'm aware of. We are more concerned about severe
15 post- injection reactions and not simple cough. That's
16 the FDA's concern, severe post-injection reactions. I
17 don't think those were reported in Dr. Mackey's paper.
18 And, in fact, the entire AERS database, 44
19 years, contains 13 cases of severe POME for all other
20 injectable testosterone products. Those are the facts
21 that we know that the FDA is aware of, but apparently
22 the sponsor has some additional data, but we have not

1 been provided access to that additional data in regard
2 to the comparisons that we saw today, and especially in
3 regard to POME. I think they showed anaphylactic
4 reaction comparison data. I'm not sure if they showed
5 POME data from that particular European database.
6 So I think our answer is that the Mackie
7 paper does not relieve our concerns in regard to
8 testosterone undecanoate. Did you have another part to
9 your question?
10 DR. SWENSON: So if I can just get you to
11 reiterate, then, do you feel what has been reported
12 with this preparation is log order or significantly
13 higher than the incidence with all other oil-based IM
14 injections?
15 DR. HIRSCH: The answer is it's impossible to
16 answer your question, given the data we have in front
17 of us. Even though we would like to, even though it
18 would help you, we are unable to tell you how this
19 compares to the other injectable testosterones. All we
20 can give you is the data from AERS and the Mackey
21 paper, and now the sponsor has additional data that we
22 have yet to access that the FDA has yet to review. We

1 cannot tell you whether it's log orders, different --
2 DR. CASTY: There is another paper in the
3 public realm --
4 DR. JOHNSON: I'm sorry.
5 DR. CASTY: Sorry.
6 DR. JOHNSON: Before you speak, if you could
7 -- yeah, because that was a question for the FDA. Did
8 you want to make a comment?
9 DR. CASTY: We could add there is another
10 publication with respect to post-injection cough with
11 short-term -- short-acting testosterone agents, if
12 you'd like us to review that. And the FDA has reviewed
13 that one. It's up to the question --
14 DR. JOHNSON: I want to ask a corollary quick
15 question. Is there any other injectable medicine that
16 has castor oil, or is this the only one?
17 DR. CASTY: Are you asking me, or -- there
18 are --
19 DR. JOHNSON: I was asking the FDA. Do you
20 know? And if you don't know, perhaps the sponsor --
21 DR. HIRSCH: The sponsor correctly referred,
22 I believe, to the three products. Faslodex, I believe,

1 has the same constituents, Makena, and estradiol
2 valerate, which is an older product. Those were the
3 three that you referred to, and we agree with those.
4 DR. JOHNSON: Thank you. Did you have a
5 corollary, Dr. Clarke? Dr. Kittelson?
6 DR. KITTELSON: I just wanted to ask about
7 the transference of label use. Is there any evidence -
8 - do you have any evidence that either an injectable,
9 but especially a long-acting injectable, has a lower
10 rate of off-label use than gels? Is there any data
11 along those lines?
12 DR. CASTY: I don't -- Dr. Danoff, do you
13 have anything on that? I don't believe we actually
14 have any evidence that there's more or less off-label
15 use of one product versus another.
16 DR. KITTELSON: Okay. So that just stands to
17 reason it's harder to get, so it would be harder to
18 transfer?
19 DR. CASTY: I think based on the -- you know,
20 the controlled distribution, it would be certainly
21 obviously more localized so that it's in the healthcare
22 provider's office, rather than being at least handed to

1 a patient to -- or picked up at the local pharmacy.
2 DR. KITTELSON: Okay. That's the basis for
3 that? Thank you.
4 DR. CASTY: Yeah.
5 DR. JOHNSON: Dr. Bockman?
6 DR. BOCKMAN: Thank you. I'm a little POME'd
7 out, so I want to go back to the fact that if you
8 review the literature, there are -- there appear to be
9 differences in the metabolism of the different
10 formulations of testosterone. And, specifically, there
11 are publications in the endocrine literature showing
12 that the undecanoate formulation of testosterone
13 results in doubling, compared to the enanthate, of DHT,
14 dihydrotestosterone.
15 So I want to come back to the question,
16 because there were some -- there was evidence, and I
17 was wondering if some of the clinicians with long-term
18 use of this agent that you brought, whether they can
19 comment on the fact whether there is increased prostate
20 enlargement. There are some rises that occur in PSA,
21 but actual increase in prostate enlargement in the
22 patients who are on this formulation.

1 Is there increased baldness that occurs over
2 long-term use? Because presumably these agents are
3 going to be utilized predominately for long-term use.
4 And is there any evidence of increased testicular
5 atresia from this particular formulation?
6 DR. CASTY: Dr. Zitzmann, would you like to
7 DR. ZITZMANN: Yes, thank you. Actually,
8 these were different questions you were asking. I
9 would like to refer to our trials in male
10 contraception, where we have tested several esters for
11 male contraception to suppress gonadotropins and to
12 suppress sperm counts, and, of course, intratesticular
13 testosterone production. And there, a comparison is
14 possible to the esters. And basically, what we wanted
15 to achieve in these trials is, of course, reduction of
16 sperm count down to azoospermia and testicular
17 shrinkage.
18 What we have seen is for the enanthate ester
19 that was given weekly in comparison to Nebido, which
20 was given every eight weeks, which is not according to
21 the normal label of treatment, there was the same rate
22 of testicular shrinkage, which recovered after we

1 stopped.

2 Then I would like to mention -- and probably

3 you are referring to testosterone undecanoate in its

4 oral form that was used? No? You're referring to the

5 injectable?

6 DR. BOCKMAN: Schubert's study.

7 DR. ZITZMANN: Oh, the Schubert study, yeah,

8 because that is compared to the enanthate ester.

9 Basically, I think -- well, to what I know is that

10 these levels of DHT were not significantly different.

11 And in addition to that, there's no data on balding

12 concerning higher levels of DHT. Thank you.

13 DR. BOCKMAN: Just a quick follow-up, this

14 formulation with castor oil and -- is this a

15 proprietary formulation?

16 DR. CASTY: Dr. Frank Diana from our

17 Formulation Department can address that question for

18 you.

19 DR. DIANA: Dr. Frank Diana from

20 Pharmaceutical Development at Endo. Yes, it is

21 patented.

22 DR. JOHNSON: Question from FDA?

1 DR. HIRSCH: To respond to Dr. Swenson about
2 the other injectable testosterone products, we had a
3 brief moment to count, and over the last ten years,
4 2003 to 2012, we count four anaphylaxis cases and two
5 POME cases in all of AERS for all injectable
6 testosterone products. And this has to be taken in
7 light of the increasing usage, as shown by Dr.
8 Kornegay. So if there is a major problem, it is
9 unclear why we wouldn't be seeing reports in AERS for
10 the other injectable testosterone products, why we
11 would have two cases of POME in ten years.
12 DR. JOHNSON: Dr. Clarke?
13 DR. CLARKE: In terms of the risk mitigation
14 strategies, we talked about reducing the dose. There's
15 been discussion of the formulation. What about
16 premedication with other agents, such as steroids, for
17 example, specifically in regards to the castor oil or
18 the benzyl benzoate issue? Is there any experience
19 that steroid premedication, for example, or other might
20 be beneficial in limiting or eliminating anaphylactic
21 reaction?
22 DR. CASTY: Well, these are events that, as

1 you, I think, heard this morning, are really quite
2 infrequent, so premedicating people, I think, would be
3 a difficult challenge to justify. But we did look for
4 risk factors to see if we could identify risk factors
5 in our clinical studies and post-marketing studies, and
6 I'll ask Dr. Danoff to make a few comments in terms of
7 what we saw there.
8 DR. DANOFF: So we -- there were obviously no
9 anaphylaxis cases in our clinical trial, and -- I'm
10 sorry to have to say POME again -- there were only
11 three POME cases in our clinical trial, so we weren't
12 able to look from the clinical trial, but we did
13 analyze the data from the post-marketing reports, and
14 the way we did that is we looked at -- we tried to
15 identify factors that we thought might be associated
16 with anaphylaxis, things including ACE inhibitors,
17 history of drug allergies to other drugs or history of
18 asthma, for instance. And we looked in the cases that
19 were adjudicated for anaphylaxis, and we abstracted
20 their medication use.
21 As a control group, we took the other cases
22 in the post-marketing reports for Nebido that were not

1 POME or anaphylaxis, so the rest of them, and used them
2 as the control group. And we looked -- we weren't able
3 to find any risk factors. Either we weren't able to
4 show that ACE inhibitors specifically were risk
5 factors, nor were we able to show that any of these
6 allergic conditions were risk factors. Now, of course,
7 it has to be remembered that there were very few
8 events.
9 DR. JOHNSON: Dr. Nelson, was that a
10 corollary or a separate question?
11 DR. NELSON: I'm sorry? Were you asking --
12 DR. JOHNSON: Oh, actually, now we're going
13 to move on to Dr. Morrato.
14 DR. MORRATO: I just had a last couple
15 questions related to the assessment piece that you were
16 talking about. So I'm trying to remember -- you had a
17 nice -- aware, prepare -- I can't remember what --
18 manage.
19 DR. CASTY: Prepare and manage.
20 DR. MORRATO: All right. Yes, so I'm trying
21 to look at how your assessment matches up with those
22 goals.

1 DR. CASTY: Uh-huh.
2 DR. MORRATO: Okay? So I can understand how
3 a survey is good at measuring awareness, but self-
4 reported behaviors that relate to preparation or manage
5 are not always indicative of actual behavior. Did you
6 consider other methods to actually get a better handle
7 of what's happening in practice?
8 DR. CASTY: Dr. Shusterman?
9 DR. SHUSTERMAN: We would certainly consider
10 other methods, but the assessments I mentioned actually
11 are the formal REMS components, so we're required to
12 test the REMS components, and those would be the goals
13 of the REMS. So we --
14 DR. MORRATO: Right.
15 DR. SHUSTERMAN: We --
16 DR. MORRATO: So that's why you --
17 DR. SHUSTERMAN: We could do others. We
18 could survey others to understand behaviors, but --
19 DR. MORRATO: But my --
20 DR. SHUSTERMAN: -- the ones that I showed
21 were
22 --

1 DR. MORRATO: My understanding is that --
2 DR. SHUSTERMAN: -- linked to the REMS.
3 DR. MORRATO: -- the survey's not a
4 requirement, but rather a common tool that's used to
5 evaluate? Do they have to do a survey? They can do
6 any sort of data collection, or am I wrong?
7 DR. ROBOTTOM: This is Suzanne Robottom from
8 the Division of Risk Management with FDA. It is true
9 that the assessments are required. How the assessments
10 are done, there's quite a lot of -- there could be
11 quite a lot of variability. Often, there are surveys,
12 is one of the most common ways, but certainly we'd be
13 open to exploring other options.
14 DR. MORRATO: Yeah. I think that would be
15 important --
16 DR. SHUSTERMAN: As we would.
17 DR. MORRATO: -- if this were to proceed. You
18 know, surveys are definitely of value, but, you know,
19 there are other methods in terms of audits and things
20 like that where you can get a better sense of the
21 waiting time and so forth. So I guess I would just
22 urge you to consider some other ones. And then as it

1 also relates to the time point, I know legally that
2 there's the requirement of 18 months -- what did you
3 have? Three years and seven years? Right?
4 DR. SHUSTERMAN: Yeah.
5 DR. MORRATO: And I know that's sort of a
6 minimal. And did you consider better integration of
7 early on -- I mean, why wait 18 months to find out for
8 instance it's working, especially since the company's
9 obligated to report quarterly on adverse events early
10 on?
11 DR. SHUSTERMAN: Right. In fact, we actually
12 reached the same conclusion that you did, and our first
13 assessment we proposed -- this hasn't been discussed
14 with the FDA -- would be 12 months, not 18 months. You
15 also need time, actually, to collect data and to get
16 agreement on the tools, so you need some leeway in
17 there. So we thought 12 months was the earliest that
18 we could get meaningful data.
19 DR. MORRATO: So we're building in the time
20 period of assuming you're approved, then you develop
21 the survey and negotiate the survey --
22 DR. SHUSTERMAN: Right.

1 DR. MORRATO: -- and then you run it; right?
2 So I know this -- the time element's challenging,
3 right, with approval, but I think this is a general
4 flaw, in that you should not be launching until you
5 know what the measures are that you're measuring and
6 not be negotiating that after the fact. I just think
7 you're missing this window of opportunity in which
8 you're establishing behaviors early on with the early
9 adopters, and by waiting -- you know, it's the
10 equivalent of saying, "I'm going to launch a drug and
11 not look at market share for 12 months, until I figure
12 out how I'm going to collect market share." No one
13 does that; right?
14 DR. SHUSTERMAN: And we'd be happy to start
15 discussions as --
16 DR. SWENSON: Yeah.
17 DR. SHUSTERMAN: -- early as possible.
18 DR. SWENSON: Yeah. So this is not just --
19 you -- it's a general comment. I think we could be
20 thinking more creatively, I guess, is the point. And
21 then the other piece of the assessment that you talk
22 about, which is nice, is this idea of active

1 surveillance.

2 And maybe it's related in part to what you

3 shared with us after lunch, where you're looking at the

4 -- sort of the pharmacoepidemiology kinds of studies.

5 So the strength of those is the degree to which the

6 measures are valid, so do you have data -- you talked

7 about in your presentation about you've tested the

8 ability of the EHR to detect cases of anaphylaxis.

9 Do you have data that you could share with us

10 in terms of the diagnostic validity of how you're

11 collecting it, in terms of what's the false negative

12 rate? And did you do any sort of validation looking at

13 the POME? And that relates to our interpretation of

14 what you shared with us after lunch as well.

15 DR. SHUSTERMAN: Uh-huh.

16 DR. SWENSON: My experience is some coding is

17 very undercoded in claims information, so low rates

18 could be a reflection of just underreporting,

19 undercoding, not necessarily a true rate. So have you

20 performed any sort of validation study with these codes

21 yet?

22 DR. SHUSTERMAN: At this point in time, we

1 haven't. We're at that point where we're developing
2 the methodology for that.
3 DR. SWENSON: Okay. So for us to interpret
4 what you shared with us after lunch, which were the
5 rates with the other ones, we don't have any
6 information on how valid that anaphylactic code is to
7 make an assessment?
8 DR. SHUSTERMAN: That would be subsequent
9 steps we need to take.
10 DR. SWENSON: Okay.
11 DR. SHUSTERMAN: This was literally very
12 recent information that we had available.
13 DR. SWENSON: Okay. No, I think it's good,
14 proceeding along that line. And then the other one is
15 I'm just trying to understand the mechanism of the med
16 guide distribution. All right? So normally when we
17 think of that, it's I'm a patient, I'm going to my
18 pharmacist, I'm picking up my medicine, and I'm getting
19 the med guide from the pharmacy.
20 In this case, the med guide is going to have
21 to come through whoever's performing the injection.
22 Right? And so if it's in a doctor's office, they're not

1 routinely used to distributing med guides, so have you
2 thought through the mechanism of how that's actually
3 going to work? Will the patient really get those med
4 guides before they have the injection, or is it more
5 likely to be handed out?
6
7
8 I mean, this is how it happens when I take my
9 kids in for vaccination. Do you want a vaccination?
10 Yes, and then I get the materials afterwards. Right?
11 So it's not really the same kind of informed discussion
12 or expectation around the med guide.
13 DR. SHUSTERMAN: Well, there are several ways
14 that would be made available. The most important way
15 that would be made available, as I'm showing on the
16 slide here, is it will be in each product carton, and,
17 therefore, the physician or healthcare provider will
18 have it to give it to the patient.
19 And as you said, obviously the ideal is that
20 the patient gets it in advance or, at the very least,
21 that the physician sits down with the patient and goes
22 through it, so one of the major purposes of the med

1 guide is so the patient can make an informed decision
2 about getting AVEED. And that, obviously, is the
3 ideal.
4 DR. SWENSON: And so the only way we'll know
5 whether or not that's being handed out currently with
6 the assessment plan is at 18 months or 12 months,
7 you'll survey patients. "Did you get a med guide?"
8 DR. SHUSTERMAN: Well, that's how a survey --
9 we could look into other methodologies, as the FDA
10 mentioned. And I should also mention in the "Dear
11 Healthcare Provider" letter, that also instructs, as
12 does the label, the prescribing physician to provide
13 the medication guide to the patient before they receive
14 the medication.
15 DR. SWENSON: Okay. Thank you.
16 DR. JOHNSON: Dr. Ownby?
17 DR. OWNBY: Yeah, I wanted to come back to
18 Dr. Clarke's question about premedication for
19 anaphylaxis. And my experience nationally goes back to
20 the epidemic we had of latex allergy about 20 years
21 ago, and it became very obvious that premedication was
22 totally ineffective -- well, at least in the

1 prevalence. You might argue that it saved some lives.
2 But it also, I think, showed that problems we
3 had with voluntary reporting, because I had the
4 dishonor of presenting and publishing the one fatal
5 case in the State of Michigan, but I'm aware of four
6 other cases that were not reported at all and never
7 showed up in the FDA database, so there are certainly
8 problems there.
9 Another thing, though, that hasn't been
10 mentioned at all in this is that I'm not aware that
11 there's any treatment for POME, other than symptomatic
12 support of the patient. Certainly for anaphylaxis, we
13 do think we can treat, although you could argue that
14 with severe anaphylaxis, that it's very touchy anyway,
15 but there's nothing that I've seen the literature could
16 find that there was an adequate treatment there.
17 DR. JOHNSON: I wanted to bring forward a
18 question that came forward during the public hearing.
19 There was some concern expressed by someone who'd used
20 injectable long-term that there was the mood
21 alterations. I also heard that in a statement from the
22 sponsor as well as from some of the other speakers.

1 And I just wanted to know if you'd look at
2 that with this particular injectable testosterone, you
3 put up a slide, CO18, that showed the rapid rise and
4 then gradual fall of testosterone levels with TRT.
5 There it is. But I see that if I look at Figure 6 in
6 your document, it looks very similar with the
7 testosterone preparation. It's a little bit later, it
8 goes up. Looks like it maxes between four and seven
9 days versus in one to two days. But you see this
10 marked rise and then this gradual fall down to the
11 nadir.
12 Have you ever looked to see if that has an
13 effect on well-being? I mean, if you look at your
14 data, it says that up to 12 percent -- this was with
15 their fourth dose -- had reported psychiatric symptoms,
16 but there's nothing asked about mood symptoms or other
17 issues. And the main argument here was that it had an
18 up and down in terms of mood.
19 What do we know about your medication? Is it
20 in some way known to be less of an issue than this
21 medication?
22 DR. CASTY: And I'll ask Dr. Danoff to

1 discuss that.

2 DR. DANOFF: So we did analyze our data for

3 mood swings. We looked at the adverse events, which

4 are shown here from the 725 men in the hypogonadism

5 study, and the frequency was less than 1 percent. In

6 the contraception studies, there were, as we mentioned,

7 more mood -- there were more mood swings, but those

8 patients were also receiving the progestational agents.

9 Just -- at -- you know, obviously when you're

10 comparing -- you can't really compare across products,

11 but just to give you a feel for what some of the other

12 products report, that AndroGel, which was one of the

13 recently approved ones, they report mood swings at 2.6

14 percent. Now, obviously, these are not -- these are

15 across label. These are different studies, but just to

16 give you a feel that we are in the same percentage

17 area.

18 DR. JOHNSON: Dr. Orza?

19 DR. ORZA: There was a slide that was up too

20 quickly for me to read the whole thing that showed the

21 advantages and disadvantages of the different

22 formulations. And was the only disadvantage of the

1 patch the irritation and the fact that you sometimes
2 had to use two, or were there other disadvantages to
3 the patch?
4 DR. CASTY: Dr. Cunningham, would you like to
5 comment on that?
6 DR. CUNNINGHAM: So it may be time for a
7 jest, but, you know, we started out with patches that
8 were transscrotal patches. Those patches fell off, and
9 they weren't very well-accepted. Then there's the
10 transtorso patch. These patches are -- have an
11 adhesive, so they adhere much more effectively than the
12 transscrotal patch, but they're prone to cause rash,
13 and so -- and sometimes more severe rash. So that's
14 one limitation.
15 The second limitation is that a lot of
16 patients cannot get effective blood levels with those
17 patches, so that's another issue. A third issue, they
18 will fall off, particularly in Houston in the
19 summertime.
20 DR. ORZA: What was the rate of the rash?
21 DR. CUNNINGHAM: It really -- the rash
22 frequency varies. It tends to be greater in older

1 patients, but it's probably on the order of 20 plus
2 percent. I think Ron said up to 15 percent, but I
3 think with the patch, it's higher than that.
4 DR. ORZA: And what's the rate of the
5 localized irritation or rash with the injection?
6 DR. CASTY: Dr. Danoff, would you like to
7 address that?
8 DR. DANOFF: So the -- this is the -- from
9 the clinical trials, the injection reaction rate, and
10 what you can see if you -- the pain is about 3.7
11 percent of the patients at -- in the 750 milligram
12 dose. So pain is 3.7, and erythema is 0.7 percent, so
13 the rate is substantially less than those other
14 numbers.
15 DR. JOHNSON: Dr. Woods?
16 DR. WOODS: It occurred to me a few minutes
17 ago that testosterone products are controlled
18 substances, and I was just curious. It sets up some
19 interesting accountability and security issues,
20 certainly, but what are the implications as far as DEA
21 licensure for physicians' offices, if they are now the
22 distributor for these products?

1 DR. CASTY: Dr. Shusterman, would you like to
2 handle that?
3 DR. SHUSTERMAN: You are correct. They are
4 DEA scheduled. They are Schedule III. So it's -- in
5 this case, it's not the facility; it's the prescriber
6 who needs to have a license. So anybody has to have
7 DEA Schedule III clearance in order to prescribe a
8 testosterone product. And, you know, we all apply for
9 our DEA licenses every couple of years, and you have to
10 have DEA III coverage for that, so
11 DR. WOODS: But it seems like there are some
12 variations state to state with respect to distribution
13 and control, and so I guess have you kind of thought
14 through the implications of that and what physicians
15 are going to need to be prepared to buy into?
16 DR. SHUSTERMAN: Yeah, I'm personally not as
17 familiar with the state-to-state variability, so I
18 can't speak in an expert manner to that. So we'd have
19 to work with, you know, each prescriber in each state
20 to properly distribute it.
21 DR. JOHNSON: Dr. Bockman?
22 DR. BOCKMAN: Just a quick comment on that,

1 Dr. Woods. I mean, in New York State, it could be a
2 potentially big problem. If you plan to store any of
3 this stuff in your office, you have to have a safe
4 that's screwed down to the floor or something that just
5 -- I'm serious. You cannot just store testosterone in
6 your refrigerator.
7 DR. JOHNSON: Well, on that insightful note -
8 - oh. Any other issues? Yes, Maria?
9 DR. SUAREZ-ALMAZOR: Yes, I had a question
10 for the FDA. We haven't talked at all about black-box
11 warnings or the potential for that, if the drug were to
12 be approved. Is that something that the FDA has
13 considered?
14 DR. GASSMAN: We will be asking the committee
15 for their input. That's certainly -- if you feel that
16 a black-box warning would be something that should be
17 considered, I think we'd like to hear that, as well as
18 any other comments that you have.
19 DR. JOHNSON: Well, I would again like to
20 thank the committees for their excellent questions and
21 to the FDA and to the sponsor for their lengthy and
22 very intelligent discussions. We're now going to take

1 a brief break, if we could, just five minutes, and then
2 we will, after that -- maybe six minutes. Then we will
3 return, and that will be our opportunity to begin our
4 voting portion of our meeting. So five minutes, and
5 we'll see everyone back.
6 (Whereupon, there was a short break.)
7 Discussion and Vote
8 DR. JOHNSON: If we could be seated within
9 the next minute. Well, if we could all be seated, we
10 will proceed with the next portion of our committee
11 meeting. So now we move on to the voting procedure. To
12 remind the committees, for the voting questions, we
13 will be using our electronic voting system.
14 Once we begin to vote, the numbers will start
15 flashing and will continue to flash until after you
16 have entered your vote. Press the button firmly to
17 correspond to your vote. If you are unsure of your
18 vote and wish to change it, while the button is still
19 flashing, you may do so. Once it stops flashing, the
20 vote is closed.
21 After everyone has placed their vote, it is
22 locked in. It will then be displayed on the screen.

1 The designated federal official will read the vote from
2 the screen into the record. Then we will next go
3 around the room, starting on my right, and each
4 individual who voted will state their name and their
5 vote into the record. At this point, you may state the
6 reason for your vote if you wish to do so. We will
7 continue in this manner until both questions are
8 answered and discussed.
9 So now allow me to read our first question.
10 Given the severe post-injection reactions that were
11 reported with testosterone undecanoate, TU, in clinical
12 studies and post-marketing experience, do you believe
13 that TU is safe for the proposed indication? Please
14 vote.
15 MS. BHATT: The voting results, yes is 9, no
16 is 9, abstain is 0, no voting is 0.
17 DR. JOHNSON: We shall start with -- if we
18 can start on the right.
19 MR. ZAAYER: Thank you. Bob Zaayer. I voted
20 yes. My concern is that we -- I think it was stated
21 earlier we may be holding Endo to a higher level than
22 what has been held in the past. Looking at some of the

1 other depo formulations that are out there, some that
2 use oil bases for carriers and others that don't,
3 virtually all of them list anaphylaxis as one of the
4 severe side effects with that formulation.
5 DR. SWENSON: I voted yes, based on this long
6 history of its use in Europe, with the thought that if
7 truly something was terribly serious about this, it
8 would have emerged. The fact there have been no deaths
9 at all and no apparent sequelae, I think that this is a
10 known risk, and if appropriately addressed to the
11 patient and providers, I think it should be manageable.
12 DR. JOHNSON: Please state your name.
13 DR. OWNBY: Dennis Ownby. I voted yes. I'm
14 persuaded by a long history of use without fatal
15 reactions and the fact that none of our drugs are
16 absolutely safe. Many of them that we're learning
17 about now do have anaphylaxis and other adverse events,
18 but I think those are usually manageable, and I know of
19 nothing that can totally eliminate all risk.
20 DR. NELSON: Lewis Nelson. I voted no. I
21 think that there's a real absence of data to prove that
22 it's truly safe. I think there's relative degrees of

1 safety. I think we could try to improve on the safety,
2 and maybe we'll talk about that with our next question.
3 But I'm still a little bit concerned that we don't
4 truly understand the mechanism of what's happening,
5 which is going to mean it's difficult to predict and to
6 prevent.
7 I do think we need better data to support the
8 safety before I would be willing to say that it's safe
9 to go to broader use, especially once it comes out of
10 clinical trials and into broader use in the U.S. I'm
11 concerned that the populations would change, the
12 indications would broaden, and the use would become
13 more widespread than it already is, lowering the
14 safety.
15 DR. MCCAMMON: Kurt McCammon. I voted yes. I
16 think with the European data and history and with the
17 fact that there is no mortalities associated with the
18 drug, I think it's been shown to be a safe drug.
19 MR. LUSTIG: Craig Lustig. I voted yes, and
20 as others have stated, the experience in Europe and the
21 fact that there haven't been deaths, I feel, is really
22 important. And I think one other comment, because

1 there were several comments made about sort of there
2 are other alternative products and why, therefore, is
3 this needed, and I would suggest, actually, that one
4 thing that we haven't talked about is actually the
5 potential health benefits of patients remaining
6 compliant, being on the drug for a long period of time,
7 and while we may not be able to quantify that, having
8 an additional option that does show the ability to be
9 more patient-friendly, if you will, I think is
10 something of real value.
11 DR. ERSTAD: I'm Brian Erstad. I voted no,
12 and my concern is that it was really not safe from an
13 overall benefit versus risk perspective in the general
14 population for -- which would be indicated and
15 promoted. I do say I really appreciate the need for a
16 long-acting product. I think that's probably safe to
17 say for virtually everyone here, and I'm especially
18 sympathetic for those that need it -- to start it at a
19 young age and have it long-term. But, again, given as
20 to how this is framed and given that it is this
21 relative benefit versus risk issue, again, I felt
22 obligated to say no.

1 DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted
2 yes because I felt that the risk overall was low. I
3 recognize that there were some cases that were very
4 severe, but in general, the numbers were quite low. And
5 I must say, though, that I wasn't entirely happy with
6 the wording of the indication, where it says,
7 "Conditions associated with deficiency or absence of
8 endogenous testosterone," I would have preferred
9 something a little bit more specific, such as
10 "significant symptoms caused by" as opposed to
11 "conditions associated with," which I felt was a little
12 vague.
13 DR. WOODS: Mark Woods. I voted a very
14 conflicted yes. I do share the concerns about safety,
15 but I also believe, based on some of the things we've
16 heard from our experts as well as our consumers today,
17 that there probably is a strong need for another
18 alternative, a long-acting alternative, and as Dr.
19 Erstad mentioned, I think something especially for
20 people that start this at a very young age, an
21 alternative like this would be good.
22 DR. MORRATO: Elaine Morrato, and I voted no,

1 and I would say I was a conflicted no. So this, I
2 think, was pretty challenging. I was persuaded by the
3 FDA's concerns on the seriousness of the events. I
4 think they look at these kinds of cases across many
5 different kinds of drugs, so for them to have noted the
6 seriousness of it and so forth, I pay attention to
7 that.
8 I'm also concerned in terms of the indication
9 as well and how that gets framed, and if it's -- as I
10 think Dr. Orza was saying, you know, there's two
11 populations here of potential kinds of patients, and if
12 it's in a population in which, you know, it's
13 congenital or some other genetic deformity that has led
14 to low T, that's a different kind of indication than
15 the broad use of low T for, you know, sites that are
16 just trying to have youth and vitality clinics.
17 And that was the piece I tried to weigh as to
18 how is it going to really be used in the market? And
19 what persuaded me is I'm fearful that it's more being
20 used, as sales have doubled in the last four years, for
21 this general population, and so that's why I voted no.
22 DR. COOPER: William Cooper. I voted yes.

1 And I found this a difficult decision as well. I
2 appreciate the position that the FDA has taken into
3 wanting to ensure public safety and having concerns
4 about both the severity and the potential rate of these
5 events, but in looking at the experience in Europe and
6 looking at other experiences, I didn't find anything
7 that was compelling enough to lead me to think that the
8 rate of events would be of a magnitude that would make
9 me concerned about the overall safety of the drug.
10 DR. JOHNSON: Julia Johnson. I voted no. I
11 think that, you know, the FDA initially, back in 2007,
12 was concerned about this product based on that initial
13 information, and they put forward some fairly
14 challenging remediation criteria for the sponsor,
15 including a new formulation and really seriously
16 limiting the use. So I can see that indeed it put a
17 great pressure on the sponsor, and then they continued
18 to use it, as people have said, in another environment
19 or another part of the country without a marked
20 increase in adverse events.
21 However, I am concerned that the post-
22 reaction data is sufficient, even though it's been nine

1 years of use, that the risks outweigh the benefits. So
2 because there is no real recognition of a change in
3 these adverse events since it was first reviewed, I
4 believe that nothing seriously has changed.
5 The only qualm I had was that indeed the
6 long- term use appears to be advantage, especially for
7 the younger population, as others have said. I would
8 caution in terms of who is given this medication for
9 use, should it be approved.
10 DR. HOEGER: Kathleen Hoeger, and I voted no.
11 DR. JOHNSON: Please syndrome.
12 DR. HOEGER: I did. The conflict, as it's
13 been stated before, I think, has to do with the
14 question of the population, and clearly as a long-term
15 agent, those that are most severely affected would
16 really benefit from this. And I wavered for a while
17 between those two because of that, but I do think that
18 the potential for broad use and what we have seen,
19 including the FDA's appropriate concerns, push me
20 towards no.
21 DR. CLARKE: Bart Clarke. I also had a
22 difficult time deciding. I think my concern would be -

1 - is that I think a large number of people would use
2 this preparation for convenience and efficacy as well
3 starting at a younger age, and I think the longer-term
4 exposure risk would be one issue.
5 The other fact that the anaphylaxis seems to
6 be unpredictable and seems to be high enough that I'd
7 say I think it's a concern relative to some of the
8 other options we have currently. So it was mainly the
9 issue of safety that I thought just wasn't quite there
10 yet, admitting that we need a long-term preparation.
11 DR. ORZA: Michelle Orza. I too voted a very
12 conflicted and reluctant yes, and ultimately what
13 tipped it to yes was the sense that this was a good
14 additional option for people who really are dependent
15 on testosterone therapy. But I would like to see the
16 indication really narrowed and the REMS really robust
17 in order to make that a less reluctant yes.
18 DR. KITTELSON: John Kittelson, and I voted
19 no for many of the reasons previously stated and for
20 all the conflicts also previously stated. I was, I
21 guess, worried by the initial FDA concern of years back
22 and what was done to address that; the severity of the

1 events, of the adverse events -- and, granted, it's
2 circumstantial evidence, given all the biases that can
3 be part of all of this, but in this situation, I
4 believe that the burden of proof is on the sponsor to
5 show that it is, in fact, safe. And so, ultimately,
6 that tipped my vote toward the no.
7 DR. CURTIS: Kate Curtis. I voted no, and
8 it's -- obviously, it's clear that these severe
9 reactions occur, and then in the absence of any context
10 to determine whether this is some appropriate level of
11 risk or not, it wasn't clear to me that the benefits
12 outweighed the risks, so I voted no.
13 I wanted to say I'm sympathetic to the
14 indication idea that other people have mentioned in Dr.
15 Orza's group one of people who are really dependent on
16 this, and a suggestion that was mentioned at the very
17 end of our discussion, black-box warning. And I might
18 suggest to the FDA to consider that a little further
19 and whether that would help in this case.
20 And, finally, we did sort of touch on some
21 creative ideas about how to get a better handle on the
22 risk, both with these drugs and similar drugs, using

1 other large databases, either here or in Europe, and
2 that may not exist exactly what we want it to be now,
3 but I think there should be ways to make that exist so
4 we can get a better handle on this.
5 DR. BOCKMAN: Richard Bockman, and I voted
6 no. I was -- I thought the pharmacokinetic profile of
7 the drug combination was very favorable; however, the
8 severity of the adverse events with regards to POME and
9 anaphylaxis, I think, abrogated the pharmacokinetic
10 advantage. And, ultimately, I thought that the risk-
11 benefit was unfavorable.
12 DR. JOHNSON: Thank you to all of the members
13 of the committee. Let me briefly summarize, and then
14 feel free to make any corrections. So those who voted
15 yes basically expressed concern that Endo is being put
16 at a higher standard. This is a medication that has
17 been used now for many years in Europe. There are no
18 reported deaths. There is a clear indication for this
19 treatment with this medication.
20 In terms of the risk, the anaphylaxis, and
21 the POME, the thought is that these are recognized
22 complications from other medications -- we can't

1 prevent all risks with all medications -- and,
2 therefore, that this was acceptable when you consider
3 the benefit versus the risk.
4 There was also a statement that indeed there
5 is a improvement in compliance. This is a more
6 patient- friendly, to use someone's term, medication,
7 especially for our younger population who has to use it
8 for many years.
9 Overall, the significant symptoms related to
10 low testosterone do deserve treatment, and that the
11 results are compelling enough to consider proceeding
12 with this medication, although some improvement in the
13 REMS was raised.
14 Now, to those who voted -- oh, any comments
15 from those who voted yes? Thank you. For those who
16 voted no, there was thought to be insufficient data to
17 really be satisfied that indeed this medication is
18 safe, and, in fact, the risks do outweigh the benefits,
19 especially for the general population.
20 A long-acting agent such as this may have
21 some potential benefit, but it also has some potential
22 harm. There was concern that once this is brought

1 forward, that it may be much more heavily used in our
2 population and markedly increase their risk. There was
3 the comment that the FDA was persuasive in terms of
4 their concerns, having fully reviewed the post-
5 injection data.
6 There also was the recognition that both POME
7 and anaphylaxis are not things that can be predicted,
8 and when we have a medication that can increase the
9 risk of these unpredictable events, that that was of
10 concern. And then also some thoughts about changes in
11 terms of recommendations and, if it is approved, to use
12 a black box and to continue to follow the database. Any
13 other thoughts from those who voted no?
14 So thank you very much. Now we'll move on to
15 Question Number 2. So whether you voted yes or no to
16 Question 1, please vote whether the applicant's
17 proposed instructions for use of product labeling that
18 testosterone undecanoate be administered using a slow,
19 30-to-60-minute injection, and that patients remain in
20 the office for 30 minutes post-injection, would be
21 sufficient to ameliorate the risk of severe post-
22 injection reactions. If you could please vote.

1 MS. BHATT: The voting results, yes is 1, no
2 17, abstain 0, no voting 0.
3 DR. JOHNSON: Thank you. This time, let's
4 start on the other side with Dr. Bockman.
5 DR. BOCKMAN: Once again, I had trouble with
6 the logic of the question, because we don't know the
7 mechanism for the severe adverse events that we're
8 discussing, and, therefore, how could we possibly know
9 the solution? Nevertheless, my problem was that we
10 basically don't know the efficacy of these remedial
11 actions of slowing the injection or keeping the problem
12 in the office for 30 minutes. And I also was not
13 convinced of what the efficacy of the educational
14 program would be. So for those reasons, I voted no.
15 DR. CURTIS: Kate Curtis. I also voted no,
16 and I agree with what Dr. Bockman said, but also I
17 think the sponsor did recommend a broader package of
18 REMS, which I would certainly encourage that with --
19 including the assessments, and as was mentioned in the
20 discussions, probably some better assessments than just
21 surveys of behavior and what's actually going on.
22 DR. KITTELSON: John Kittelson. I voted no.

1 And I agree with the summary by Dr. Bockman. The only
2 thing I would add is that it seems like the program
3 might be difficult to implement in a way where you can
4 actually measure its quality and assure its objectives.
5 Thanks.
6 DR. ORZA: I voted -- Michelle Orza. I voted
7 no because in the current state, it doesn't support my
8 earlier yes vote, and I think that a lot of the things
9 that have been suggested around the labeling, I think
10 the black box is a good idea. I think anything that
11 can be done with the REMS to narrow the indication and
12 the population to which it gets offered -- I don't know
13 if -- you know, we had a discussion earlier about
14 guidelines. I don't know if distributing the guidelines
15 requiring that We also talked earlier about the allergy
16 testing to help prevent the anaphylactic, and even
17 though that would be onerous, I think it would be
18 worthwhile, because we could eliminate that. And I
19 think, you know, in terms of the bigger picture, we
20 just -- there just needs -- this is not FDA's
21 bailiwick, but there needs to be much better
22 information available to patients when considering this

1 option.

2 DR. CLARKE: Bart Clarke. I voted no as

3 well. I think the items mentioned make sense

4 clinically. They make perfect sense, especially where

5 we don't really know what the risk is, but I'm not sure

6 that doing these things will ameliorate the risk of the

7 reaction. The reactions seem to be unpredictable and,

8 like anaphylaxis, it's oftentimes not able to be

9 identified through risk factors. So doing these things

10 makes sense, but I don't think it's going to actually

11 minimize the risk of the injection reaction when it

12 occurs.

13 DR. HOEGER: Kathleen Hoeger, and I voted no

14 for similar reasons. And a little education concern

15 that others have raised and applying this to

16 populations where there may be increased risk, because

17 we don't have that in the dataset, but there may indeed

18 be conditions for which we would not want to expose

19 this risk. And it wasn't clear that that that would

20 come through, based on what was proposed.

21 DR. JOHNSON: Julia Johnson. I voted no. I

22 think there may be some value in just guidelines, as

1 was already stated. In terms of this not being the
2 first choice of treatment, in terms of it being really
3 something more appropriate for someone who does require
4 long-term use of this medication, someone with primary
5 hypogonadism.
6 I really also think that there would be some
7 value in considering who should not use it. I know
8 that that's not occurred in Europe, but if you have
9 someone with severe uncontrolled asthma or serious
10 cardiovascular disease, I would say that it's a
11 reasonable caution to advise against use in those
12 individuals.
13 DR. COOPER: William Cooper. I voted no,
14 particularly for many of the reasons previously stated,
15 those reasons stated by Dr. Bockman, and then the
16 additional measures stated by Dr. Orza, I completely
17 agree with. I think those will be important.
18 One additional thought I would have is that
19 the data from -- presented by the FDA suggested that
20 only a fourth of these medications are administered in
21 specialists' offices, in urologist's office, and a lot
22 of those are in general practice settings. And so a

1 risk management scenario that would ensure that if the
2 drug were used, that there are appropriate
3 resuscitative measures and training in place in those
4 settings where they're going to be administered,
5 acknowledging the fact that it's not just going to be
6 where we would think it would be logically, but it's
7 going to be used in a more widespread setting.
8 DR. MORRATO: I'm Elaine Morrato, and I voted
9 no for all of the reasons that have been previously
10 stated. I'm just going to make one point that relates
11 to the risk assessment or the assessment of the plan. I
12 would encourage the FDA and the sponsor to consider
13 better integration of the evaluation with their regular
14 pharmacovigilance reporting, so earlier rather than
15 later, assessment.
16 And I liked the idea of the active
17 pharmacovigilance that they had planned, but I -- it
18 wasn't explicitly stated, but I would hope that this
19 would be something that the FDA would review the
20 protocol, the validity of the measures, et cetera, and
21 that would be part of sign-off by FDA as well.
22 DR. WOODS: Mark Woods. I voted no and was

1 not at all conflicted. I think the system, as
2 designed, did not make me feel very good about my yes
3 vote. I also think that there are some -- needs to be
4 some serious rethinking about the distribution network
5 and some of the downstream issues that come with that.
6 DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted
7 no. I think the instructions for the use, the way they
8 are presented, are generally okay, but there are pieces
9 that are missing that have been mentioned by others,
10 and I would be a proponent of a black-box warning. I
11 think that's really necessary.
12 DR. ERSTAD: Brian Erstad. No. Events
13 unpredictable, so they're non-preventable; plus, I have
14 concerns related to the prompt recognition and
15 treatment in many of the administration settings. Also,
16 even with labeling changes, I think the benefit would
17 not exceed the risk in the general low T population,
18 given the difficulties in enforcing these
19 administration and monitoring restrictions, and while
20 limiting to particular patient subgroups and M.D.
21 specialties might help, but then you run into
22 these practicality and feasibility issues.

1 And, finally, something that I raised in my
2 second question of the morning, I think how the
3 information is presented to patients is critical,
4 especially if this is approved, because I suspect many,
5 if not most, patients in the general population, if
6 they were to receive this, would -- many of those would
7 actually refer more to frequent dosing interval, if
8 they were informed they're potentially rare, but
9 serious side effects. And so I think how this is
10 presented to the patients is crucially important.
11 MR. LUSTIG: Craig Lustig. I voted no,
12 largely because -- I almost voted -- I almost
13 abstained, because clearly there's no evidence to
14 support whether this is effective or not, but I voted
15 no. And I would just add one more thing, which I find
16 -- around these issues of REMS and control and
17 supplying and all of that, which I find sort of
18 peculiar, because as a patient who's been on
19 replacement testosterone therapy for now just a little
20 bit over 20 years and have used every delivery
21 mechanism that's kind of come through over time, and
22 given the data that we saw about the drop-off in

1 patient compliance for those chronic use -- I don't
2 share the fears about that even with -- will likely be
3 vigorous promotion, as we know there are with some of
4 the other products. I don't necessarily share that
5 same concern.
6 These products, no matter -- if this is
7 approved, it's one more option for patients and may be
8 easier for some people, but all of them come with
9 challenges, and I don't have the same -- I really just
10 don't share those same concerns about there being
11 inappropriate use or use by patients for whom there
12 aren't really the appropriate symptoms to suggest that
13 they actually need to be on a replacement testosterone
14 therapy.
15 DR. MCCAMMON: Kurt McCammon. I voted no. I
16 want to echo the comments of Dr. Bockman and Dr.
17 Cooper. I think it's -- Dr. Cooper's comments about
18 making sure that the physicians are aware, maybe
19 consider an online course or 30 minutes where they can
20 take some quiz afterwards to confirm that they
21 understand the severe effects of the medication or the
22 complications that are associated would be appropriate.

1 DR. NELSON: Sorry. Lewis Nelson. I voted
2 no. And I think, you know, my general approach to this
3 is that we're looking at several different issues, each
4 of which is complicated. You know, we want to secure a
5 specific indication, we want to prevent abuse, we want
6 to collect data, and I don't think we can do that with
7 the -- and, of course, ensure safety. I don't think we
8 could do that with the system that has been suggested.
9 You know, I'm a believer in implementing
10 fairly ironclad REMS that could then be scaled back.
11 And Dr. Robottom's suggestions might have been a little
12 strong, perhaps, and you didn't think they were the
13 right model, but some of the suggestions that have come
14 from around the table, I think, are very reasonable as
15 first starts to ensure that things go well, and when we
16 find that this isn't a problem, or that it's a problem
17 that's mitigatable, in some way we can always remove
18 some of the aspects of the REMS or eliminate it
19 altogether. But I would suggest, which is what you're
20 looking for, some sort of strengthened REMS.
21 DR. OWNBY: Dennis Ownby. I voted yes. I'm
22 obviously the Lone Ranger here. There are both the

1 problem of words, what is safe and what is ameliorate,
2 and I hate to sound like a lawyer, but defining those
3 are obviously critical to our deliberations today. And
4 I find them very difficult, because I don't think it's
5 possible to eliminate all risk in our practice of
6 medicine with agents that have any great biologic
7 effect.
8 Related to that, perhaps I'm persuaded by the
9 fact that I've been a practicing allergist for almost
10 40 years, and giving allergy injections is asking to
11 treat anaphylaxis frequently, and these are the same
12 kind of guidelines that we follow for allergy that we
13 followed for many of the new biologic agents that have
14 a relatively high rate of anaphylaxis, and so I thought
15 that those were reasonable suggestions.
16 I'm also a little concerned by the fact that
17 our -- the longer we delay, that means that there are
18 people who need this therapy who will get -- have fewer
19 choices and that that is a concern. You're never sure
20 of what non-approval means in the lives of other
21 individuals.
22 And related to that, I'm also struck by the

1 fact that if you look at the clinical trials data,
2 there is a very marked lack of racial diversity, and
3 suggesting that this isn't a disease of affluence, or
4 at least in the clinical trials data, and that as you
5 have multiple prescriptions and other copays and so on,
6 that certainly limits the people who can apply for
7 therapy. So I thought reasonable restrictions were
8 appropriate, but I thought that those proposed were
9 reasonable and not overly burdensome in our healthcare
10 climate today.
11 DR. SWENSON: Erick Swenson. I voted no.
12 However, I voted no strictly as it was worded. I think
13 that what's there will not prevent this and won't even
14 reduce it, but on the -- thinking of the patient who
15 might experience this, it would certainly be far better
16 to be in a doctor's office than on a bus, with the
17 appearance of these things.
18 But I think -- I move toward yes when I look
19 at the entire package that the sponsor has suggested,
20 and I think there's been so many great ideas here that
21 between the sponsor and the FDA that some possibly
22 slightly stricter REMS program, I think, could address

1 the issues.

2 MR. ZAAYER: Good thing I'm going last. Bob

3 Zaayer, and I voted no. I've got a list of about 12

4 reasons why, so please bear with me. I'm just kidding.

5 It's been so eloquently stated before, so I'm not going

6 to rehash it.

7 DR. JOHNSON: Thank you very much. So allow

8 me to summarize. In terms of voting yes, there was

9 some concern regarding the delay that it would take to

10 bring this to the market and the need that is out there

11 for this product. This is a very similar program to

12 the one that's currently used for other injectables,

13 such as allergy medications; and that, indeed, safety

14 is very difficult to truly identify, and this was a

15 reasonable restriction in administration.

16 In terms of those voting no, we had the

17 recognized issue that indeed the risk is unknown and

18 very difficult to predict and therefore the 30-minute

19 timeframe may not be of sufficient value. Having said

20 that, there was a general consensus to strengthen the

21 REMS proposal to assure that the educational value is

22 readable and usable by patients, that there indeed is a

1 strong training program for physicians who are going to
2 administer this medication.
3 There also was a thought that indeed there
4 may be some limitations in terms of the sites where
5 this is offered, not just that there be training, but
6 also that there is the opportunity for resuscitation to
7 give reassurance, should an adverse effect -- event
8 occur.
9 There was also statements that a black box
10 may be needed. There was also thoughts that perhaps
11 the indication may be narrowed with some strict
12 guidelines for use and for this not to be a medication
13 that is a first choice; however, good comment was made
14 that it really has to be considered for each individual
15 and that physicians do that already and we don't need
16 to presume that this will be immediately a heavy (sic)
17 used medication.
18 There was also a very important statement
19 regarding continuing the pharmovigilance (sic), that
20 there should be early reporting, that we really need to
21 look and see how this information is being communicated
22 to make sure that it's being -- that it is effective

1 and that we need to have a network that allows us to
2 look at the outcomes of this REMS to make sure that it
3 is offering the best safety to patients; and, finally,
4 that allergy testing, although it may be a -- something
5 that would be an impediment, should at least be
6 considered.
7 So comments or corrections? So I would like
8 to offer my most sincere appreciation to the committees
9 for your great work. We're hopeful that this is
10 helpful to the FDA and also to the sponsors in moving
11 forward. And please, everyone, have a safe trip home.
12 Thank you.
13 (Whereupon, at 3:31 p.m., the meeting was
14 adjourned.)
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