



U.S. Food and Drug Administration

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

WEDNESDAY, DECEMBER 1, 2010

8:00 a.m. to 5:00 p.m.

FDA White Oak Campus
Building 31, The Great Room
White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, Maryland

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1	I N D E X	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Wyndham Wilson, M.D., Ph.D.	14
5	Conflict of Interest Statement	
6	Nicole Vesely, Pharm.D.	17
7	Opening Remarks	
8	Richard Pazdur, M.D.	22
9	Sponsor Presentation - Proscar	
10	Introduction, Regulatory History	
11	Vivian Fuh, M.D.	29
12	Prostate Cancer Prevention Trial	
13	Ian Thompson, Jr., M.D.	34
14	Labeling Proposal	
15	Vivian Fuh, M.D.	63
16	FDA Presentation	
17	NDA 020180/s034: Proscar	
18	Marc Theoret, M.D.	67
19		
20		
21		
22		

1	I N D E X (continued)	
2	AGENDA ITEM	PAGE
3	Sponsor Presentation - Avodart	
4	Introduction	
5	Paolo Paoletti, M.D.	102
6	Efficacy and Safety	
7	Gerald Andriole, M.D.	106
8	High Grade Cancers	
9	Christopher Logothetis, M.D.	115
10	Clinical Perspective	
11	Claus Roehrborn, M.D.	125
12	Risk Management and Concluding Remarks	
13	Anne Phillips, M.D.	136
14	FDA Presentation	
15	NDA 21319/s024: Avodart	
16	Yang-Min Ning, M.D., Ph.D.	143
17	Comparison of PCPT and REDUCE	
18	Marc Theoret, M.D.	173
19	Speaker Presentation	
20	Comments on Chemoprevention for	
21	Prostate Cancer	
22	Peter Scardino, M.D., FACS	187

1	I N D E X (continued)	
2	AGENDA ITEM	PAGE
3	Speaker Presentation	
4	The Use of 5a-reductase Inhibitors (5-ARIs)	
5	for the Chemoprevention of Prostate Cancer	
6	Patrick Walsh, M.D.	213
7	Questions to Presenters	234
8	Open Public Hearing	327
9	Questions to ODAC and ODAC Discussion	333
10	Adjournment	395
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. WILSON: Ladies and gentlemen, I would like to welcome you all to today's ODAC meeting where we will be discussing two agents for the prevention of prostate cancer. And I would like to have each member of the panel introduce themselves, and why don't we start on the left side? And if you could just say your name and your specialty. Thank you.

DR. PAZDUR: Richard Pazdur, Office of Oncology Drug Products.

DR. KEEGAN: Patricia Keegan, Office of Oncology Drug Products.

DR. THEORET: Marc Theoret, Office of Oncology Drug Products.

DR. NING: Max Ning, medical officer, FDA.

DR. ROSNER: Inger Rosner, urologic oncology, Walter Reed Army Medical Center.

DR. KIEFERT: Jim Kiefert, patient representative.

1 DR. MAJUMDER: Mary Majumder, acting
2 consumer representative.

3 DR. LOEHRER: Pat Loehrer, medical
4 oncologist from Indiana.

5 DR. KELLY: William Kelly, medical
6 oncologist from Tom Jefferson University.

7 DR. VESELY: Nicole Vesely, designated
8 federal official, ODAC.

9 DR. WILSON: Wyndham Wilson, medical
10 oncologist, NCI.

11 DR. FREEDMAN: Ralph Freedman, gynecologic
12 oncologist, MD Anderson Cancer Center.

13 DR. SEKERES: Mikkael Sekeres, medical
14 oncologist, Cleveland Clinic.

15 DR. TEMPERO: Margaret Tempero, medical
16 oncologist, University of California, San
17 Francisco.

18 DR. LOGAN: Brent Logan, biostatistician,
19 Medical College of Wisconsin.

20 DR. D'AGOSTINO: Ralph D'Agostino,
21 statistician, Boston University.

1 DR. FURGERG: Curt Furberg, Wake Forest
2 University, public health.

3 DR. GARNICK: Marc Garnick, medical
4 oncologist, Beth Israel Deaconess Medical Center,
5 Boston.

6 DR. HAWK: Ernie Hawk from the Division of
7 Cancer Prevention, MD Anderson.

8 DR. STEERS: Bill Steers, urologist,
9 University of Virginia, Charlottesville.

10 DR. CURT: Gregory Curt, medical oncologist
11 and industry representative to ODAC.

12 DR. WILSON: Welcome. For topics such as
13 those being discussed at today's meeting, there are
14 often a variety of opinions, some of which are
15 quite strongly held. Our goal is that today's
16 meeting will be a fair and open forum for
17 discussion of these issues and that individuals can
18 express their views without interruption. Thus, as
19 a gentle reminder, individuals will be allowed to
20 speak into the record only if recognized by the
21 chair. We look forward to a productive meeting.

1 In the spirit of the Federal Advisory
2 Committee Act and the Government in the Sunshine
3 Act, we ask that the advisory committee members
4 take care that their conversations about the topic
5 at hand take place in the open forum of the
6 meeting. We are aware that members of the media
7 are anxious to speak with the FDA about these
8 proceedings. However, FDA will refrain from
9 discussing the details of this meeting with the
10 media until its conclusion. Also, the committee is
11 reminded to please refrain from discussing the
12 meeting topic during breaks or lunch. Thank you.

13 Now we will have a conflict of interest
14 statement read.

15 **Conflict of Interest Statement**

16 DR. VESELY: The Food and Drug
17 Administration is convening today's meeting of the
18 Oncologic Drugs Advisory Committee under the
19 authority of the Federal Advisory Committee Act of
20 1972. All members and temporary voting members of
21 the committee are special government employees or
22 regular federal employees from other agencies and

1 are subject to federal conflict of interest laws
2 and regulations.

3 The following information on the status of
4 the committee's compliance with federal ethics and
5 conflict of interest laws, covered by but not
6 limited to those found at 18 USC Section 208 and
7 Section 712 of the Federal Food, Drug and Cosmetic
8 Act, is being provided to participants in today's
9 meeting and to the public. FDA has determined that
10 members and temporary voting members of the
11 committee are in compliance with federal ethics and
12 conflict of interest laws.

13 Under 18 USC Section 208, Congress has
14 authorized FDA to grant waivers to special
15 government employees and regular federal employees
16 who have potential financial conflicts when it is
17 determined that the agency's need for particular
18 individual services outweighs his or her potential
19 financial conflict of interest.

20 Under Section 712 of the FD&C Act, Congress
21 has authorized FDA to grant waivers to special
22 government employees and regular federal employees

1 with potential financial conflicts when necessary
2 to afford the committee essential expertise.

3 Related to the discussions of today's
4 meeting, members and temporary voting members of
5 the committee have been screened for potential
6 financial conflicts of interest of their own as
7 well as those imputed to them, including those of
8 their spouses or minor children and, for purposes
9 of 18 USC Section 208, their employers. These
10 interests may include investments, consulting,
11 expert witness testimony, contracts, grants,
12 CRADAs, teaching, speaking, writing, patents and
13 royalty and primary employment.

14 Today's agenda involves, one, discussion of
15 supplemental indication for GlaxoSmithKline's
16 Avodart, dutasteride, for the proposed indication
17 of reduction in the risk of prostate cancer in men
18 at increased risk of developing the disease, and,
19 two, discussion of the prostate prevention trial
20 which demonstrated a statistically significant
21 reduction in the seven-year period prevalence of
22 prostate cancer with Proscar, finasteride,

1 treatment and which reported an imbalance in high
2 Gleason grade prostate cancers, indicating more
3 aggressive cancers in the Proscar, finasteride,
4 treatment arm versus placebo.

5 Merck's Proscar, finasteride, was approved
6 by the agency in 1992 for treatment of symptomatic,
7 benign prostate hyperplasia in men with an enlarged
8 prostate. There is no proposed expansion of the
9 indication for Proscar; however, the efficacy and
10 safety of both Proscar and Avodart for use in
11 prostate cancer risk reduction will be examined by
12 the committee.

13 This is a particular matters meeting during
14 which specific matters related to GlaxoSmithKline's
15 Avodart, dutasteride, and Merck's Proscar,
16 finasteride, will be discussed. Based on the
17 agenda and all financial interests reported by the
18 committee members and temporary voting members, no
19 conflict of interest waivers were issued in
20 connection with this meeting.

21 To ensure transparency, we encourage all
22 standing committee members and temporary voting

1 members to disclose any public statements that they
2 have made concerning the products at issue.

3 With respect to FDA's invited industry
4 representative, we would like to disclose that
5 Dr. Gregory Curt is participating in this meeting
6 as a nonvoting industry representative acting on
7 behalf of regulated industry. Dr. Curt's role at
8 this meeting is to represent industry in general
9 and not any particular company. Dr. Curt is an
10 employee of AstraZeneca.

11 We would like to remind members and
12 temporary voting members that if the discussions
13 involve any other products, firms or issues not
14 already on the agenda for which an FDA participant
15 has a personal or imputed financial interest, the
16 participants need to exclude themselves from such
17 involvement, and their exclusion will be noted for
18 the record.

19 FDA encourages all other participants to
20 advise the committee of any financial relationships
21 that they may have with any firms at issue. Thank
22 you.

1 DR. WILSON: I would like to now invite
2 Dr. Pazdur to give opening remarks.

3 **Opening Remarks**

4 DR. PAZDUR: Good morning. Two supplemental
5 applications, one for Proscar and one for Avodart,
6 will be discussed today dealing with the use of
7 5 alpha-reductase inhibitors for reduction in risk
8 of prostate cancer, commonly referred to as a
9 chemoprevention strategy. Both Proscar and Avodart
10 are 5 alpha-reductase inhibitors and have been
11 previously marketed for the treatment of
12 symptomatic benign prostatic hyperplasia in men
13 with enlarged prostates.

14 The first applicant, Merck, the commercial
15 applicant for Proscar, has not proposed a new
16 indication for reduction in risk of prostate
17 cancer, but has proposed to include information in
18 the clinical study section and in the adverse
19 events section of the Proscar or finasteride label.
20 This information is derived from the Prostate
21 Cancer Prevention Trial or PCPT. The proposed
22 changes could be interpreted to suggest that

1 Proscar is safe and effective for the reduction in
2 risk of prostate cancer in otherwise healthy men
3 age 55 years or older.

4 The second application that will be
5 discussed this morning is for Avodart, or
6 dutasteride, for the proposed indication of
7 reduction in the risk of prostate cancer in men at
8 increased risk of developing the disease. This
9 application has been submitted by GlaxoSmithKline
10 and is supported by the REDUCE or reduction by
11 dutasteride of prostate cancer events trial. The
12 population of men in this trial had a negative
13 single prostate biopsy due to clinical concerns and
14 had elevated PSA levels.

15 No other drugs have been evaluated or
16 approved by the FDA for the reduction in risk of
17 prostate cancer. With the known high prevalence of
18 prostate cancer and the heterogeneity of the
19 disease, an effective product for this indication
20 should be evaluated both from the perspective of an
21 individual risk-benefit profile and from a public
22 health risk-benefit profile.

1 A cancer risk reduction strategy exposes
2 individuals who do not have cancer and who may
3 never develop cancer to a drug and its potential
4 for adverse events. Only the highest level of
5 evidence and certainty that a favorable risk-
6 benefit profile exists for the use in healthy
7 individuals should support drug approval. From a
8 public health perspective, a very high level of
9 certainty regarding a favorable risk-benefit
10 profile must exist due to the very large number of
11 men in the United States who could be exposed to
12 the use of these drugs.

13 Dr. Marc Theoret will present the FDA review
14 of the PCPT trial evaluating Proscar. Dr. Max Ning
15 will present the FDA review of the REDUCE trial
16 evaluating Avodart in a prostate cancer risk
17 reduction study. Both Drs. Theoret and Ning's
18 presentations focus on three major issues noted in
19 both applications: first, the increase in high-
20 grade tumors associated with the use of both
21 Proscar and Avodart; second, the fact that risk
22 reduction of prostate cancer is almost entirely

1 limited to tumors that are less than or equal to a
2 Gleason score of 6; third, whether the results are
3 generalizable to the United States' population.

4 The PCPT randomized over 18,000 men age 55
5 years or older without prostate cancer and with
6 normal digital rectal examinations and PSA levels
7 less than 3 nanograms per milliliter at baseline.
8 Individuals were randomized to receive either
9 Proscar or placebo daily for seven years. Men on
10 the Proscar arm of the trial had a 26 percent lower
11 risk of being diagnosed with prostate cancer when
12 compared to the placebo arm. The reduction in risk
13 of prostate cancer was limited to Gleason score 6
14 or lower prostate cancers.

15 An unexpected finding was that men on the
16 Proscar arm had a 1.3 percent absolute increase
17 representing a 26 percent relative increase in
18 high-grade Gleason score 7 through 10 prostate
19 cancers.

20 The REDUCE trial is a randomized, double-
21 blind, placebo-controlled trial of Avodart for four
22 years in men without a diagnosis of prostate cancer

1 but at high risk for prostate cancer at enrollment.
2 Prostate cancer incidence was assessed primarily
3 with scheduled biopsies after two and four years of
4 treatment.

5 Similar to the findings from the PCPT, the
6 REDUCE trial also demonstrated that men on a
7 5 alpha-reductase inhibitor, in this case Avodart,
8 had a 23 percent lower risk of being diagnosed with
9 prostate cancer when compared to placebo. This
10 risk reduction appears limited to decreases in
11 Gleason 6 or 5 prostate cancers but with no
12 decrease in Gleason score 7 to 10 tumors. There
13 was a notable increase in Gleason score 8 to 10
14 prostate cancers with dutasteride.

15 The data from both of these large multi-
16 center placebo-controlled trials were intended to
17 establish a statistically significant reduction in
18 the cumulative incidence of biopsy proven prostate
19 cancer. However, this benefit was driven primarily
20 by a reduction in risk of Gleason score 6 or less
21 prostate cancers. In both trials, there was the
22 unexpected increased detection of high-grade

1 Gleason score 8 through 10 prostate cancers among
2 men receiving 5 alpha-reductase inhibitors.

3 The balance between decreased low-grade
4 prostate cancer, the increased high-grade prostate
5 cancer, and the treatment duration of four to seven
6 years are important in evaluating either drug in a
7 risk reduction strategy in otherwise healthy men 50
8 to 70 years of age. This consideration must be
9 viewed in the context that low risk or very low
10 risk prostate cancers pose little threat to men
11 with life expectancies of less than 10 or 20 years
12 respectively and may be managed by active
13 surveillance.

14 The FDA will be asking ODAC to consider the
15 demonstrated efficacy and safety in the population
16 studied in the respective trials of Proscar and
17 Avodart and to provide advice in response to a
18 single voting question on each product.

19 For Proscar, is the finasteride risk-benefit
20 profile favorable for reduction in the risk of
21 prostate cancer in men greater than or equal to 55
22 years of age with a normal digital rectal

1 examination and a PSA of less than or equal to 3
2 nanograms per milliliter.

3 For Avodart, is the dutasteride risk-benefit
4 profile favorable for reduction in risk of prostate
5 cancer in men at increased risk of developing the
6 disease defined as those who have had a prior
7 negative biopsy due to clinical concern and have an
8 elevated serum prostate specific antigen.

9 Thank you.

10 DR. WILSON: I have a statement to read
11 before we turn to the sponsor.

12 Both the Food and Drug Administration and
13 the public believe in a transparent process for
14 information gathering and decision-making. To
15 ensure such transparency at the advisory committee
16 meeting, FDA believes it is important to understand
17 the context of an individual's presentation. For
18 this reason, FDA encourages all participants,
19 including the sponsor's nonemployee presenters, to
20 advise the committee of any financial relationships
21 that they may have with the firm at issue, such as
22 consulting fees, travel expenses, honoraria and

1 interest in the sponsor, including equity interests
2 and those based upon the outcome of the meeting.
3 Likewise, FDA encourages you at the beginning of
4 your presentation to advise the committee if you do
5 not have any such financial relationships.

6 If you choose not to address this issue of
7 financial relationships at the beginning of your
8 presentation, it will not preclude you from
9 speaking.

10 So with that, let me invite Dr. Fuh from
11 Merck. Thank you.

12 **Proscar Presentation - Vivian Fuh**

13 DR. FUH: Good morning, Mr. Chairman,
14 Dr. Pazdur, members of the advisory committee, and
15 FDA. My name is Vivian Fuh, director of Regulatory
16 Affairs at Merck. In a few moments, you will be
17 hearing from Professor Ian Thompson from the
18 Southwest Oncology Group and principal clinical
19 investigator of the Prostate Cancer Prevention
20 Trial, or PCPT, who will present and discuss the
21 results of this study on behalf of SWOG.

1 In addition to Dr. Thompson, we have several
2 members from SWOG here, including Dr. Cathy Tangen
3 and Ms. Phyllis Goodman, principal and lead
4 statistician for the PCPT, and Dr. Scott Lucia, the
5 principal pathologist for the study.

6 We also have Dr. Janet Wittes who is here as
7 a consultant. Dr. Wittes is a statistician and
8 coauthor on the 2008 clinical practice guideline on
9 the use of 5 alpha-reductase inhibitors for
10 prostate cancer chemoprevention jointly developed
11 by the American Society of Clinical Oncology and
12 the American Urological Association.

13 PCPT was a landmark study that was initiated
14 nearly 20 years ago. The trial was independently
15 sponsored by the National Cancer Institute and
16 conducted by SWOG. Merck supplied study drug
17 Proscar and matching placebo for the study. The
18 study was designed to test the hypothesis as to
19 whether finasteride, 5 milligrams, a type 2
20 5 alpha-reductase inhibitor, would reduce the risk
21 of developing prostate cancer.

1 In 2003, 15 months before the anticipated
2 completion of the PCPT, the data and safety
3 monitoring committee identified that the primary
4 hypothesis was met, that continuation of the trial
5 was unlikely to impact the results and recommended
6 early termination of the study. The study was
7 unblinded and the results reported in 2003. PCPT
8 demonstrated a significant reduction in the period
9 prevalence of histologically proven prostate cancer
10 over the duration of the trial with finasteride
11 relative to placebo. However, an unexpected
12 increase in high-grade prostate cancer was observed
13 with finasteride.

14 Merck promptly and voluntarily filed a
15 labeling supplement shortly thereafter updating the
16 Proscar label to include the high-grade disease
17 findings from the study publication.

18 In 2004, Merck conducted its own data review
19 after receiving the datasets from SWOG. And also
20 during this time, SWOG, Merck and others conducted
21 numerous analyses to further evaluate the high-
22 grade disease findings. The results of these

1 analyses supported the hypothesis that these
2 findings may be explained by detection bias.

3 In 2005, Merck filed a second PCPT labeling
4 supplement for Proscar. The totality of the data
5 from PCPT supported revisions to the labeling,
6 including the addition of primary study outcome as
7 well as information regarding the detection bias
8 that may explain the high-grade findings. Merck
9 did not propose to extend the indication for
10 Proscar for prostate cancer chemoprevention. These
11 changes to the Proscar labeling were consistent
12 with the labeling proposed filed worldwide.

13 At the time, FDA was not supportive of
14 Merck's labeling proposal, stating that the
15 analysis of high-grade findings were hypothesis
16 generating and do not rise to the level of the
17 label and the inclusion of primary study outcome
18 was an implied claim. Based on the clarity of
19 FDA's position, Merck withdrew the labeling
20 supplement in the U.S.

21 Since 2005, multiple additional analyses of
22 PCPT have been published. As you will hear shortly

1 from Dr. Thompson's presentation, these subsequent
2 analyses were consistent with the prior hypothesis
3 of detection bias and expanded our understanding of
4 the sources of potential bias.

5 In 2009, the American Society of Clinical
6 Oncology and the American Urological Association
7 jointly published a clinical practice guideline on
8 the use of 5 alpha-reductase inhibitors for
9 prostate cancer chemoprevention and recommended
10 consideration of the benefits and risks of
11 finasteride treatment for men concerned with their
12 risk of developing prostate cancer.

13 In 2009, FDA expressed intent to discuss the
14 results of PCPT with ODAC. To support the
15 discussions, FDA requested that Merck file a
16 supplemental new drug application with accompanying
17 labeling. Merck responded by filing a labeling
18 supplement in October 2009.

19 Merck's position continues to be that a more
20 complete summary of the PCPT results in labeling
21 allows for better informed decisions by physicians
22 and patients when considering use of Proscar as

1 indicated for the treatment of symptomatic BPH in
2 men with an enlarged prostate. As presented in the
3 briefing document, the proposed labeling with this
4 application incorporates the following features:
5 the addition of the primary study outcome to the
6 high-grade findings, the potential of detection
7 bias to explain the high-grade findings; reference
8 to the ASCO/AUA clinical practice guideline; and a
9 clarification that this information is provided for
10 consideration by physicians when treating men or
11 evaluating men for treatment with Proscar for BPH.
12 As in 2005, Merck did not request an indication for
13 prostate cancer prevention.

14 Well, at this time, I would like to
15 introduce Dr. Ian Thompson, professor and chair,
16 Department of Urology, University of Texas Health
17 Science Center, and the principal clinical
18 investigator for the PCPT.

19 Dr. Thompson.

20 **Proscar Presentation - Ian Thompson, Jr.**

21 DR. THOMPSON: Mr. Chairman, committee
22 members, Dr. Pazdur, thank you for the opportunity

1 to be here. I'm the cancer center director at San
2 Antonio at the University of Texas, and I am
3 representing, along with my colleagues here, the
4 Southwest Oncology Group, without conflicts with
5 regards to the this agent or the company.

6 What we will show today is three things;
7 one, that finasteride significantly reduces a man's
8 risk of prostate cancer; that the increased risk of
9 high-grade tumors observed with finasteride is
10 likely to be due to an artifact due to improved
11 detection; and, finally, that the safety of the
12 product is consistent with its established profile,
13 to include the increased risk of sexual and breast
14 toxicity as well as decreased BPH symptoms and
15 complications.

16 The Prostate Cancer Prevention Trial was
17 funded by the National Cancer Institute, the
18 Division of Cancer Prevention. It was designed and
19 coordinated by the Southwest Oncology Group, and it
20 was initiated in 1993. We employed finasteride 5
21 milligrams versus a matching placebo. The study
22 drug was provided to SWOG and distributed, provided

1 by Merck. It was a randomized, double-blind,
2 seven-year treatment trial of 18,882 men from 218
3 sites in the U.S. and one site in Canada, and it
4 was overseen by an independent data and safety
5 monitoring committee.

6 With regards to prostate cancer, as
7 Dr. Pazdur pointed out, it's a very important
8 public health issue affecting over 200,000 men per
9 year in the United States and associated with over
10 30,000 deaths. Prostate cancer will represent 28
11 percent of all cancer diagnoses in men and 11
12 percent of all cancer deaths among U.S. men. And
13 as a result, the lifetime risk of diagnosis of
14 prostate cancer is almost 16 percent, and thus,
15 about one man in six in the United States will be
16 diagnosed with the disease during his lifetime.
17 And we anticipate that there will be an increase of
18 diagnosis with the aging of the population and with
19 continued use of PSA screening.

20 The majority of tumors diagnosed in the
21 United States today are done so by PSA screening,
22 and an elevated PSA or an abnormal digital rectal

1 examination, otherwise known as a DRE, prompts an
2 ultrasound-guided prostate biopsy, usually
3 employing several prostate cores.

4 Screening is controversial in the United
5 States as a result of two randomized trials. The
6 U.S. trial, the PLCO trial, conducted by the
7 National Cancer Institute, did not demonstrate an
8 improvement in mortality, but a European trial
9 conducted concurrently in a larger patient
10 population found a 20 percent risk reduction in
11 prostate cancer death. And as a result in the
12 United States, about 50 percent of men over the age
13 of 50 have a PSA performed annually for screening
14 purposes.

15 To understand prostate cancer and especially
16 these two trials, it's important to understand the
17 Gleason scoring system. As displayed in the left-
18 hand side, Don Gleason, who was a pathologist, was
19 the first to recognize the heterogeneity of the
20 disease and the different growth patterns of the
21 disease, a Gleason score 1 at the top on the left,
22 as you see, going all the way up to Gleason 5. And

1 when a core is obtained from the prostate -- this
2 is a prostate core as you see here -- oftentimes,
3 you'll be sampling more than one tumor. As such,
4 this large area is a Gleason pattern 3, smaller
5 area Gleason pattern 4. And Dr. Gleason
6 recommended, and to this day it's a standard in the
7 United States, that you sum the two -- 3 the
8 largest pattern, 4 the second largest pattern; --
9 thus, this a Gleason 7 tumor.

10 The most common prostate cancer diagnosed in
11 the United States is a Gleason pattern 6. And
12 although cure rates with this, with radical
13 radiation or radical surgery are quite high,
14 nonetheless, with untreated Gleason 6 prostate
15 cancer followed for prolonged periods of time,
16 there is a reasonable rate of mortality that may be
17 as high as 30 percent. As a result, over 90
18 percent of men diagnosed with prostate cancer in
19 the United States, to include Gleason pattern 6,
20 receive treatment with either surgery or radiation.

21 It's also important to understand that
22 prostate cancer as from a biopsy standpoint may not

1 illustrate what is actually going on in the
2 prostate. This is the whole mount of the prostate.
3 This is the rectal surface projection posteriorly,
4 and you can see that there are two tumors in the
5 prostate, this large tumor here, which is a Gleason
6 pattern 6. Here's a Gleason pattern 3 and a
7 Gleason pattern 4. And as such, because there's a
8 greater likelihood that you would biopsy that
9 Gleason pattern 3 and miss the Gleason pattern 4,
10 we see from biopsy to prostatectomy, about 20 to 30
11 percent of all tumors end up being upgraded to the
12 true Gleason score, which is found at
13 prostatectomy.

14 In terms of treatment options, surgery,
15 radiation, hormonal therapy and surveillance are
16 all options, and over 90 percent of men opt for one
17 of these, even the Gleason 6 tumors. With surgery
18 or radiation, there's a risk of erectile
19 dysfunction of 50 percent or more; incontinence
20 requiring pads of 3 to 20 percent; gastrointestinal
21 pain, bleeding and urethral stricture. With
22 hormones, there's a risk of sexual dysfunction,

1 insulin resistance and increasing evidence of
2 cardiovascular disease.

3 Despite therapy, as many as a third of men
4 will suffer cancer recurrence. With surveillance,
5 which is increasingly advocated, nonetheless, there
6 is a risk of cancer progression, there's a risk of
7 bleeding or infection with repeated biopsies, and,
8 certainly, the diagnosis of prostate cancer
9 untreated is associated with anxiety in many men.
10 Regardless of the treatment selected, diagnosis of
11 prostate cancer in the U.S. today has a profound
12 negative impact on a man with that diagnosis.

13 Vis-à-vis the background of the Prostate
14 Cancer Prevention Trial, in the 1980s, PSA
15 screening commenced. As a result in the late
16 1980s, we saw this dramatic increase in the risk of
17 detection of prostate cancer leading to the
18 question of whether or not prevention was a
19 possibility. This public health concern as well as
20 the understanding of a relationship between
21 androgens and the risk of prostate cancer, as well
22 as the registration of finasteride in 1992, the

1 first 5 alpha-reductase inhibitor, which was
2 available for the treatment of BPH, which
3 significantly reduces the primary intraprostatic
4 androgen, dihydrotestosterone, led to the unique
5 opportunity to test the hypothesis that lowering
6 intraprostatic dihydrotestosterone may reduce the
7 risk of prostate cancer.

8 In this graphic as you see here,
9 testosterone complexes with the androgen receptor.
10 It is also converted to dihydrotestosterone, which
11 has a greater affinity for the androgen receptor.
12 It's the primary intraprostatic androgen. And
13 blockade of 5 alpha-reductase leads to substantial
14 changes in the prostate, a 50 percent fall in PSA,
15 involution of the prostate, and clinically we see
16 an improvement in urinary symptoms.

17 When we designed the Prostate Cancer
18 Prevention Trial with this agent, we considered
19 several primary endpoints. The first we considered
20 was a survival endpoint but recognized that it was
21 not feasible due to the size, cost containment and
22 other issues. A cancer endpoint without using

1 diagnosis over a period of exposure was considered
2 with a end-of-study biopsy in all subjects, but
3 this was inconsistent with the clinical practice at
4 the time, and there were also ethical
5 considerations with regards to that.

6 A cancer endpoint with a diagnostic
7 intervention during the treatment, with an end-of-
8 study biopsy on those without cancer, was felt to
9 be feasible, acceptable to patients, and because of
10 the impact of a prostate cancer diagnosis being so
11 profound, was felt to be a clinically important
12 endpoint.

13 Thus, the endpoint selected was cancer
14 prevalence. PSA and DRE screening would led to
15 biopsy prompts, and at the end of the study to make
16 sure that a prostate cancer diagnosis was not
17 present, or that biases associated with PSA or DRE
18 were not operational, the end-of-study biopsy was
19 included. And the sum of these two were then the
20 period prevalence of prostate cancer over that
21 period of time.

1 The problem or the challenge with designing
2 such a trial is that finasteride affects prostate
3 cancer detection by lowering PSA by about 50
4 percent in men with BPH. This is a significant
5 bias without adjustment, and a PSA multiplied by 2
6 was used for men taking finasteride for BPH.

7 In PCPT, we adjusted for this by all the
8 PSAs being performed centrally, with the initial
9 PSA being multiplied by 2 based on data for men
10 with BPH and a targeted adjustment in the PSA
11 reporting such that we would equalize the number of
12 biopsy recommendations between both groups. And
13 beginning at year 4, our data and safety monitoring
14 committee adjusted this upward to a multiplication
15 factor of 2.3.

16 The primary endpoint options would include
17 obviously the period prevalence, which was our pre-
18 specified primary endpoint. This included
19 histologically proven presence or absence of
20 prostate cancer over seven years, as well as
21 absence of prostate cancer defined as a negative
22 end-of-study biopsy at year 7. We dismissed the

1 clinical incidence, excluding the end-of-study
2 biopsy data because the diagnosis was dependent
3 only of for-cause biopsies prompted by PSA or an
4 abnormal digital rectal examination. And we
5 predicted that PSA, DRE, and other potential
6 factors, which we suspected at the outset would
7 have biased the interpretation of the study, and we
8 predicted this in the original study design.

9 We decided to study a general, broad low to
10 moderate risk population, as it would be most
11 generalizable and allow us to make conclusions with
12 regards to high-risk groups. The eligibility
13 criteria, as Dr. Pazdur pointed out, were men 55
14 years of age or older, overall good health, a
15 normal rectal examination, a PSA less than or equal
16 to 3 measured by a central laboratory, and an AUA
17 symptom score less than 20, which included men with
18 moderate obstructive voiding symptoms consistent
19 with BPH, and that would be in the 8 to 19 range.

20 The scheme of the trial, as you see here,
21 enrolling about 24,000 men, randomizing almost
22 19,000 men to finasteride or placebo; interim

1 annual PSAs and rectal examinations prompting
2 biopsies that could lead to interim prostate
3 cancers; and at the end of seven years, an end-of-
4 study biopsy leading to the cumulative seven-year
5 period prevalence.

6 The cancers were categorized in two
7 fashions, one, somewhat arbitrary, understanding
8 that now we understand that PSA is not elevated or
9 normal, but, nonetheless, at the onset of the
10 trial, we categorized these as for cause, which are
11 biopsies with PSAs above 4 and abnormal DRE, which
12 was the common threshold used at that time, or any
13 prostate cancer diagnosis made over the usual
14 course of clinical practice, which might be a
15 cystectomy or a TUR of the prostate.

16 We also then categorized them as end-of-
17 study biopsies, which were with PSAs less than or
18 equal to 4 and a normal digital rectal examination.
19 And these biopsies were necessary to reduce the
20 impact of potential bias in cancer detection due to
21 the known actions of finasteride. We now know that

1 clinically significant cancers occur with PSAs less
2 than 4 and a normal rectal examination.

3 In terms of follow-up, they had clinic
4 visits every six months, assessed for side effects
5 and medical events. Previous study was returned
6 for assessment of adherence, and the study drug was
7 re-dispensed. Annual visits, we had limited
8 physical examinations, so rectal exam and a PSA,
9 and a biopsy recommendation for an abnormal rectal
10 exam or a PSA in excess of 4 with an adjustment of
11 the PSA in the finasteride-treated individuals,
12 telephone calls at three and nine months, and
13 blinded central pathology review.

14 When the study opened, the sites were
15 overwhelmed by interest in men for chemoprevention
16 of prostate cancer. Fully two-thirds of the
17 subjects enrolled in the trial occurred over the
18 first three years, and we over-accrued during the
19 three-year accrual period.

20 The baseline characteristics of the
21 subjects, a large distribution of age, this was
22 predominantly in Caucasians, 92 percent; 4 percent

1 were African-Americans. Family history of prostate
2 cancer parallels the general population at about 15
3 percent. About half the men had a PSA less than 4
4 but distributions up to a PSA of 3. An important
5 consideration is that about a third of men in this
6 trial had an AUA symptom score that would have
7 given them moderate obstructive voiding symptoms
8 which is oftentimes treated for BPH.

9 The study began and went on. At the end of
10 seven years, the end-of-study biopsies began, as
11 you can see here; because the majority of the
12 individuals enrolled early, the first biopsies
13 began. And in February of 2003, our data and
14 safety monitoring committee recognized that the
15 primary endpoint had been met and recommended study
16 closure.

17 In March the 19th, the New England Journal
18 of Medicine dataset cutoff was established. June
19 the 23rd, the trial was unblinded. Investigators
20 and subjects were notified; online publication the
21 next day; print publication in July. December 31st
22 was the cutoff date for final prostate biopsies.

1 As men had not reached their seven-year endpoint,
2 we gave them the opportunity for an end-of-study
3 biopsy, and the dataset was then frozen January
4 15th of 2004.

5 Our pre-specified primary analysis were men
6 with an endpoint determination within seven years
7 plus 90 days of randomization. This would include
8 prostate cancer diagnosed prior to end-of-study
9 biopsy, end-of-study biopsy either negative or
10 positive for prostate cancer, and we excluded
11 prostate cancers diagnosed after seven years plus
12 90 days. The total numbers of subjects, as you see
13 here -- and this estimate, this pre-specified
14 analysis, best reflects the true impact of
15 finasteride on cancer prevention as only men with
16 an endpoint determination are included in the
17 analysis.

18 A second analysis, which we're presenting to
19 you, is a modified intent to treat, which includes
20 all randomized eligible men, excluding two men with
21 prostate cancer at enrollment, and it includes all
22 prostate cancers detected. Men without an end-of-

1 study biopsy were assumed not to have prostate
2 cancer, and it included, as we see, 18,880 men.
3 This preserves the randomization for between group
4 comparisons, but it underestimates period
5 prevalence of prostate cancer in both groups.

6 An analysis that we rejected was to analyze
7 only cancers performed for-cause biopsies. It was
8 clinically intuitive. However, it was known at the
9 study outset that finasteride affects the prostate.
10 Both PSA and prostate volume are reduced. It was
11 uncertain how PSA adjustment would work and whether
12 performance of PSA would be affected. It was
13 unknown as well whether DRE and prostate biopsy
14 would be impacted by the change in the volume, and
15 there was no way to control for these potential
16 biases other than the end-of-study biopsy. And
17 this analysis was rejected a priori because we
18 could not ensure that prostate cancer detection
19 would be equivalent in both treatment groups.

20 The risk reduction by both analyses is
21 actually quite similar, the smaller number in the
22 SWOG analysis, the MITT analysis of 26 percent

1 relative risk reduction, 30 percent in the MITT.
2 The absolute risk reduction was 6.5 percent in the
3 SWOG. And because there were more individuals
4 without an endpoint determination, the absolute
5 risk reduction was 4.5 percent in the MITT.

6 This risk reduction was seen across all risk
7 strata for prostate cancer to include age, race,
8 prostate cancer at a first degree, relative in this
9 forest plot. And importantly for this analysis, as
10 we're speaking about the BPH indication and as PSA
11 is associated with larger prostate volumes, you can
12 see that there is a risk reduction across all
13 strata of PSA as well as both AUA symptom scores
14 less than 8 or between 8 and 19.

15 The analysis found that there was a risk
16 reduction of relative risk of .74 for prostate
17 cancer overall, which is the 6.5 percent absolute
18 risk reduction. The greatest risk reduction was
19 with the Gleason 2 through 5 and the Gleason 6, as
20 you see here, with a 1.5 or 5.8 absolute risk
21 reduction, but an increase in Gleason 7, increased

1 Gleason 8 through 10; smaller numbers, so you see a
2 smaller absolute risk increase.

3 What we saw early on as well is that if you
4 look at all the high-grade cancers, these two bar
5 graphs you see on the left-hand side, you can see
6 the excess number. The orange represents the
7 Gleason 7. The aqua is the Gleason 8 through 10,
8 and you can see this increase which is also
9 mirrored in these for-cause biopsies. Important
10 for our discussion is that the end-of-study
11 biopsies, the magnitude of this difference was
12 substantially less, which was after seven years of
13 exposure to the study drug.

14 In terms of safety, annually, participants
15 completed urinary symptom and sexual function
16 questionnaires. Symptoms and adverse experiences
17 were assessed at baseline each sixth month visit
18 and the year 7 end-of-study visit, and AEs
19 reporting in PCPT were confirmed the established
20 safety profile of finasteride.

21 With regards to safety, AEs were relatively
22 well distributed between the two. Sexual side

1 effects were more commonly seen in finasteride, as
2 were breast; and I'll show you some slides on that
3 in just a moment. The cardiac risk was slightly
4 reduced in the finasteride group. Congestive heart
5 failure was quite similar. The number of deaths
6 were the same, and the number of prostate cancer
7 deaths were very small and were essentially the
8 same in the two groups. The most common reason for
9 discontinuation, as you can see here, was due to a
10 sexual adverse event.

11 The sexual and breast-related adverse events
12 included erectile dysfunction, loss of libido, and
13 diminution in semen volume, and, as you can see,
14 were very common in the placebo group but were
15 increased in the finasteride group. Breast related
16 were uncommon in both, but were slightly increased
17 in the finasteride group.

18 On the other hand, we know that the impact
19 of finasteride is on BPH, and it was seen with a
20 reduction in BPH-related AEs and procedures,
21 including BPH, prostatitis, urinary retention,
22 urinary tract infections, incontinence, and the

1 need for surgical resection of the prostate, which
2 was about half.

3 So in conclusions of the PCPT, there was a
4 substantial reduction in the risk of prostate
5 cancer overall. The relative risk reduction was
6 consistent across all subgroups, including AUA
7 symptom score at baseline, But there was an
8 increased detection of high-grade disease.

9 Finasteride was generally well tolerated
10 with an increase in sexual and breast-related
11 adverse events, reduction in BPH-related adverse
12 events and surgery for prostate enlargement, and
13 was consistent with the known safety profile. And
14 so the question after the initial analysis of the
15 study is, what is then the role of finasteride in
16 chemoprevention of prostate cancer?

17 At the time of the study design, there were
18 several critical assumptions with regards to the
19 detection of prostate cancer, number of biopsies,
20 PSA/DRE biopsy performance. And the question that
21 we asked afterwards, did these assumptions cause
22 the apparent paradox between overall cancer risk

1 reduction and the overall increased risk of high-
2 grade disease?

3 These critical assumptions, including
4 others, are found in Appendix 3 of your background
5 document, and they included an equal number of
6 biopsies in both groups. PSA performance was the
7 same in both groups. Finasteride did not affect
8 DRE detection of prostate cancer nor did it affect
9 biopsy detection.

10 What we found was that all four of these
11 were incorrect. The first off is that there was an
12 unequal number of biopsies by treatment group. The
13 sensitivity of PSA was improved with finasteride.
14 Sensitivity of DRE was improved with finasteride.
15 And finasteride was associated with more accurate
16 Gleason scoring at the time of biopsy.

17 With regards to the unequal number of
18 biopsies by treatment group, as you can see here,
19 54 percent of men in the placebo group had known
20 prostate cancer status as opposed to 50.7 percent,
21 leading to this difference in the total number of
22 cancers. If we assumed that the men who did not

1 have a biopsy in the finasteride group had the same
2 risk as the men who did not, if you will, a worst-
3 case analysis, and assign the same cancer detection
4 rate in that, it would have increased the number of
5 cancers to 966 and decreased the relative risk
6 reduction from 26 percent to 23.9 percent,
7 remaining a statistically highly significant
8 difference.

9 The second observation with regards to PSA
10 performance being the same in both groups, this was
11 not indeed seen. And for those of you with a
12 statistical bent, these are the receiver operating
13 characteristic curves for PSA for all cancers
14 Gleason 7 and higher and Gleason 8 and higher. And
15 you can see the substantial increase in the area
16 under the receiver operating characteristic curve.
17 These are big changes in these ROC curves in the
18 area of biomarkers.

19 For those of you who want to see from a
20 clinical perspective what occurs, with a PSA of 4
21 as your cut point using the same specificity, so
22 you match the PSAs in the two, it improves the

1 sensitivity for cancer detection overall, from 24
2 to 38 percent; for Gleason 7 through 10 cancer
3 detection, from 39 percent to 53 percent; and for
4 Gleason 8 through 10, from 49 percent to 64
5 percent; substantial improvements in the
6 sensitivity and, thus, the detection of cancer.

7 With regards to rectal examination, we found
8 effectively a similar finding with a significant
9 improvement in the sensitivity of rectal
10 examination for the detection of all cancers as
11 well as an increase of detection for high grade as
12 measured by 7 through 10.

13 With regards to biopsy detection, we assumed
14 that there would be equal detection by biopsy and
15 found that this was not indeed the case. Why that
16 occurs is most likely due to the volume reduction
17 in the prostate in men who are taking finasteride.
18 Here are all the men measured, here are all the men
19 with cancer, all the men with Gleason 7 through 10.

20 You can see substantial reductions in
21 prostate volume with all of these. And when you
22 have a prostate with a cancer within it, the

1 likelihood that your biopsy will detect the cancer
2 and the high-grade cancer is related to the
3 proportion of the cancer and the prostate volume,
4 and this has been shown in a number of other
5 studies as well.

6 The way to actually explore this is to ask
7 what would truth be. In that prostatectomy you
8 saw, it would be a potentially a Gleason 3 plus 3,
9 and at the time of prostatectomy, it would be a 3
10 plus 4. So truth is in prostatectomy, and we had
11 489 participants in whom we knew their final
12 Gleason score. And what we asked, the question, is
13 not the positive predictive value but the
14 sensitivity for detection of high-grade cancer; we
15 asked what it was. And somewhat challenging is men
16 who were on the placebo group, if they had high-
17 grade cancer in their prostate, you only found it
18 50 percent of the time. In the finasteride group,
19 you found it 70 percent of the time, a substantial
20 improvement in sensitivity for detection of high-
21 grade disease.

1 We subsequently asked the question how would
2 you then incorporate all of these biases knowing
3 the finasteride improves the detection of prostate
4 cancer and high-grade cancer by enhancing PSA and
5 digital rectal exam sensitivity and biopsy
6 performance and accounting for these biases as well
7 as the imbalance in the number of biopsies to
8 understand what would effectively be the true rate
9 of cancer in the two groups. This has been done by
10 a number of authors. I'll show you a table in a
11 moment.

12 This is our analysis by Dr. Mary Redman and
13 colleagues, and you can see overall, we anticipate
14 the relative risk reduction is about 30 percent.
15 The Gleason 6 or less is a relative risk of .66,
16 and the Gleason 7 through 10 is a relative risk of
17 .73. The high-grade increase is not seen with this
18 analysis. And when you look at multiple other
19 independent analyses for Gleason 7 through 10
20 disease, you no longer see increased relative risk.
21 You see it for the Gleason 8 through 10s, but,
22 again, these are very small numbers as opposed to

1 the 7 through 10s, with very high confidence
2 intervals.

3 The other question we then asked is that if
4 finasteride indeed induced prostate cancer, high-
5 grade disease, what would we expect? We would
6 expect over time as men were taking the drug over
7 time, over the seven years, an increasing hazard
8 ratio for the diagnosis with greater duration of
9 treatment. We would expect that the tumors would
10 be larger and that tumors would more likely be
11 multi-focal or bilateral if it was inducing these.

12 With regards to the hazard ratio over time,
13 if finasteride were inducing high-grade disease,
14 you would see that the hazard ratio for high-grade
15 disease with finasteride would increase over time.
16 In actuality, for Gleason 7 through 10 disease, you
17 can see that it does not increase over time, and
18 similar data are available for Gleason 8 through 10
19 disease as well.

20 If it's inducing high-grade cancer, you
21 would also expect larger tumors in the finasteride
22 group, as well as multiple tumors, so that when you

1 did a biopsy, there would be a larger volume of
2 tumor in the biopsy and it would more likely be
3 bilateral if it were inducing high-grade disease.

4 When Dr. Lucia blindly looked at the
5 biopsy material himself and asked that question, he
6 found out the exact opposite, finding that if we
7 just take the Gleason 8 through 10s, that there
8 were more cores positive in the placebo group, the
9 percent of positive cores were increased. The
10 amount of tumor was increased. It was more
11 commonly multifocal as measured by being bilateral.

12 So the summary of the high-grade analyses
13 are that improved detection and grading of prostate
14 cancer occurred in the finasteride group. With
15 finasteride, PSA is more likely to prompt biopsy if
16 cancer is present and if high-grade cancer is
17 present. Rectal examination is more likely to
18 prompt biopsy if cancer is present. And the biopsy
19 needle, because the prostate is smaller, is more
20 likely to strike the tumor and the high-grade
21 tumor. There is no evidence that finasteride
22 induces high-grade disease as the hazard ratio does

1 not increase with time, and the high-grade tumors
2 in the finasteride group are smaller and less
3 likely to be multifocal.

4 Now, some have suggested that these cancers
5 in the Prostate Cancer Prevention Trial, including
6 those that were diagnosed by end-of-study biopsies,
7 are inconsequential, as many men had PSA than or
8 equal to 4. Increasingly, since PCPT was reported
9 and many of the significant advances in the
10 detection of prostate cancer have come as a result
11 of this observation, many prostate cancers are
12 detected with a PSA less and equal to 4. Most of
13 these cancers are clinically significant, and these
14 cancers in the United States are effectively
15 treated the same as cancers that are detected, if
16 you will, by the PCPT for-cause criteria.

17 With regards to clinical significance, using
18 the criteria of Drs. Epstein and Walsh from Johns
19 Hopkins, which incorporates information on clinical
20 stage, PSA density, Gleason score and tumor volume,
21 we found that the majority of these cancers that
22 were detected with PSAs less than 4 and a normal

1 rectal examination were clinically significant.
2 These are cancers that are operated upon and
3 receive radiation therapy in the United States. If
4 your PSA is less than 4 in the United States,
5 additionally, the likelihood that you will receive
6 radical radiation or radical surgery is effectively
7 the same.

8 Finally, with regards to the impact of this
9 on a population scale, assaying this with regards
10 to the numbers needed to treat, it's within the
11 same range for many prevention sort of activities
12 that we do. For cancers overall, 15 to 22, if you
13 include only for cause, it's within that range, but
14 that negates the fact that many men are having
15 biopsies for PSAs between 2 and a half and 4,
16 including the NCCN guidelines that recommend this
17 consideration, which are a even lower number.

18 So in conclusion, finasteride significantly
19 reduces a man's risk of prostate cancer. That
20 relative risk reduction is about 26 percent. The
21 increase in high-grade cancer as observed with
22 finasteride is likely due to improved detection.

1 There is no evidence that finasteride induces high-
2 grade cancer, and the safety of finasteride is
3 consistent with the established profile to include
4 an increase in sexual and breast-related side
5 effects and decrease in BPH symptoms and
6 complications.

7 Thus, Southwest Oncology Group, speaking for
8 our investigators, feel that complete results of
9 PCPT should be available during physician-patient
10 interactions for men who are using or considering
11 treatment with finasteride.

12 **Proscar Presentation - Vivian Fuh**

13 DR. FUH: So, as Dr. Thompson has just
14 presented, the results of PCPT demonstrated a
15 significant reduction in the period prevalence of
16 prostate cancer overall with finasteride. However,
17 this was accompanied by an unexpected imbalance in
18 high-grade disease, which required further analysis
19 after the study was unblinded.

20 While the results of the numerous analyses
21 to understand the high-grade findings were
22 consistent and in totality support the hypothesis

1 that detection bias may explain the high-grade
2 findings, in Merck's opinion, these addition
3 analyses by their nature do not meet typical
4 regulatory evidentiary standards to inform an
5 indication of use.

6 Nonetheless, as stated earlier, the
7 information on the results of PCPT is important to
8 a physician when making treatment decisions for
9 their patients with BPH. And, therefore, a more
10 complete summary of the results of PCPT in Proscar
11 labeling will allow for better informed decisions
12 by physicians and patients when considering the use
13 of Proscar as indicated for the treatment of
14 symptomatic BPH.

15 Before we review the proposed labeling, we
16 should first look at the current labeling for PCPT,
17 which is a single paragraph located in adverse
18 reactions that has been in the label since 2003.
19 Results of PCPT are limited to the observed
20 imbalance in high-grade disease, the clinical
21 significance of which is unknown. Clarification is
22 provided that this information is from the

1 literature and is provided for consideration by
2 physicians when Proscar is used as indicated.

3 In the proposed labeling, included with this
4 application, the results of PCPT are described in
5 both clinical studies and adverse reactions. In
6 clinical studies, we describe the study design and
7 patient population. We added the primary study
8 outcome and referred the physician to the adverse
9 reaction section of the label.

10 Clarification is included that this
11 information is provided for consideration by
12 physicians when treating men or evaluating men for
13 treatment with Proscar for BPH. A similar
14 statement appears in the adverse reaction section
15 of the current labeling. We have relocated the
16 statement to clinical studies and have revised it
17 to provide greater clarity on the appropriate
18 patient population.

19 In Merck's opinion, this affirmative
20 statement, coupled with the indication language,
21 provides sufficient clarity that Proscar is
22 indicated only for the treatment of men with

1 symptomatic BPH. Thus, we have not also included
2 the statement from the current label that Proscar
3 is not approved to reduce the risk of prostate
4 cancer. Finally, in this section we reference the
5 ASCO AUA guideline.

6 The second reference to PCPT is in the
7 adverse reaction section, which is currently the
8 only section referring to PCPT in the label. In
9 addition to a description of the imbalance in high-
10 grade disease, we proposed additional text
11 referring to the analysis conducted since 2003 that
12 suggests that high-grade findings may be explained
13 by detection bias. The statement regarding the
14 unknown clinical significance of these findings has
15 been retained.

16 In conclusion, a more complete summary of
17 the results of PCPT and Proscar labeling allows
18 better informed decisions by physicians and
19 patients when considering the use of Proscar as
20 indicated for the treatment of symptomatic BPH.
21 Merck looks forward to the discussions with ODAC
22 today. Thank you for your attention.

1 DR. WILSON: Okay. Thank you.

2 I'd like to now invite Dr. Theoret to
3 present the FDA's presentation.

4 May I also remind all speakers to please
5 keep on time because we have a very long schedule.
6 Thank you.

7 **FDA Presentation - Marc Theoret**

8 DR. THEORET: Good morning. My name is Marc
9 Theoret. I'm a clinical reviewer in the Office of
10 Oncology Drug Products. I will be presenting the
11 FDA review of the Proscar application.

12 This is the FDA review team for this
13 application. In this application, Merck proposes
14 to include information in the clinical study
15 section and in the adverse reaction section of the
16 Proscar label, which could be interpreted to
17 suggest that Proscar is safe for use in prevention
18 of prostate cancer. Highlighted here are the key
19 proposed labeling revisions.

20 The following issues identified within the
21 application highlight the difficulty in determining
22 whether the results of the PCPT provides

1 substantial evidence of a clinically meaningful
2 benefit. First, a paradoxical increase in high-
3 grade prostate cancer, evident by an increase in
4 Gleason score 7 to 10 tumors, was observed on the
5 finasteride arm of this trial. Moreover, the
6 increase in high-grade tumors occur predominantly
7 due to an imbalance in Gleason score 8 to 10
8 tumors, the worst prognostic category of prostate
9 cancer. Second, the observed risk reduction in
10 prostate cancer was present only in Gleason score 6
11 or lower tumors.

12 The third concern revolves around the
13 generalizability of the results through the U.S.
14 population of men. Approximately 60 percent of the
15 prostate cancers observed on this study were
16 diagnosed based on scheduled end-of-study biopsies
17 performed as mandated by the protocol. In
18 addition, African-Americans, a sub-group who are at
19 particularly increased risk for prostate cancer and
20 dying from prostate cancer compared to other races,
21 were underrepresented in this study. As you will
22 hear later in the morning from Dr. Ning, FDA, these

1 are the same key FDA concerns identified by the
2 dutasteride review team.

3 This is an outline of the FDA presentation.
4 I presented an overview of the applicant's proposed
5 labeling revisions and the major concerns
6 identified in the FDA review. Next, a brief
7 overview of regulatory history for this application
8 will be discussed. Following, only the major
9 design features of the PCPT will be presented since
10 the applicant has just discussed this in detail.
11 Finally, the FDA review of efficacy and safety
12 highlighting FDA's concerns will be presented.

13 The pertinent regulatory history is shown on
14 this slide. Since this has just been summarized by
15 Dr. Fuh in detail, I will just highlight a few key
16 items here.

17 In June of 1992, FDA approved Proscar for
18 use in men with symptomatic BPH with enlarged
19 prostates. In June of 1993, the Southwest Oncology
20 Group submitted a new IND to conduct the Prostate
21 Cancer Prevention Trial or PCPT. This trial was
22 funded by the Division of Cancer Prevention of the

1 National Cancer Institute. In January of 2002,
2 Merck submitted a data analysis plan for the PCPT.

3 In September 2003, based on the results of
4 the PCPT reported in the New England Journal of
5 Medicine, Merck submitted a revised Proscar label
6 to update the adverse reaction section. This was
7 done to include information about the increase in
8 high-grade cancers.

9 In January of 2005, Merck submitted a
10 labeling supplement proposing to include
11 information about the reduction in prostate cancer
12 in men treated with finasteride based on the
13 published PCPT results. The applicant was informed
14 that the labeling revisions, to the extent
15 proposed, was a de facto efficacy claim. In June of
16 2005, Merck withdrew their application without
17 prejudice allowing the possibility of a
18 resubmission.

19 In 2009, at FDA's request, Merck resubmitted
20 the PCPT efficacy and safety databases in this
21 labeling supplement. These were requested by the
22 FDA in order for the Oncology Drug Advisory

1 Committee to discuss the available evidence from
2 the PCPT and REDUCE trial.

3 The PCPT enrolled otherwise healthy men, age
4 55 or older, with normal digital rectal
5 examinations. Following a placebo run-in period,
6 participants were assessed for side effects and
7 compliance; participants who were compliant with
8 their medications, who did not have a substantial
9 increase in side effects on a placebo pill, and who
10 had PSA values less than or equal to 3 measured out
11 at a centralized laboratory facility for a
12 randomized one-to-one arm study. Participants
13 received finasteride 5 milligrams or a placebo pill
14 taken daily until the development of unacceptable
15 toxicity, a diagnosis of prostate cancer, or
16 completion of the seven years.

17 The primary endpoint of the trial was the
18 histologically proven presence or absence of
19 prostate cancer after seven years. A key secondary
20 endpoint was to assess whether finasteride had an
21 effect on the grade or stage of prostate cancers.

1 The estimated prevalence of prostate cancer
2 in men on the placebo arm was 6 percent. At 25
3 percent, relative reduction in prostate cancer on
4 finasteride compared to placebo was determined to
5 be of clinical significance. With a 92 percent
6 power and two-sided alpha of 5 percent, and an
7 estimate that 40 percent of the men would not have
8 the end-of-study biopsy, the sample size of 18,000
9 participants was calculated.

10 Although there were no formal stopping rules
11 and interim efficacy analyses were not planned in
12 the protocol, the data safety monitoring committee
13 reviewed efficacy data at frequent intervals and
14 monitored for key trial assumptions as described by
15 the applicant.

16 Key efficacy study assessments included
17 annual digital rectal examinations and an annual
18 PSA test that was measured at a centralized
19 facility. The protocol specified that PSA values
20 would be adjusted by an index factor for men on
21 finasteride since finasteride was known to lower
22 PSA values by approximately 50 percent. The index

1 factor at the beginning of the trial was 2. That
2 is, the actual PSA level for men on finasteride arm
3 was double.

4 The protocol defined biopsy technique was a
5 six core prostate biopsy. This was performed for
6 an abnormal DRE or PSA level or adjusted PSA level
7 on the finasteride arm greater than 4. If a biopsy
8 resulted in a high-grade prostatic intraepithelial
9 neoplasia diagnosis, a re-biopsy was recommended
10 within two months.

11 In addition, the protocol mandated that all
12 men have a prostate biopsy performed at the end of
13 their seventh year on study. Men who had
14 discontinued treatment for any reason during study
15 were encouraged for their end-of-study prostate
16 biopsies.

17 All prostate specimens were to be reviewed
18 by a centralized pathology core laboratory.
19 Although the grading system was not pre-specified,
20 one central pathologist assigned a modified Gleason
21 score to 93 percent of the graded specimens.

1 Key study revisions are listed on this
2 slide. The PSA index or multiplication factor used
3 to adjust the PSA that would trigger a biopsy for
4 participants on the finasteride arm changed from 2
5 to 2.3, beginning with each participant's fourth
6 year on the trial, to increase the number of
7 biopsies being performed on the finasteride arm.

8 The protocol was revised to allow prostate
9 cancers to be detected by TRP for the primary
10 endpoint with a change from biopsy proven to
11 histologically proven throughout the protocol. In
12 addition, the technique for assessing the primary
13 endpoint of the trial was revised in November of
14 2000, prior to the first participant completing
15 seven years on the study. The change in
16 biopsy technique was prompted by the concern that
17 gland volume enhances the ability to detect
18 prostate cancer, potentially biasing the results
19 against finasteride. Finasteride shrinks the
20 prostate gland volume predominantly in the
21 periurethral zone. Thus, the new biopsy protocol
22 instructed investigators to direct the prostate

1 core biopsy as much as possible laterally to direct
2 the needle towards the peripheral zone.

3 Finally, following one of the interim
4 analyses, including sensitivity analyses reviewed
5 by the DSMC in February 2003, a recommendation that
6 further end-of-study prostate biopsies be
7 terminated and that all study participants be
8 informed of the results of the trial since the
9 observed treatment effects were sufficiently large
10 in magnitude, and a statistical significance that
11 they were unlikely to be affected by further
12 endpoint determinations was made.

13 The DSMC also noted that the results were
14 sufficiently complex as to make it difficult to
15 provide straightforward recommendations for
16 clinical decision-making.

17 Next, I'll discuss the PCPT study results.
18 Approximately 24,000 men were enrolled and nearly
19 19,000 were randomized, over 9,000 to each arm.
20 Fifty-six hundred men were ineligible to proceed to
21 randomization in 70 percent of the cases because of
22 a PSA greater than 3.

1 The primary analysis population included
2 4,775 men on the finasteride arm and 5,123 men on
3 the placebo arm. Participants who either did not
4 have an end-of-study biopsy performed or who were
5 not diagnosed with prostate cancer prior to the
6 end-of-study biopsy window were excluded from the
7 primary analysis population.

8 Demographics and baseline characteristics
9 were well balanced between study arms for the major
10 prognostic factors, including age, race and family
11 history of prostate cancer. Note that less than
12 4 percent of participants were African-American.
13 Approximately 17 percent had a family history of
14 prostate cancer in a first-degree relative. Median
15 PSA was 1.1, and approximately 7 percent of the men
16 had a prior history of a negative prior prostate
17 biopsy.

18 The primary analysis population is referred
19 by Merck as the SWOG population. The cumulative
20 incidence of prostate cancer on the finasteride arm
21 was 18.4 percent compared to the 24.9 percent on
22 the placebo arm, for a 26 percent relative risk

1 reduction of being diagnosed with prostate cancer
2 on study favoring finasteride.

3 The pre-specified primary efficacy analysis
4 in the protocol was a logistic regression model
5 with adjustment for the major prognostic variables,
6 age, race and family history. This analysis
7 demonstrated a 32 percent reduction in the odds of
8 being diagnosed with prostate cancer in favor of
9 the finasteride arm.

10 As a sensitivity analysis, FDA analyzed the
11 relative risk reduction based on the all biopsy
12 population, which included an additional 1,079 men
13 who had a negative prostate biopsy performed prior
14 to the end of study biopsy window. The relative
15 risk reduction of 26 percent is similar to that
16 calculated based on the SWOG population, which
17 excluded these patients.

18 This slide demonstrates that the decrease in
19 overall prostate cancer observed on the finasteride
20 arm was consistent across all major prognostic
21 subgroups. The 95 percent confidence intervals are
22 relatively wide for all racial subgroups, with the

1 exception of Caucasians. This is due to the
2 relatively small number of participants enrolled
3 from racial subgroups other than Caucasians.

4 A key secondary endpoint was to assess the
5 effect of finasteride on the grade of prostate
6 cancer. Approximately 95 percent of the prostate
7 cancers diagnosed on the PCPT were graded by the
8 pathology core laboratory of which 93 percent were
9 assigned a modified Gleason score by a single
10 central pathologist, Dr. Lucia.

11 The modified Gleason scoring system is
12 slightly different than the original Gleason
13 scoring system in the fact that not only is the
14 first most predominant pattern considered in the
15 Gleason score, but any high-grade pattern, even if
16 that pattern is a very small percentage, is
17 considered as the second pattern in the Gleason
18 sum.

19 This slide demonstrates the cumulative
20 incidence of prostate cancer by Gleason score. As
21 you can see, the most common prostate cancers

1 diagnosed on both arms of the trial was a Gleason
2 score 6 tumor.

3 I will now present the key FDA concerns for
4 the application. The first issue is the increased
5 risk of high-grade prostate cancer observed on the
6 finasteride arm. In the applicant's submission,
7 Gleason score of 7 to 10, prostate cancer was
8 classified as high-grade disease. A closer view of
9 the Gleason score 7 to 10 prostate cancers is
10 illustrated on the next slide.

11 The increased high-grade tumors on the
12 finasteride arm becomes apparent in the Gleason
13 score of 7 tumors but specifically within the
14 Gleason 4 plus 3 tumors where Gleason pattern 4 is
15 the predominant pattern. Gleason 4 plus 3 tumors
16 are associated with the worst prognosis than
17 Gleason 7 tumors with Gleason pattern 3 as the most
18 predominant pattern.

19 In total, 6.3 percent on the finasteride arm
20 compared to 5 percent on the placebo arm were
21 diagnosed with Gleason score 7 to 10 prostate
22 cancer for a 26 percent increased risk of

1 developing high-grade cancer with finasteride.
2 Moreover, the majority of the absolute difference
3 in high-grade tumors was accounted for by an
4 increase in Gleason score 8 to 10 cancers.

5 Now, biopsies performed for cause that is
6 due to an elevated PSA or abnormal DRE are of
7 particular interest since biopsies prompted by PSA
8 or DRE are most consistent with clinical practice
9 in men who opt for prostate cancer screening.

10 The applicant's for-cause populations
11 consisted of prostate cancers from two categories:
12 First, all end-of-study biopsies performed within
13 the end-of-study biopsy window that also had a for-
14 cause reason, such as an elevated PSA or abnormal
15 DRE, were considered for cause. Second, all
16 prostate specimens positive for prostate cancer
17 obtained prior to the end-of-study biopsy window,
18 that is, prior to seven years minus 90 days from
19 the date of randomization, were considered to be
20 for cause.

21 FDA defined a for-cause biopsy as a biopsy
22 prompted by the PSA test or DRE. On review, there

1 are 228 total prostate cancers classified by the
2 applicant as for cause that were actually performed
3 based on the protocol mandated scheduled end-of-
4 study biopsy, the majority of which fell outside of
5 the end-of-study biopsy window.

6 One hundred forty-nine biopsies were
7 prompted only by the end-of-study biopsy; 79
8 cancers were diagnosed not due to elevated PSA or
9 abnormal DRE, but based on incidental findings,
10 clinical symptoms, or no clear reason was provided.

11 The net result of the FDA reassignment of
12 prostate cancers, based on the reason that prompted
13 the histological evaluation, is that there were
14 approximately 100 fewer for-cause cancers and 70
15 more end-of-study cancers on each study arm than
16 those reported by the applicant. Some of this
17 difference resulted from FDA classification of the
18 applicant's for-cause cancers into an other
19 category that included prostate cancers not
20 diagnosed based on elevated PSA, abnormal DRE, or
21 end of study.

1 This slide demonstrates the consistent
2 increase in Gleason score 8 to 10 and 7 to 10
3 prostate cancers that occurred across tumors
4 diagnosed based on an end-of-study biopsy or a for-
5 cause biopsy, in addition to the all observed high-
6 grade cancers irrespective of the reason that
7 prompted the biopsy. The only end-of-study biopsy,
8 shown here on the left-hand side of the figure, is
9 a subgroup of men whose first prostate biopsy was
10 prompted by the scheduled biopsy at the end of
11 study. These men would not have had a prior for-
12 cause or other biopsy performed.

13 This slide demonstrates that the increase in
14 high-grade prostate cancer observed on the
15 finasteride arm was consistent across most major
16 prognostic subgroups with the exception of African-
17 Americans and Asian racial subgroups. The odds
18 ratio for racial subgroups, with the exception of
19 Caucasians, had associated wide confidence
20 intervals surrounding these odds ratios,
21 highlighting the relatively small numbers of
22 participants in key study subgroups.

1 Based on an early interim analysis and
2 recommendations by the Data Safety and Monitoring
3 Committee, the results of the PCPT were published
4 in the New England Journal of Medicine in 2003.
5 Since the publication, the applicant and others
6 have conducted post-hoc analyses to explore the
7 increased high-grade cancers observed on the
8 finasteride arm. An important issue with this
9 application is the validity and reliability of the
10 conclusions drawn from a multitude of post-hoc
11 exploratory analyses.

12 I will start with some general caveats for
13 post-hoc analyses, then discuss selected
14 exploratory analyses conducted or referenced by the
15 applicant. Exploratory analyses could be used for
16 hypothesis generation, but any conclusions drawn
17 must be confirmed in a separate, well controlled
18 study.

19 The Type 1 error or false positive rate is
20 uncontrolled when a multitude of exploratory
21 analyses are conducted in search of more favorable
22 evidence, and positive results are more likely to

1 be reported. Thus, the best result will tend to be
2 a random over estimate of the true effect known as
3 random high bias.

4 The applicant found an increased sensitivity
5 of PSA and DRE on finasteride in post-hoc analyses.
6 This means that given a patient with a positive
7 biopsy for prostate cancer, the probability that
8 his PSA test or DRE was also positive was higher
9 for those on finasteride as compared to placebo.
10 The increased PSA sensitivity could have led to
11 more prostate cancer diagnoses that were prompted
12 by a positive PSA test or DRE in men on the
13 finasteride arm. Thus, the applicant claims that
14 increased PSA and DRE sensitivity led to the
15 increased incidence of high-grade cancers on
16 finasteride.

17 There are two main issues with this claim:
18 First, for-cause diagnoses, supposedly missed in
19 placebo patients due to decreased PSA or DRE
20 sensitivity in placebo, should have been detected
21 at the end of study. Thus, PSA and DRE sensitivity
22 should not have affected the observed incidence of

1 high-grade cancers in the all biopsied population,
2 either.

3 Second, all patients not diagnosed with
4 cancer by seven years were to be given an end-of-
5 study biopsy, which was independent of PSA and DRE.
6 The relative risk was 1.21 for Gleason score 7 to
7 10 prostate cancers in participants whose only
8 biopsy was prompted by the scheduled biopsy
9 mandated at the end of seven years. Thus, in a
10 setting where PSA and DRE played no role, the risk
11 of high-grade cancer on finasteride was still
12 increased by 21 percent as compared to placebo.
13 This risk was further increased when looking only
14 at the Gleason score 8 to 10 cancers.

15 Another group of post-hoc analyses were
16 conducted to support the hypothesis that detection
17 bias resulting from higher sampling density on
18 finasteride due to prostate shrinkage led to
19 increased incidence of high-grade cancers. This
20 diagram illustrates the two potential causal
21 pathways. The red pathway supports the applicant's
22 hypothesis that detection bias due to finasteride-

1 induced prostate shrinkage led to increased high-
2 grade cancer incidence. The blue pathway states
3 that the treatment caused the increase in high-
4 grade cancers on finasteride. The challenge lies
5 in distinguishing between these two causal
6 pathways, which is complicated by the high
7 correlation between finasteride treatment and
8 prostate volume.

9 In this exploratory analysis, FDA looked at
10 the rate of high-grade prostate cancers based on
11 different prostate volume cutoffs. In the low
12 volume group, represented on this slide by the
13 black arrow, the rate of Gleason score 7 to 10
14 tumors that were diagnosed in men with prostate
15 volumes below a certain cutoff was calculated by
16 study arm. In the high volume group, represented
17 by the red arrow, the rate of Gleason score 7 to 10
18 tumors that were diagnosed in men with prostate
19 volumes above that cutoff was calculated.

20 If detection bias due to finasteride-induced
21 prostate volume reduction led to an increased rate
22 of high-grade cancers, then the rate of Gleason

1 score 7 to 10 cancers on finasteride should only be
2 higher than placebo for patients with low prostate
3 volumes, whereas the rate of high-grade prostate
4 cancer on finasteride should be similar to or lower
5 than placebo for patients with high prostate
6 volumes.

7 However, it can be seen here in these two
8 figures that the rate of high-grade cancers, shown
9 on the Y axis, on finasteride is consistently
10 higher than placebo across prostate volume cutoffs,
11 shown on the X axis, for those high-grade cancers
12 diagnosed in men with prostate volumes that fall
13 below each volume cutoff on the left, so below 20,
14 or as well as those cancers diagnosed in those
15 patients falling above that cutoff, shown on the
16 right-hand side; so in this example, above 20. The
17 higher rate of high-grade cancers on finasteride
18 seen in the high-grade volume on the right is not
19 supported by the applicant's detection bias
20 hypothesis.

21 On the PCPT study, information regarding how
22 a patient diagnosed with prostate cancer was

1 managed is not available. Thus, it is unknown how
2 many participants actually underwent a
3 prostatectomy. Nevertheless, only about one-
4 quarter of patients diagnosed with cancer had a
5 prostatectomy specimen submitted to the pathology
6 core laboratory for review. Post-hoc
7 analyses were performed in the subgroup of
8 participants to evaluate the hypothesis that high-
9 grade cancer was not significantly increased in
10 prostatectomy samples. There are two major issues
11 with this claim. First, since prostatectomy subset
12 is not a random subgroup, patients who had a
13 prostatectomy specimen cannot be assumed to be
14 representative of those who did not have a
15 prostatectomy submitted. Second, the relative risk
16 for being diagnosed with a high-grade prostate
17 cancer in the prostatectomy sample still showed an
18 approximate 20 percent increase in Gleason score 7
19 to 10 cancers and 80 percent increase in Gleason
20 score 8 to 10 cancers.

21 This slide shows additional exploratory
22 analyses presented by the applicant to estimate the

1 relative risks of Gleason score 7 to 10 cancer,
2 assuming that all biopsy diagnosed cancer patients
3 underwent prostatectomy. Since only 25 percent of
4 biopsy diagnosed cancer patients had a
5 prostatectomy sample submitted, these analyses
6 methods imputes over 80 percent of the high-grade
7 Gleason score 7 to 10 cases.

8 For example, in the Redman et al. analysis,
9 approximately 200 observed prostatectomy Gleason
10 score 7 to 10 cases were used to impute over 900
11 additional cases.

12 Although not listed on this slide, another
13 issue is the large discrepancies between covariate
14 subgroups with respect to how patients are
15 weighted. All relative risks are below 1,
16 suggesting that there's actually a decrease in
17 high-grade disease with finasteride. However, the
18 interpretation and reliability of these results is
19 not clear due to heavy imputation of data and large
20 weighting discrepancies between covariate
21 subgroups.

1 An additional issue with this analysis is
2 illustrated by the Gleason score 8 to 10 category
3 of tumors for which all relative risks are greater
4 than 1 and are inconsistent with the Gleason score
5 7 to 10 results. As previously discussed,
6 approximately 75 percent of the increased high-
7 grade tumors were accounted for by the increase in
8 Gleason score 8 to 10 tumors. Thus, the
9 inconsistency between Gleason score 7 to 10 results
10 and 8 to 10 results cast doubt on the robustness of
11 this data. In addition, the sensitivity of biopsy
12 grading as compared to prostatectomy for Gleason
13 score 8 to 10 cancers was similar between treatment
14 arms.

15 In summary, none of the post-hoc analyses
16 conducted provides sufficient evidence that the
17 increase in high-grade cancers seen on finasteride
18 is due solely to bias. The end-of-study biopsies
19 were important in understanding the effects of
20 higher sensitivity of PSA and DRE on finasteride.

21 There was still an increased risk of high-
22 grade cancer on finasteride in the end-of-study

1 only biopsies that did not depend on PSA/DRE
2 results, especially in the Gleason score 8 to 10
3 category of high-grade tumors. The hypothesis that
4 detection bias, due to finasteride-induced prostate
5 shrinkage, led to increase in high-grade cancers on
6 finasteride cannot be supported by the higher rate
7 of high-grade cancers on finasteride seen in men
8 with high prostate volumes.

9 Results from post-hoc analyses conducted
10 using the available prostatectomy data lack
11 reliability and robustness due to heavy imputation,
12 inconsistency of the results. Furthermore, the FDA
13 statistical reviewer has replicated most of the
14 applicant's post-hoc analyses on Gleason score 8 to
15 10 tumors and found inconsistent results compared
16 to the Gleason score 7 to 10 tumors.

17 Given that over three-quarters of the
18 increase in Gleason score 7 to 10 cancers is due to
19 an increase in the Gleason score 8 to 10 category,
20 this inconsistency is concerning and question the
21 overall reliability and robustness of the Gleason
22 score 7 to 10 post-hoc analyses results.

1 The second and third major issues both
2 revolve around the clinical relevance of the
3 results. This figure illustrates the point that
4 benefit of finasteride in risk reduction of
5 prostate cancer was entirely in the subset of
6 patients diagnosed with Gleason score 6 or lower
7 tumors.

8 Shown in this figure is the relative risk of
9 prostate cancer grouped by Gleason score 8 to 10, 7
10 to 10, 2 to 6, and all prostate cancers on
11 finasteride compared to placebo as you move from
12 left to right on the X axis of this figure. The
13 relative risk of prostate cancer is diagnosed for
14 cause, which are in the white bars, only end of
15 study, represented by the gray bars, and the all
16 biopsied population, represented by the gray
17 diagonal bars are shown. Values below the dotted
18 line indicate a reduction in risk of prostate
19 cancer, and values above the dotted line represent
20 an increase in risk for prostate cancer on the
21 finasteride arm.

1 The relative risk reduction for prostate
2 cancer is reduced only in Gleason score 6 or less
3 tumors and drives the overall reduction in prostate
4 cancers shown in the far right of this figure.

5 This is a consistent finding in men for whom
6 biopsies were prompted by for-cause reasons or were
7 biopsied only prompted by the scheduled protocol
8 mandated biopsy at the end of the seven-year study.

9 There's a well described lead time bias for
10 prostate cancers picked up by screening PSA and DRE
11 testing. There's also uncertainty in the
12 literature regarding the optimal strategy for
13 treating men diagnosed with localized prostate
14 cancer with Gleason score 6 or lower tumors because
15 of the concern for over-diagnose and treating men
16 for whom their diagnosed prostate cancer would
17 never have caused morbidity or mortality. There
18 are current guidelines employing risk
19 stratification to help inform management decisions
20 for newly diagnosed patients with clinically and
21 localized prostate cancer.

1 Information for the low-risk stratification
2 criteria were prospectively collected for prostate
3 cancer patients on the PCPT. Approximately 70
4 percent of patients with a Gleason score 6 or lower
5 tumors would have met this criteria for low risk.

6 Information for all the very low-risk
7 stratification criteria, which are based on the
8 criteria of Dr. Epstein, were not prospectively
9 collected for prostate cancer patients on the PCPT.
10 Based on a retrospective histopathologic analysis
11 on a subset of the Gleason 6 or lower tumors,
12 approximately 38 percent met these criteria.

13 Information for Epstein pathologic criteria were
14 collected prospectively for the REDUCE trial and
15 will be discussed by Dr. Ning.

16 The third concern revolves around the
17 generalizability of the results to the U.S.
18 population of men. As mentioned, with the strategy
19 of PSA screening, there is concern for over-
20 diagnosis of prostate cancers that would not
21 otherwise cause morbidity or mortality in men.
22 This concern is poignant, based on the fact that 60

1 percent of prostate cancers diagnosed in men
2 randomized on the PCPT were diagnosed by scheduled
3 biopsies at the end of seven years.

4 Additionally, under-representation of
5 African-Americans, a subgroup at particularly high
6 risk of being diagnosed with prostate cancer and
7 dying from prostate cancer as compared to
8 Caucasians, results in uncertainty for translating
9 the PCPT results to this subgroup in the general
10 U.S. population.

11 Of particular concern is the increase in
12 high-grade Gleason score 8 to 10 cancers observed
13 on the finasteride arm in men whose first prostate
14 biopsy was prompted by the mandated scheduled end-
15 of-study biopsy. The question one must ask is
16 whether these high-grade cancers would have been
17 picked up in the general population, and most
18 importantly, at what stage.

19 On this slide, the results of the number
20 needed to treat analyses are shown. For otherwise
21 healthy men aged 55 or older with normal PSA and
22 digital rectal examinations, the number of men

1 needed to treat to reduce one man from being
2 diagnosed with prostate cancer ranged from 17 to
3 73, depending on the group of men used in the
4 numerator; that is, whether all prostate cancers
5 diagnosed no matter what the reason are considered
6 or whether only cancers diagnosed for cause are
7 considered.

8 This calculation also depends on how many
9 men were considered to be at risk for a prostate
10 cancer diagnosis used in the denominator; that is,
11 whether you limit the analysis only to the men who
12 had a prostate biopsy performed or included the
13 approximately 40 percent of men who did not have a
14 prostate biopsy.

15 In contrast, 150 to 270 men would need to be
16 treated with seven years of finasteride for one
17 additional man to develop a high-grade Gleason
18 score 8 to 10 prostate cancer.

19 The key safety issue; that is, the increase
20 in high-grade cancer on finasteride, has already
21 been discussed. In terms of prostate cancer
22 specific deaths, there were relatively few observed

1 during the study, five on the finasteride arm and
2 six on the placebo arm. The most common adverse
3 events were consistent with those already listed in
4 the package insert. These are adverse events
5 related to sexual dysfunction, such as erectile
6 dysfunction and loss of libido, as well as breast-
7 related events such gynecomastia.

8 In summary, in otherwise healthy men, age 55
9 years and older, there was a 26 percent relative
10 reduction in risk of prostate cancer diagnosed on
11 the finasteride arm as compared to the placebo arm
12 in the PCPT.

13 The FDA concerns pertaining to the risk-
14 benefit analysis already discussed this morning are
15 listed on this slide.

16 Number 1. The increased risk of Gleason
17 score 7 to 10 tumors predominantly accounted for by
18 an increase in Gleason score 8 to 10 tumors
19 observed on the finasteride arm is a safety
20 concern. The increase in high-grade cancer was
21 observed in both cancers diagnosed for cause as

1 well as cancers diagnosed on scheduled biopsies at
2 the end of study.

3 Number 2. The reduction in risk of prostate
4 cancer is limited to the Gleason score of 6 or
5 lower tumors, a category of prostate cancer which
6 includes tumors that may never cause morbidity or
7 mortality. Large randomized trials are ongoing
8 intended to determine what the optimal strategy is
9 for managing a man diagnosed with a Gleason score
10 of 6 or lower tumor with favorable pathologic and
11 clinical features, active surveillance or
12 definitive therapy such as radiation or surgery.

13 Number 3. The generalizability of the
14 results to the general U.S. population is in
15 question considering that 60 percent of the
16 prostate cancers diagnosed on the PCPT were
17 diagnosed based on scheduled, end-of-study
18 biopsies. In addition, African-Americans, a
19 subgroup of the U.S. population at particularly
20 high risk of developing clinically significant
21 prostate cancer, were underrepresented in this

1 study, constituting less than 4 percent of the
2 participants randomized.

3 Issues 1, 2 and 3 are similar issues
4 identified by the FDA in review of the Avodart
5 application, which will be presented by Dr. Ning
6 later in the morning.

7 I will conclude the FDA presentation of the
8 finasteride supplemental application with this
9 final point. Chemoprevention strategies expose
10 otherwise healthy individuals who may never develop
11 the target disease to a drug and potential adverse
12 effects. Therefore, only the highest level of
13 evidence with the greatest degree of certainty in
14 that evidence, demonstrating a clinically
15 meaningful benefit in the context of a favorable
16 risk-benefit profile, should support the use of a
17 drug for cancer prevention in a population of
18 healthy individuals. In the risk-benefit
19 consideration for this application, the analyses to
20 investigate high-grade prostate cancer data
21 observed on the PCPT must be examined.

1 Keeping in mind all the caveats of post-hoc
2 analyses and the inconsistency of the results
3 between Gleason score 7 to 10 and 8 to 10 cancers,
4 the exploratory analyses presented by the
5 applicant, suggesting that detection bias explains
6 the increased risk of high-grade cancers seen on
7 finasteride, were not robust and lack reliability.
8 The post-hoc analyses presented by the applicant
9 today are certainly thought provoking, but they are
10 not confirmatory evidence. In addition, based on
11 the PCPT trial design considerations, data on hard
12 clinical endpoints are not available to help guide
13 a risk-benefit analysis.

14 DR. WILSON: Okay. Thank you.

15 At this point, we're going to go ahead and
16 take a break, and we will reconvene at 10:00.
17 Thank you.

18 (Whereupon, a recess was taken.)

19 DR. WILSON: All right. So before we hear
20 from the sponsor, I'd like to reread a statement
21 that we read earlier.

1 Both the Food and Drug Administration and
2 the public believe in a transparent process for
3 information gathering and decision-making. To
4 ensure such transparency at the advisory committee
5 meeting, FDA believes that it is important to
6 understand the context of an individual's
7 presentation. For this reason, FDA encourages all
8 participants, including the sponsor's nonemployee
9 presenters, to advise the committee of any
10 financial relationships that they may have with the
11 firm at issue, such as consulting fees, travel
12 expenses, honoraria, and interest in the sponsor,
13 including equity interest and those based upon the
14 outcome of the meeting.

15 Likewise, FDA encourages you at the
16 beginning of your presentation to advise the
17 committee if you do not have any such financial
18 relationships. If you choose not to address this
19 issue of financial relationships at the beginning
20 of your presentation, it will not preclude you from
21 speaking.

1 So with that, I'd like to invite Dr.
2 Paoletti from GlaxoSmithKline.

3 **Avodart Presentation - Paolo Paoletti**

4 DR. PAOLETTI: Good morning. I am Paolo
5 Paoletti, head of Oncology Research and Development
6 at GlaxoSmithKline. I would like to thank Dr.
7 Pazdur with the oncology division of the FDA and
8 the members of the Oncology Drugs Advisory
9 Committee for the opportunity to present the data
10 from our application for Avodart, a 5 alpha-
11 reductase inhibitor for the reduction of risk of
12 prostate cancer.

13 Here is the agenda for our presentation
14 today. Dr. Gerald Andriole will present the
15 clinical efficacy and safety data from our pivotal
16 study, REDUCE. Dr. Chris Logothetis will discuss
17 high-grade cancer in PSA utility in detecting these
18 cancers. Dr. Claus Roehrborn will provide his
19 perspective on the clinical relevance of REDUCE
20 findings. And finally, Dr. Anne Phillips of GSK
21 will discuss the benefits, risks and uncertainties
22 of dutasteride for prostate cancer risk reduction

1 and will outline GSK's commitment and plans for
2 risk management. Additional experts are here today
3 to answer questions.

4 Prostate cancer is extremely common, and its
5 incidence is rising. It is also an heterogeneous
6 disease with particular clinical challenges. While
7 high-grade prostate cancer must be treated
8 aggressively, most newly diagnosed cancer present
9 as low grade, and the benefits of aggressive
10 treatment often do not outweigh the risks. Yet, up
11 to 90 percent of men diagnosed with low-grade
12 cancer do receive aggressive intervention with the
13 potential for significant complication and
14 morbidities, along with the anxiety of cancer
15 diagnosis and treatment.

16 Thus, a diagnosis of even low-grade cancer
17 imposes a substantial burden on a man and his
18 family. The reduction of overall numbers of
19 prostate cancer, including low-grade cancer, is an
20 important achievement while, and this is important,
21 preserving our ability to diagnose high-grade
22 cancer.

1 In addition to REDUCE, our pivotal trial, we
2 will present data from CombAT, a four-year BPH
3 study with over 4,000 patients; pathology review of
4 positive biopsy from REDUCE using an alternative
5 scoring method, and REDEEM, a three-year expectant
6 management study and approximately 300 patients
7 enrolled with low-grade prostate cancer.

8 Avodart is approved in over 90 countries for
9 the treatment of symptomatic benign prostate
10 hyperplasia, and it has been on the market in U.S.
11 since 2003. And it has a very well established
12 efficacy and safety profile with more than 5.5
13 million patient years of exposure.

14 We will show to you in our presentation
15 today that Avodart reduces the overall incidence of
16 biopsy detectable prostate cancer, especially low-
17 grade cancer; reduces intervention associated with
18 a prostate cancer diagnosis; reduces the number of
19 biopsy associated and associated complication. And
20 importantly, Avodart preserves the ability to
21 detect high-grade cancer.

1 We will also address important issues, the
2 difference in number of high-grade cancers seen
3 with Avodart compared to placebo in REDUCE; the
4 relevance of protocol-dependent biopsies in the
5 REDUCE trial in relation to for-cause biopsies
6 usually performed in clinical practice and why
7 reducing diagnosis of low-grade cancer is an
8 important public health objective.

9 Indeed, this objective was recognized by the
10 American Society for Clinical Oncology and the
11 American Urological Association in clinical
12 practice guidelines published in 2009. They stated
13 that even if 5 alpha-reductase inhibitor treatment
14 never translates into a reduction overall of
15 prostate specific mortality, reduction in risk of
16 prostate cancer diagnosis with a consequent
17 morbidity of treatment is a clinical beneficial
18 endpoint in and of itself.

19 In conclusion, we are proposing the
20 following indication. Avodart is indicated for the
21 reduction in the risk of prostate cancer in men who
22 are at increased risk of developing the disease,

1 specifically men who have had a prior negative
2 biopsy performed for clinical concern and an
3 elevated PSA level, the population studied in our
4 pivotal trial.

5 I will now ask Dr. Andriole to present the
6 results of REDUCE.

7 **Avodart Presentation - Gerald Andriole**

8 DR. ANDRIOLE: Thank you. Good morning.
9 I'm Gerry Andriole. I was the principal
10 investigator of the REDUCE trial. In that
11 capacity, I have received payment for expenses
12 along with consulting fees from GSK, and I do so
13 today as well. My area of expertise has been early
14 detection of prostate cancer, and I've been
15 involved in the development of 5 alpha-reductase
16 inhibitors.

17 Before I present the REDUCE data, I want to
18 provide some background on the trial to help place
19 in perspective the important issues we are dealing
20 with today. REDUCE was initiated because of both
21 the striking risk reduction in prostate cancer seen
22 in the pivotal phase 3 BPH studies with dutasteride

1 and also its mechanism of action. Dutasteride is
2 unique in that it inhibits both Type 1 and Type 2
3 5 alpha-reductase inhibitors, the enzyme
4 responsible for converting testosterone into
5 dihydrotestosterone. And DHT is the androgen
6 associated with prostate growth in cancer.

7 Type 1 5 alpha-reductase specifically has
8 been shown to have increased activity in prostate
9 cancer, depicted here as multifocal lesions within
10 the prostate, as well as in precursor lesions and
11 other prostate cancer associated abnormalities.

12 Thus, REDUCE was designed to demonstrate
13 whether dutasteride could reduce the incidence of
14 biopsy-detectable prostate cancer over four years.
15 The trial enrolled men at increased risk of
16 prostate cancer as evidenced by their age, elevated
17 PSA, and, importantly, these men had to have had a
18 negative biopsy triggered by the clinical suspicion
19 of prostate cancer independent of and prior to the
20 study.

21 I'd now like to tell you more about the
22 study design. We designed the study to ensure an

1 equal opportunity for a prostate cancer diagnosis
2 in each group. So men in REDUCE were required to
3 undergo repeat, 10 core, protocol-dependent
4 biopsies at years 2 and 4, as well as for-cause
5 biopsies whenever deemed clinically necessary.
6 Protocol-dependent biopsies were processed and read
7 centrally, and all positive biopsies were read by a
8 single pathologist using classic Gleason scoring.

9 One of the issues raised by the FDA was the
10 relevance of protocol-dependent biopsies in REDUCE
11 to clinical practice. I see men like those
12 enrolled in the REDUCE trial every day in my
13 practice. They come in with an abnormal PSA, and
14 they are biopsied for clinical concern. Even if
15 the initial biopsy is negative, I tell them they
16 need close follow-up because prostate biopsies are
17 done in a random fashion and frequently miss
18 important cancers. Thus, the patient will likely
19 get one or more additional biopsies.

20 The medical community at large has also
21 taken the view that these men should be biopsied
22 more than once, as is illustrated in reports from

1 the CDER database and from the NCI PLCO cancer
2 screening trial. Thus, the repeat biopsies
3 conducted in the REDUCE study often reflect
4 standard clinical practice.

5 The primary endpoint of REDCUE was biopsy-
6 detectable prostate cancer at years 2 and 4. Key
7 secondary endpoints included the impact of
8 dutasteride on prostate cancer interventions, high-
9 grade PIN and ASAP, BPH-related complications,
10 Gleason score, and patient safety.

11 In REDUCE, 8,231 men were randomized;
12 99 percent received at least one dose of the study
13 drug, and 83 percent of these men had at least one
14 prostate biopsy during the study. As you can see
15 from this slide, the treatment groups were well
16 balanced for important baseline characteristics.
17 The high mean PSA and enlarged prostates indicate
18 that these men were at increased risk for prostate
19 cancer and for BPH-related complications.

20 Now, let's turn to the results. Over the
21 four years of REDUCE, dutasteride reduced the
22 relative risk of biopsy-detectable prostate cancer

1 by 23 percent. In raw numbers, there were about
2 200 fewer cancer cases among men taking
3 dutasteride, and their absolute risk reduction for
4 a cancer diagnosis was 5 percent. The associated
5 number needed to treat is 19.

6 Dutasteride's ability to reduce the risk of
7 prostate cancer was consistent throughout the
8 trial. This is especially noteworthy, as there
9 were potential biases between the dutasteride and
10 placebo groups as they entered the third and fourth
11 years of the study.

12 Let me explain. First, more cancers were
13 diagnosed in the placebo group during years 1 and
14 2. Since these cancers were removed from the
15 trial, there were fewer remaining to be detected in
16 the placebo arm during years 3 and 4. Second, the
17 prostates of dutasteride-treated men were smaller
18 than those in the placebo arm, thus making it more
19 probable that a biopsy would detect prostate cancer
20 if it was present. The finding of fewer cancers in
21 the dutasteride group during years 3 and 4
22 indicates continued tumor suppression by

1 dutasteride for the duration of the study. These
2 potential biases are also relevant to the finding
3 of high-grade cancer during the second round of
4 biopsies as Dr. Logothetis will discuss.

5 The overall relative risk reduction of
6 approximately 23 percent was consistent across key
7 baseline parameters: age, family history of
8 prostate cancer, severity of BPH symptoms, baseline
9 prostate volume and baseline PSA Turttox.

10 Despite efforts to enhance enrollment, only
11 a small proportion of the overall REDUCE population
12 was African-American. However, 138 men, or 8
13 percent of U.S. subjects in REDUCE, were African-
14 American. This is similar to their 9.5 percent
15 representation in the U.S. population of men aged
16 50 to 74. However, the relatively small number of
17 cancers in this subgroup make the confidence
18 interval assessing dutasteride's impact on prostate
19 cancer detection uninformatively wide.

20 This slide shows the protocol-specified
21 classic Gleason scores of the cancers detected in
22 REDUCE. There was a highly significant relative

1 risk reduction for Gleason score 6 or less cancers.
2 There was no difference in Gleason 7 to 10 cancers.
3 There were 29 Gleason 8 to 10 cancers in the
4 dutasteride arm and 19 in the placebo arm.

5 After the REDUCE study was concluded, the
6 FDA requested that all available positive biopsies
7 be read by a study independent pathologist using a
8 modified Gleason scoring system adopted by an
9 international society of urological pathologists
10 consensus conference in 2005. Using this modified
11 Gleason scoring system, there were 19 fewer Gleason
12 7 to 10 cancers.

13 Overall, there were the same number of
14 Gleason 8 to 10 cancers. However, there were three
15 more in the dutasteride arm and three fewer in the
16 placebo arm. So there was overall a higher level
17 of concordance between the two expert pathologists
18 demonstrating that the overall trial results were
19 robust and independent of the Gleason scoring
20 system used.

21 In addition to the overall reduction in
22 prostate cancer, dutasteride also significantly

1 reduced prostate cancer associated lesions, both
2 high-grade PIN and ASAP. This suggests that
3 dutasteride not only suppresses growth of
4 preexisting prostate cancers but also reduces the
5 development of precancerous changes that can lead to
6 later cancer development.

7 Since dutasteride reduced the diagnosis of
8 prostate cancer, it also reduced prostate cancer
9 interventions. For patients, this means avoiding
10 the anxiety of a cancer diagnosis and the
11 morbidities associated with these treatments and
12 their complications. As should be expected,
13 dutasteride also significantly reduced BPH
14 complications, including acute urinary retention,
15 BPH-related surgery and urinary tract infections.

16 Now, let's turn to the safety of dutasteride
17 in REDUCE. The safety profile of dutasteride is
18 well known from over 10,000 men exposed to
19 dutasteride in clinical trials and more than seven
20 years of post-marketing experience. This slide
21 shows the incidence of the most common drug-related
22 adverse events that occurred in 1 percent or more

1 of subjects in REDUCE. The nature and frequency of
2 these events are consistent with previous clinical
3 experience with dutasteride and product labeling.
4 In general, these events infrequently led to drug
5 withdrawal.

6 There were no significant differences
7 between dutasteride and placebo in overall
8 cardiovascular events of interest, major
9 cardiovascular events, or cardiac deaths. However,
10 there was an unexpected imbalance in cardiac
11 failure events between treatment arms with more
12 cardiac failure events noted in the dutasteride
13 arm. These events were extensively investigated by
14 GSK and the FDA, and as noted in the FDA's briefing
15 document, the imbalance was likely due to normal
16 variation.

17 So to summarize, despite study biases that
18 may have contributed to the difference in Gleason 8
19 to 10 cancers seen with dutasteride, the REDUCE
20 study demonstrated that dutasteride significantly
21 reduced biopsy detectable prostate cancer and
22 reduced prostate cancer interventions,

1 significantly reduced precancerous lesion, high-
2 grade PIN and ASAP, and significantly reduced BPH
3 complications. The safety profile was generally
4 consistent with previous experience with
5 dutasteride with the exceptions of cardiac failure
6 and Gleason 8 to 10 cancers.

7 Thank you for your attention. Dr.
8 Logothetis will now elaborate on the high-grade
9 prostate cancers seen with dutasteride.

10 **Avodart Presentation - Christopher Logothetis**

11 DR. LOGOTHETIS: Thank you, Gerry.

12 My name is Chris Logothetis. I'm the chair
13 of the department of GU medical oncology at MD
14 Anderson Cancer, and my travel expenses and
15 consulting fees associated with this meeting have
16 been paid by GSK.

17 I'm here to provide my perspective on the
18 reported increase in Gleason score 8 to 10 cancers
19 as presented by Dr. Andriole in the context of the
20 23 percent relative reduction in prostate cancer
21 incidence. Specifically, I'll consider design
22 issues or the underlying biological heterogeneity

1 that may account for the observation. I'll also
2 illustrate that there is no evidence to suggest
3 interference of dutasteride with the predictive
4 value of PSA and feel it can be safely used to
5 reduce the risk of prostate cancer without exposing
6 patients to an increase of developing an undetected
7 and meaningful cancer.

8 Seen on this next slide are the details of
9 the Gleason score by treatment arm. As mentioned,
10 there was a significant difference in the number of
11 Gleason score 8 and 10 cancers in the dutasteride
12 arm relative to the control in REDUCE. There were
13 a total of 29 high-grade cancers detected in the
14 dutasteride arm and 19 in the placebo arm, for an
15 increment of 10 cancers over four years in the
16 entire population.

17 The overall incidence of high-grade cancer
18 in the dutasteride cohort did not change over time,
19 0.5 percent in each of the two time periods, early
20 and late. However, there was only one such cancer
21 in the placebo group in years 3 and 4, out of 2,343

1 patients biopsied, which accounts for this very
2 puzzling imbalance.

3 An understanding of the mechanism of action
4 of dutasteride and its potential effect on prostate
5 cancer may provide an explanation for this
6 observation.

7 Seen on this slide is the complexity of
8 androgen receptor signaling in prostate cancer. It
9 is not surprising that the modulation of this
10 signaling network by 5 ARI may result in an
11 adaptive response in some but not all cancers.

12 Such an adaptive response may account for failure
13 to prevent some cancers, and that may be associated
14 with a morphologic counterpart that is reflected in
15 the Gleason score. This complexity would likely
16 result in some cancers being more responsive to the
17 effects of dutasteride while others would not.

18 For example, seen on this schematic
19 representation is the comparison of baseline
20 prostates with the hypothetically present cancers
21 and a plausible effect of dutasteride over time if
22 dutasteride preferentially inhibits Gleason score 3

1 component. The dual effect of a preferential
2 suppression of Gleason score 3 and overall
3 reduction in the size of the gland will result in
4 an increased efficiency of detection of cancer and
5 enrichment for the Gleason score 4 component. This
6 would explain why 5 ARIs, which are more effective
7 in reducing low-grade cancers, may increase the
8 relative representation of high-grade cancers.

9 To gain further insight on the relationship
10 of dutasteride and grade and frequency of detected
11 cancer, we turn to other prospectively controlled
12 trials. CombAT, which was a randomized four years
13 BPH study of 4,800 men who received tamsulosin,
14 dutasteride or the combination, patients were
15 assessed annually with a PSA and digital rectal
16 exam, and biopsies were performed exclusively for
17 cause in this trial. Prostate cancer was reported
18 as an adverse event in the context of this BPH
19 study.

20 In contrast to REDUCE, in CombAT, there was
21 a reduction in all grades of prostate cancer in
22 dutasteride-treated patients. This slide

1 illustrates the number of cancers by Gleason score
2 and study arm. White is tamsulosin, orange is
3 dutasteride and blue is the combination of the two.
4 Consistent with the dutasteride-induced risk
5 reduction, we observed fewer cancers of all grades
6 in the dutasteride containing arms of this trial,
7 importantly, in a for-cause setting.

8 The dutasteride arms were also associated
9 with a reduced number of for-cause biopsies. The
10 lower number of biopsies may account for the
11 reduced detection of cancers but does not account
12 for the absence of a grade-specific effect of
13 dutasteride.

14 So now let's examine the relationship
15 between Gleason score and dutasteride in an active
16 surveillance study in men with localized and
17 diagnosed low-grade cancers.

18 In REDEEM, the schema of that trial design
19 as seen here, an expectant management study, 302
20 men with localized Gleason score 5 and 6 cancers
21 received three years of dutasteride or placebo.
22 Protocol-dependent biopsies were performed at one

1 and half years and at three years. Patients were
2 removed from study if predetermined pathological
3 criteria were met or if they underwent therapy for
4 prostate cancer prompted by a physician or a
5 patient.

6 Summarized on the following slide are the
7 Gleason scores on final biopsy for those patients
8 who had a post-baseline biopsy. In contrast to
9 REDUCE but similar to the BPH study, no increase in
10 Gleason score 8 and 10 cancers was observed. Here
11 we see placebo represented in the white columns and
12 dutasteride in the orange columns. More patients
13 on dutasteride did not have detectable cancer on
14 final biopsy when compared to placebo, and there
15 were no differences in the frequency of high
16 Gleason score cancers in the two arms of this
17 study.

18 Though the studies were not designed to
19 examine prostate cancer risk reduction, the results
20 from both are in line for what would be expected if
21 5 ARIs functioned as risk-reducing agents.

1 Now, let's examine the link between the
2 duration of therapy and the Gleason score. It is
3 noteworthy that protocol-dependent biopsies in
4 REDUCE altered the patients in the latter portions
5 of the study in contrast to the BPH and active
6 surveillance study. In years 1 and 2 of the REDUCE
7 study, the study period when all patients were
8 randomized and were equally at risk, similar
9 numbers of Gleason score 8 and 10 cancers were
10 detected. In contrast, in BPH and CombAT study
11 where biopsies were for cause, there were fewer
12 Gleason 8 and 10 cancers in the two dutasteride
13 containing arms over the entire four-year study
14 period.

15 In the first one and a half years of the
16 REDEEM active surveillance study, the truly
17 randomized period, there were fewer high-grade
18 cancers overall. These findings raised the
19 possibility that the apparent increase in high-
20 grade cancers in years 3 and 4 may be a study bias
21 specific to REDUCE, and this potential bias may be
22 as explained as follows.

1 By year 2, there were more patients removed
2 from the placebo group compared to dutasteride, 558
3 versus 417, due to cancer detection with a Gleason
4 score between 5 and 7. These patients had no
5 additional study biopsies, and the placebo group
6 had 140 more such patients.

7 Without such removal and the hypothesized
8 progression rate to Gleason score 8 and 10 of 5
9 percent, there would have been 28 imputed Gleason
10 score 8 and 10 cancers in the placebo group by
11 years 4 versus 21 in the dutasteride group. The
12 calculation predicts for similar number of Gleason
13 score 8 and 10 cancers in placebo and dutasteride-
14 treated groups, 29 and 33 respectively.

15 It is critical, given the REDUCE findings on
16 high-grade cancer, to see if there's any evidence
17 that dutasteride interferes with the performance of
18 PSA as a predictive marker to detect Gleason score
19 8 and 10 cancers. Let's start with looking at mean
20 PSA values by treatment and cancer status in the
21 REDUCE trial.

1 The purpose of this slide is to illustrate
2 dutasteride's effect on PSA and its change over
3 time in relationship to grades of cancer and by
4 treatment arm. The slide illustrates mean PSA
5 values in the placebo group, shown in white,
6 dutasteride group, shown in orange, and triangles
7 representing the 7 to 10 Gleason score meaningful
8 cancers.

9 The first point is that mean PSA levels
10 decreased on the dutasteride arms in the first six
11 months regardless of ultimate prostate cancer
12 status. The second key point is that mean PSA rose
13 over time in all three groups in the placebo arm.
14 However, in the dutasteride group, mean PSA rose
15 primarily in men with the meaningful Gleason score
16 7 to 10 cancers.

17 To examine this important issue further,
18 let's look at the number of Gleason score 8 to 10
19 cancers that would have been detected in the REDUCE
20 trial using current recommended guidelines. To
21 model this, we applied the current NCCN guidelines
22 that recommend a biopsy based on PSA velocity to

1 the placebo-treated patients in REDUCE. Based on
2 these calculations, 74 percent of Gleason 8 and 10
3 cancers in the placebo arm would have been
4 detected.

5 In comparison, if we apply the current
6 guidance in the dutasteride label, namely, any rise
7 in PSA from nadir, to the dutasteride-treated
8 patients in REDUCE, 76 percent of Gleason score 8
9 and 10 cancers in the dutasteride arm would have
10 been detected. This demonstrates that dutasteride
11 does not interfere with the detection of Gleason
12 score 8 and 10 cancers, as similar percentages of 8
13 and 10 cancers would have been detected in both
14 arms whether they were on placebo or treated with
15 dutasteride. The results of the Gleason score 8
16 and 10 parallels those of the entire group of
17 relevant 7 and 10 cancers as seen here. This is
18 not specific to one set of meaningful cancers.

19 So in conclusion, dutasteride reduces the
20 risk of low-grade cancers. We saw a difference in
21 numbers of high-grade cancers in years 3 and 4 in
22 REDUCE, which was not seen in other dutasteride

1 trials. There is no evidence of an overall increase
2 in total high-grade cancers. REDUCE additionally
3 demonstrates that dutasteride does not interfere
4 with the diagnostic performance of PSA, providing
5 confidence in the ability to detect high-grade
6 cancer in men on dutasteride.

7 Based on those conclusions, we recommend men
8 at risk with an elevated PSA concentration and a
9 negative biopsy be treated with dutasteride to
10 reduce the risk of prostate cancer; men on
11 dutasteride be closely monitored with PSA to assure
12 safety and rapid detection of cancer.

13 Dr. Roehrborn will now discuss the
14 implications of prostate cancer risk reduction with
15 dutasteride in the clinic, and thank you very much.

16 **Avodart Presentation - Claus Roehrborn**

17 DR. ROEHRBORN: Good morning. My name is
18 Claus Roehrborn. I'm a paid consultant to GSK and
19 was the lead investigator in the CombAT trial. My
20 travel expenses along with consulting fees
21 associated with this meeting have been paid by GSK.

1 As a urologist with a longstanding clinical
2 and research interest in prostate diseases, I aim
3 to give you a clinician's perspective on the
4 dutasteride data presented here today. 5 ARIs hold
5 certain promises, reduction in number of TRUS
6 biopsies performed and the associated morbidity;
7 reduction in the number of prostate cancer
8 diagnoses;; maintaining the ability to identify men
9 with significant high-grade cancers; and
10 improvement in BPH symptoms and outcomes. There are
11 also hopes, more difficult to prove, reduction in
12 the cost, morbidity, and mortality associated with
13 prostate cancer care in the United States.

14 What are my clinical challenges in practice?
15 The high number of TRUS-guided biopsies; the over-
16 diagnosis and over-treatment of low-grade disease;
17 the difficulties in using PSA or any other marker
18 to identify men with high-grade prostate cancer;
19 and managing the co-existent lower urinary tract
20 symptoms and BPH in patients at risk for prostate
21 cancer.

1 Let's talk for a moment about the TRUS
2 biopsies. Neither DRE nor PSA are perfect, and,
3 ultimately, the most common way to diagnose
4 prostate cancer is a TRUS-guided biopsy. More than
5 650,000 will be done in 2010 in the United States,
6 resulting in over 200,000 cancer diagnoses and more
7 in the future due to the aging of the population.
8 And while for us urologists, biopsies are routine,
9 for the patients, they are uncomfortable and often
10 associated with minor, sometimes major,
11 complications: infections, sepsis or even death.

12 Biopsy-related adverse events in REDUCE were
13 significantly less common in dutasteride-treated
14 patients compared to placebo-treated patients. The
15 overall reduction of any AEs was 40 percent, and as
16 you can see, this is seen across common adverse
17 events such as hematuria, hemospermia and urinary
18 tract infection.

19 What about my second challenge, the over-
20 diagnosis and over-treatment of prostate cancer?
21 It is estimated that in any given year,
22 approximately 1 million men in the United States

1 are at increased for prostate cancer if we define
2 them as those with a previous negative biopsy, a
3 PSA 2.5 to 10, which is the REDUCE population.

4 Based on previous references about the use
5 of tamoxifen for breast cancer prevention, a
6 reasonable estimate of dutasteride use would be
7 25 percent of such at-risk population, which is
8 about 250,000 men.

9 Based on an 8.8 percent annual biopsy rate
10 and a 25 percent positive rate reported in SEER,
11 this would result in 5,700 prostate cancer
12 diagnoses, over 3,000 cases of high-grade PIN.
13 Given the fear that patients have, and their
14 physicians, that the cancer may be undergraded and
15 underestimated, even if a Gleason 6 cancer is
16 found, as well as a patient's fear of living and
17 watching their cancer, about 90 percent of these
18 cancers will be treated. This results in nearly
19 3,000 radical prostatectomies, 1,600 radiation
20 treatment courses, and 700 hormone therapy courses.

21 How would dutasteride affect if we assume
22 25 percent use these numbers? Dutasteride, when we

1 apply the REDUCE data, would result in 1,300 fewer
2 cancer diagnoses with a commensurate reduction in
3 precancerous lesions, high-grade PIN, as well as
4 surgeries, radiation and hormone treatment.

5 Now, since the precancerous lesions need to
6 be closely followed with regular PSA testing and
7 repeat biopsies, clearly, dutasteride would in my
8 practice reduce both invasive diagnostic and
9 therapeutic interventions.

10 The FDA is, of course, charged with the
11 protection and promotion of public health. A
12 concern has arisen regarding the Epstein criteria
13 which are used to differentiate low-risk patients
14 that may be followed with active surveillance
15 without immediate treatment intervention, and in the
16 briefing document, it is stated that assessed by
17 the Epstein criteria, 80 percent of patients with a
18 Gleason score 6 or less, confirmed in both the
19 reread and initial read, had low or very low
20 prostate cancer. One caveat, though, the original
21 Epstein criteria applied to the complete cohort of
22 patients and not just those with a score of 6 or

1 less, which would result in a number of 60 percent
2 in the case of REDUCE.

3 The issue with the Epstein criteria is not
4 neither black or white nor simple. From a
5 patient's perspective, any diagnosis of prostate
6 cancer is significant, and we know that with
7 increasing duration of follow-up, patients with
8 low-grade cancers in active surveillance protocols
9 switch to active intervention, not infrequently,
10 because of their anxieties, and that is despite the
11 reassurances of their doctors. We also know that
12 between 40 and 60 percent of biopsy Gleason score 6
13 cancers are upgraded to 7 or higher on
14 prostatectomies.

15 The question a physician has to ask him or
16 herself is whether the cancer is truly
17 insignificant or whether the biopsy underestimated
18 the cancer. And in a very recent paper from the
19 Cleveland Clinic, it is stated that the Epstein
20 criteria are insufficiently robust to predict
21 biologically insignificant disease. So, clearly,

1 the issues surrounding the Epstein criteria are
2 neither simple nor black and white.

3 The FDA is also concerned about the
4 questionable relevance of the results of REDUCE to
5 clinical practice where only for-cause biopsies are
6 performed, and further, that the supporting CombAT
7 protocol did not specify criteria for when to
8 perform a biopsy or how the biopsy should be
9 performed.

10 Now, there are dilemmas with study design,
11 and I for one agree with Dr. Walsh who stated in
12 his editorial, "Protocol-driven end-of-study
13 biopsies are not relevant for a clinical practice
14 situation and for-cause biopsies in patients on 5
15 ARIs are confounded by the PSA kinetics." But
16 protocol-dependent biopsies aim to ensure that
17 patients have an equal opportunity of being
18 assessed for the primary endpoint, avoiding
19 ascertainment bias. In addition, many of the
20 protocol-dependent biopsies in REDUCE actually are
21 done for cause; 72 percent of patients on placebo
22 had some degree of PSA elevation, for example.

1 So the PSA complaint of a lack of specific
2 biopsy criteria, and Dr. Walsh mentioned the
3 confounding PSA kinetics, ultimately, the for-cause
4 biopsies may be subject to bias, but so is most or
5 even all of medicine. Let me offer some
6 considerations and insights.

7 A cohort of patients on 5 ARIs followed for
8 several years and unencumbered by any protocol-
9 driven biopsies or presence or absence of criteria,
10 thus representing really true life, would be ideal,
11 but unfortunately, we don't have such a cohort.
12 Instead, we can look at the for-cause biopsy in the
13 CombAT trial. We can compare this to the truly
14 randomized phase in REDUCE, which are the for-cause
15 biopsies in the first 24 months before 143 excess
16 cancers were removed from the placebo arm, and then
17 learn from the results of the end-of-study
18 protocol-dependent biopsies how to interpret and
19 how to respond to the PSA changes that take place
20 during the treatment and when to do a for-cause
21 biopsy.

1 Now, in the CombAT trial, we have to assume
2 that tamsulosin has a nil effect on prostate cancer
3 diagnosis, and all biopsies were for cause. On the
4 left-hand side, you see that the biopsy rate in the
5 arms containing dutasteride was lower than the
6 tamsulosin arm in white. On the right-hand side,
7 you see that the proportion of positive biopsies,
8 the yield of the biopsy, is greater in both
9 dutasteride contained arms compared to the
10 tamsulosin arm in white; i.e., the doctors in
11 CombAT did fewer biopsies but each biopsy mattered
12 more.

13 Overall, fewer cancers were diagnosed in the
14 dutasteride-containing arms, and the cancer risk
15 reduction was around 40 percent against tamsulosin.
16 And this is in a case where the population was at
17 risk but not biopsied at study entry as they were
18 in REDUCE. The prostate cancer incidence was
19 reduced across all Gleason groupings, shown here,
20 Gleason 6 in gray, Gleason 7 in yellow, and 8 to 10
21 in red.

1 Now, let's look at the REDUCE trial. This
2 slide shows the for-cause biopsies in proportion of
3 positive biopsies during years 1 to 2, the truly
4 randomized phase of the trial. On the left-hand
5 side, again, you see fewer biopsies done in the
6 dutasteride arm in orange compared to the placebo
7 in white, 5.6 versus 7.1.

8 Now, it may be surprising that the rate is
9 lower than in CombAT, but remember that all these
10 patients already had a pre-study baseline biopsy.
11 Of equal importance is the fact, shown on the
12 right-hand side, the yield, the rate of positive
13 biopsies, is slightly higher in the dutasteride
14 compared to the placebo arm. And overall, this
15 leads to a 15.4 percent risk reduction in
16 dutasteride compared to placebo in a population
17 pre-biopsied at entry and is due to a reduction of
18 cancers with a Gleason score of 6 or less with an
19 equal number, 22 patients, of a Gleason 8 to 10.

20 So doing fewer biopsies but having a higher
21 diagnostic yield, and finding fewer Gleason 6 or

1 less cancers, often not requiring treatment, this
2 could be laudable and desirable goals.

3 To my sur challenge, how can we learn from
4 the results of the end-of-study protocol-dependent
5 biopsies, how to interpret the PSA changes, and how
6 to best respond to them by doing for-cause
7 biopsies? If we apply PSA velocity criteria to the
8 placebo-treated patients and respond to increases
9 from nadir PSA in the dutasteride ones, we will
10 detect 64 and 75 percent of the cancer of Gleason 7
11 to 10 respectively in the placebo and dutasteride
12 arm, and, as Dr. Logothetis already showed you, 74
13 to 76 percent of those with a Gleason 8 to 10.
14 And, thus, the ability to detect these cancers that
15 have clinical significance is preserved.

16 So in conclusion, dutasteride in my practice
17 is already a valuable drug in my armamentarium in
18 men with LUTS and BPH, with proven long-term safety
19 in millions of men -- and I will not repeat the
20 data -- on the demonstrated reduction in AUR, BPH
21 surgeries and UTIs, which address my fourth
22 challenge.

1 The frequently discussed risk of high-grade
2 disease, despite the many biases that proof is to
3 be largely an artifact, must be mitigated by
4 patient and healthcare provider information and
5 education, regular monitoring of PSA, and
6 appropriately responding to changes in PSA. On
7 balance, though, to me, dutasteride's ability to
8 reduce the number of biopsies, improve the
9 statistical performance of the biopsies and the
10 safety of the biopsies, reduce the number of
11 clinically insignificant cancers diagnosed while
12 allowing me to diagnose the worrisome Gleason 7 to
13 10 cancers, make it also a valuable drug in men at
14 risk for prostate cancer with a prior negative
15 biopsy and an elevated PSA in the studied range
16 between 2.5 and 10.

17 Thank you. I will now turn the podium over
18 to Dr. Anne Phillips for concluding risk-benefit
19 remarks.

20 **Avodart Presentation - Anne Phillips**

21 DR. PHILLIPS: Good morning. I'm Anne
22 Phillips, medicine development leader for

1 dutasteride at GSK. To close our session today,
2 I'll review the data that we believe demonstrate
3 the positive benefit risk of dutasteride in our
4 specific target population and will help you
5 address the FDA's question.

6 To put our purpose in perspective, we're
7 here to evaluate the benefit risk of dutasteride
8 for prostate cancer risk reduction in a population
9 of men at increased risk. This represents an
10 important medical need in a prevalent, serious and
11 complex disease. It's critical that we meet this
12 need while at the same time exercise caution. Like
13 all medications and all indications, there are
14 potential benefits, risks and uncertainties. Thus,
15 I want to be very clear. GSK is not proposing that
16 dutasteride be used for every man over 50 with a
17 rising PSA. We are proposing to proceed carefully
18 in the population that we studied in our trial,
19 REDUCE.

20 We propose that dutasteride be used, as it
21 was in REDUCE, in men who have had a previous
22 negative prostate biopsy for clinical concern and

1 an elevated PSA. This comprises approximately 1
2 million men in the U.S. in 2010. Why these men?
3 Because they have a medical need that clinicians
4 are struggling to manage, and this is where the
5 benefits outweigh the risks. Still, they must be
6 carefully monitored, and in a few moments, I'll
7 review our plan to manage the risks.

8 First, to provide more context around the
9 medical need in this population. A man visits his
10 physician and he has a rising PSA, so he gets a
11 biopsy. If he is found to have cancer and is like
12 the majority of men, 70 percent, his cancer is low
13 grade. His physician knows that this is unlikely
14 to result in major morbidity or mortality if left
15 untreated. Yet the variability in prostate cancer
16 behavior is unlike any other cancer, and so the
17 odds are that he and his physician will opt for
18 active treatment. Ninety percent of all positive
19 biopsies due result in active medical treatment for
20 reasons which we have addressed.

21 So this is the challenge. Men are getting
22 aggressive surgeries that might be avoided. We

1 need to reduce the detection of low-grade indolent
2 cancers leading to invasive intervention. At the
3 same time, we must identify the medically important
4 high-grade cancers. This is where aggressive
5 intervention is necessary. This is what
6 dutasteride has been shown to do.

7 Introduced, dutasteride showed significant
8 reductions relative to placebo in prostate cancer
9 and its associated lesions, in surgical and
10 nonsurgical interventions, in biopsy and biopsy-
11 associated adverse events. Dutasteride improved
12 the symptoms in complications of BPH, including the
13 risk of acute urinary retention, prostate
14 enlargement, and the need for BPH-related surgery,
15 and it reduced the need for alpha blockers. Men on
16 dutasteride suffered fewer urinary tract
17 infections. Importantly, dutasteride did not
18 interfere with the ability of PSA to detect
19 prostate cancer, including high-grade cancers that
20 require aggressive treatment.

21 One final benefit of the drug is its long
22 history of use with established safety. It's been

1 on the market since 2003 with 5 and a half million
2 patient years of exposure. Thus, we have a lot of
3 experience with dutasteride and its risks are well
4 known. They include the risk of sexual dysfunction
5 and breast disorders.

6 There are uncertainties around dutasteride
7 use in this indication. We don't yet know its
8 impact on prostate cancer-related mortality. The
9 maximum duration of treatment is also not certain;
10 and, finally, the difference in numbers of high-
11 grade cancers relative to placebo.

12 We do not believe this is a risk but rather
13 an uncertainty because it has not been seen in
14 preclinical studies, nor in the first two years of
15 REDUCE, nor in our other clinical trials, nor in
16 our post-marketing experience. It will be
17 carefully investigated and managed in our risk
18 management program to support a favorable benefit
19 risk.

20 GSK has a comprehensive program to
21 investigate, communicate and mitigate potential
22 safety risks as well as uncertainties. Knowledge,

1 education and communication through labeling are
2 the pillars of our program. It begins with
3 commitment to advancing the science for prostate
4 cancer, including high-grade tumors. We will
5 conduct research in genetics, epidemiology, and
6 pharmacoepidemiology to better understand the
7 difference in Gleason score 8 to 10 cancers during
8 years 3 and 4 in REDUCE. We will continue to
9 deploy targeted follow-up questionnaires for all
10 spontaneous reports of high-grade cancers and will
11 actively investigate cancers detected in our
12 clinical trials.

13 Through educational materials and the
14 product label, we'll work to ensure that patients
15 and providers understand our specific target
16 population, the uncertainties around high-grade
17 cancer, and the fact that dutasteride does not
18 eliminate the risk of prostate cancer, and that any
19 confirmed rise in PSA from nadir while a patient is
20 on dutasteride may be indicative of a high-grade
21 cancer. Thus, continued regular assessments are
22 crucial.

1 So to conclude our presentation, as with all
2 medicines, there are potential benefits, risks and
3 uncertainties. The over-diagnosis and over-
4 treatment of prostate cancer is a serious problem
5 in healthcare today. By decreasing the relative
6 risk of prostate cancer detection by 23 percent,
7 dutasteride helps to reduce the burden of over-
8 diagnosis in treatment of prostate cancer on
9 patients, their families and society while allowing
10 continued detection of high-grade cancers that
11 require aggressive treatment. It reduces the
12 number of medical interventions for prostate
13 cancer, many of which may be unnecessary, as well
14 as the symptoms and complications of BPH.

15 Although the uncertainties around high-grade
16 cancers have not been fully discharged, they will
17 be detectable by PSA and medical monitoring, and we
18 have a comprehensive risk management plan to
19 support appropriate clinical use of dutasteride.

20 Given the totality of the data, the benefit-
21 risk profile for the use of dutasteride in our

1 target population seen here is favorable. Thank
2 you, and we look forward to your questions.

3 DR. WILSON: I would like to thank the
4 sponsor, and now I would like to have Dr. Ning from
5 the FDA. And once more, may I remind all speakers
6 to please keep on time. Thank you.

7 **FDA Presentation - Yang-Min Ning**

8 DR. NING: Good morning. My name is Yang-
9 Min Ning. I'm a medical officer at the Office of
10 Oncology Drug Products. I have no conflict of
11 interests to report to the committee.

12 I'm going to present the FDA evaluation of
13 this supplement NDA for dutasteride for risk
14 reduction of prostate cancer in men at increased
15 risk. First, I'd like to thank all the review team
16 members for their invaluable help and advice.

17 According to the applicant's most recent
18 submission on October 25th, the proposed indication
19 was revised to, Avodart is indicated for reduction
20 in the risk of prostate cancer in men at increased
21 risk of developing the disease, defined as those
22 who have had a prior negative biopsy due to

1 clinical concern and have a elevated serum prostate
2 specific antigen, PSA. This new indication
3 targeted population is different from the
4 originally proposed one, but it is consistent with
5 the study population in the trial supporting this
6 application. In addition, the applicant specified
7 that dutasteride is not indicated for the treatment
8 of prostate cancer.

9 Based on the information you've just heard
10 from the applicant's presentation and the
11 information contained in the FDA briefing document,
12 as well as with the information from the
13 finasteride PCPT trial, I'd like first to show you
14 the key FDA concern about the dutasteride
15 application pertinent to the proposed indication.

16 Issue 1 is about the increased risk of a
17 high-grade Gleason 8 to 10 prostate cancer. This
18 increased risk is consistently demonstrated using
19 either the original or the current modified Gleason
20 scoring system, but appears more evident with the
21 current Gleason scoring system. In addition, this
22 increased risk is demonstrated in both for-cause

1 biopsies and scheduled without-cause biopsies. As
2 shown later in our presentation, the estimated
3 treatment to increased risk ratio for high-grade
4 Gleason 8 to 10 prostate cancer is approximately
5 200 to 1, which means that if approximately 200 men
6 are treated with dutasteride for four years, there
7 will be one additional man diagnosed with Gleason 8
8 to 10 prostate cancer.

9 Is this increased risk for high-grade
10 prostate cancer at a ratio 200 to 1 clinically
11 acceptable for use of dutasteride for prevention of
12 prostate cancer?

13 Issue 2 concerns the benefit of dutasteride.
14 As you just heard from the applicant, there was an
15 overall 23 percent relative risk reduction in
16 biopsy-detectable prostate cancer in the trial.
17 However, that overall risk reduction was almost
18 entirely limited to the decreased detection of
19 Gleason 6 or less prostate cancers at early stage
20 T1C.

21 Our evaluation shows that the majority of
22 the Gleason 6 or less tumors as assessed by Epstein

1 criteria represent very low risk disease,
2 suggestive of the detection of latent prostate
3 cancers that would not have been diagnosed if
4 repeated prostate biopsies without cause had not
5 been performed in the trial.

6 These very low-risk tumors pose little
7 threat to men during their lifetime. On the other
8 hand, about 20 percent of the Gleason 6 or less
9 tumors do not meet the Epstein criteria, and they
10 may be clinically important. For these possibly
11 clinically meaningful tumors, along with the small
12 decrease in Gleason 7 prostate cancer in the trial,
13 the difference between the two treatment arms, as
14 shown later, suggests as estimated treatment to
15 prevention ratio of 60 to 1, meaning that 60 men
16 would need to be treated with dutasteride for four
17 years in order to prevent a clinically meaningful
18 prostate cancer in one man.

19 Given the increased risk for high-grade
20 prostate cancer, as shown on the previous slide, is
21 the risk reduction for low or intermediate grade

1 tumors at a ratio of 60 to 1 clinically meaningful
2 for prevention of prostate cancer?

3 Issue 3 is about generalizability of the
4 REDUCE trial results to clinical practice. There
5 are two elements concerning this issue. The key
6 element is that the trial results depend mainly on
7 time-mandated repeated biopsies without a clinical
8 indication at years 2 and 4. However, such
9 biopsies are not used in all -- not consistent with
10 routine clinical practice, where only for-cause
11 biopsies are performed in men when clinically
12 indicated. Please note, for-cause biopsies do not
13 exclude clinically indicated repeat prostate
14 biopsy.

15 Given the high prevalence of latent prostate
16 cancers at autopsies, about 40 to 70 percent in
17 men, 50 to 70 years of age, who died of diseases
18 other than prostate cancer, repeated prostate
19 biopsies without cause are likely to detect
20 clinically irrelevant latent prostate cancers,
21 contributing to the currently well-known over-
22 diagnosis and over-treatment of prostate cancer.

1 Thus, the result from the time-mandated repeated
2 prostate biopsies without cause in the trial have
3 limited clinical value in a practice setting for
4 prevention of prostate cancer.

5 The other element of generalizability is
6 that there was a marked underrepresentation of
7 black men in the trial, only about 2 percent,
8 raising a question as to whether the results are
9 applicable to African-American men who are at
10 increased risk of developing prostate cancer.

11 Because of the valid FDA concerns, we'd like
12 to focus our evaluation and presentation on
13 relevant data and the results in order to reveal
14 whether the detected overall risk reduction of
15 prostate cancer in the REDUCE trial is clinically
16 relevant or meaningful for men at increased risk of
17 developing prostate cancer.

18 For this presentation, I will discuss the
19 regulatory background, highlight the study design
20 and the key efficacy results of the REDUCE trial,
21 and elucidate the key FDA concerns by examining the
22 clinical relevance of the efficacy results,

1 followed by a brief discussion of the key safety
2 information. And lastly, I will summarize the key
3 finding and present our benefit-risk analysis for
4 use of dutasteride for prevention of prostate
5 cancer, based on the REDUCE trial.

6 The clinical development program for
7 investigation of dutasteride's effectiveness in
8 reducing the risk of biopsy-detectable prostate
9 cancer was proposed in November of 2002, about one
10 year after dutasteride's initial approval for the
11 treatment of symptomatic BPH in men with an
12 enlarged prostate. The study protocol was
13 initiated in March 2003, which was about three
14 months earlier than the time when the finasteride
15 PCPT trial results were published in the New
16 England Journal of Medicine in July of 2003.

17 It may be important to point out that this
18 NDA was initially submitted in September of 2009,
19 but later was withdrawn by the applicant because of
20 the identification of the investigator -- studied
21 patient mismatches in their datasets. In March of
22 this year, this application was resubmitted.

1 The key study supporting the proposed
2 indication, as you just heard, is REDUCE trial.
3 It's not CombAT trial. REDUCE trial was a
4 randomized, double-blind, placebo-controlled study
5 to examine the efficacy and the safety of
6 dutasteride once daily for four years in reducing
7 the risk of biopsy-detectable prostate cancers.
8 Since the applicant has presented the design, I
9 will limit myself to highlighting a few things
10 regarding the design.

11 The trial studied men at increased risk for
12 prostate cancer and considered them eligible for
13 the study if they were 50 to 75 years of age, had a
14 PSA level between 2.5 to 10, and single initial
15 negative prostate biopsies of 6 to 12 cores within
16 the previous six months. This population likely
17 represents a population at risk for being diagnosed
18 with prostate cancer rather than a population at
19 increased risk of developing clinically relevant
20 prostate cancer.

21 After a four-week placebo run, men were
22 randomized one to one to receive placebo or

1 dutasteride at .5 milligrams once daily for a total
2 of four years. The primary endpoint was biopsy-
3 detectable prostate cancer after two and four years
4 of treatment. The key secondary endpoint was a
5 total Gleason score of prostate cancer at
6 diagnosis.

7 The treatment effect was assessed primarily
8 with protocol-mandated scheduled biopsies performed
9 at years 2 and 4 without a clinical indication.
10 These biopsies were performed under ultrasound and
11 had to follow predefined clinical patterns, as
12 shown on the slide at the right corner.

13 During the interims, unscheduled for-cause
14 biopsies were discouraged but allowed if clinically
15 indicated at the discretion of the investigator;
16 for example, if there was a considerable increase
17 in serum PSA, such as more than 50 percent
18 increase, compared to the month 6 assessment during
19 the first 24 months, or a more than 75 percent
20 increase during the second 24 months, or an
21 abnormal digital rectal examination of the
22 prostate.

1 All biopsy specimens were evaluated in a
2 central pathology laboratory at Richmond, Virginia,
3 and the Gleason scores for positive biopsies were
4 assigned according to the original Gleason scoring
5 system during the study period, ranging from 2003
6 to 2009. Please note that the original Gleason
7 scoring system was not used for the evaluation of
8 prostate cancer in the finasteride PCPT trial.
9 That was completed by 2003. If prostate cancer was
10 diagnosed during the REDUCE trial, study treatment
11 was discontinued.

12 A total of 8,231 men from 42 countries were
13 randomized, 4,102 placebo and 4,105 to dutasteride.
14 The patient enrollment by geographic region is
15 summarized on this slide. About 20 percent of the
16 men were enrolled from the United States.

17 Patients' baseline demographics and the
18 prostate characteristics were found well balanced
19 between the two arms. The median age was 63. The
20 majority of the patients were white men. In
21 contrast, only 2 percent of study patients were
22 black men.

1 In terms of the prostate conditions at
2 enrollment, two-thirds of the men had a diagnosis
3 of BPH. Before enrollment, 96 percent of the men
4 had a normal digital rectal examination of
5 prostate. In contrast, 95 percent of them had a
6 rising PSA value for which they had their baseline
7 biopsies performed within the preceding six-month
8 period, but the pathology results were negative for
9 prostate cancer.

10 Now, let us look at some key analyses of the
11 overall risk reduction of biopsy-detectable
12 prostate cancers with dutasteride treatment. This
13 slide shows the results of biopsy-detectable
14 prostate cancer in the ITT population. The overall
15 detection rate was about 16 percent with
16 dutasteride as compared to a rate of 21 percent
17 with placebo. The hazard ratio was .77 with a 95
18 percent confidence interval from .70 to .85, which
19 was statistically significant. The calculated
20 relative risk reduction in prostate cancer
21 detection was 22.8 percent.

1 These results represent the primary analysis
2 according to the original protocol, which was to
3 compare the difference in the incidence of biopsy-
4 detectable prostate cancers between the two arms in
5 the ITT population.

6 The difference in biopsy-detectable prostate
7 cancers was also examined in the biopsy population
8 that included all patients who had at least one
9 positive baseline biopsy during the study. As
10 shown here, the detection rates in biopsy
11 population were higher than those in the ITT
12 analysis. However, overall hazard ratio and the
13 relative risk reduction remain essentially
14 unchanged.

15 Results in different analysis populations
16 demonstrates that treatment with dutasteride for
17 four years significantly reduced the incidence of
18 biopsy-detectable prostate cancers when compared
19 with placebo. And the relative risk reduction rate
20 was approximately 23 percent.

21 The question now is whether the detected
22 overall risk reduction is clinically meaningful or

1 relevant. Answers to this question are critical
2 for appropriate evaluation of this application
3 because prostate cancer is highly prevalent in
4 aging men, and the disease is highly heterogeneous
5 in prognosis. In other words, not all prostate
6 cancers are the same. In reduction, high-grade
7 prostate cancer is more meaningful than in
8 reduction in low-grade prostate cancer. Therefore,
9 we analyzed the observed overall reduction
10 carefully to understand the clinical relevance.

11 So I will now review each of the FDA
12 concerns mentioned at the beginning of the
13 presentation and show the findings and all
14 rationales in support of those concerns.

15 First, let us look at Issue 1, the increase
16 in high-grade prostate cancer, which represents a
17 critical safety signal in our evaluation.

18 Determination of Gleason score was the key
19 secondary endpoint of the trial since the clinical
20 importance of biopsy-detectable prostate cancers is
21 primarily related to their total Gleason score.

22 This table lays the Gleason score distribution of

1 the diagnosed prostate cancers as assessed with the
2 original Gleason scoring system from the central
3 laboratory in Virginia. Obviously, as shown in
4 blue, the observed overall reduction in biopsy-
5 detectable prostate cancer was almost entirely due
6 to the decrease in Gleason score 6 or less prostate
7 cancers, from 18.1 percent in the placebo arm to
8 13.2 percent in the dutasteride arm.

9 There was no reduction in the incidence of
10 Gleason score 7 to 10 prostate cancers. In
11 contrast, there was a trend toward an increased
12 incidence of Gleason 8 to 10 prostate cancers, from
13 19 patients on placebo to 29 patients on
14 dutasteride.

15 Is this signal of an increase in high-grade
16 prostate cancer reliable? Since the Gleason scores
17 were determined using the original Gleason scoring
18 system, FDA was concerned about the possibility
19 that high-grade prostate cancers in the trial might
20 have been underestimated. Why? This is because
21 the original Gleason scoring system does not

1 consider the tertiary Gleason grade in calculating
2 the total Gleason score for needle biopsies.

3 For example, if the most predominant pattern
4 is Gleason grade 3 and the second most predominant
5 pattern is Gleason grade 3, the total Gleason score
6 will be 3 plus 3, equal to 6, according to the
7 original Gleason scoring system, even when a
8 tertiary pattern grade 4 or 5 is present in the
9 tumor.

10 In contrast, the current or modified Gleason
11 scoring system uses the tertiary pattern Gleason
12 grade instead of the secondary most predominant
13 Gleason grade in total Gleason score calculation if
14 the tertiary Gleason grade is higher. For the same
15 biopsy as shown on the slide, the total Gleason
16 score, according to the current Gleason scoring
17 criteria, will be 3 plus 4, equal to 7, or 3 plus
18 5, equal to 8.

19 This current Gleason scoring system was used
20 in the finasteride PCPT trial, which was completed
21 before the initiation of the REDUCE trial in 2003.
22 Evidence suggests that use of the current Gleason

1 scoring system may better reflect true tumor grade
2 in the prostate and better help make a proper
3 treatment decision or predict prognosis of the
4 disease.

5 Because of the difference between the
6 original and the current Gleason scoring systems
7 for evaluation of needle biopsies, FDA requested a
8 Gleason score reassessment of the prostate cancer
9 biopsy specimens of the REDUCE trial during the
10 review. The key reasons are as listed.

11 FDA reviewers found clear evidence of the
12 presence of a tertiary Gleason grade 4 or 5 in the
13 applicant's pathological datasets but not
14 considered because of the use of the original
15 Gleason scoring system. And FDA believes that the
16 results based on the original Gleason scoring are
17 not consistent with the current clinical practice
18 in assessing and reporting needle biopsies for
19 prostate cancer diagnosis.

20 FDA believed that a reassessment using the
21 current Gleason scoring system would allow
22 comparison of the REDUCE trial to the finasteride

1 PCPT trial, especially for better evaluation of the
2 increased risk of high-grade prostate cancer.

3 The independent reassessment was performed
4 by Dr. Lucia, who was also the single central
5 pathologist for the finasteride PCPT trial and who
6 was blinded to both treatment arms in the original
7 Gleason score result of the REDUCE trial.

8 The reread mainly involved the reevaluation
9 of Gleason scores using the current Gleason scoring
10 criteria for biopsy specimens positive for prostate
11 biopsy, for prostate cancer as diagnosed in the
12 initial central evaluation. Approximately 97
13 percent of the slides positive for prostate cancer
14 were reassessed in the reread, suggesting the
15 adequacy of the reread results for reanalysis of
16 overall Gleason score distribution of the prostate
17 cancers in the trial. The overall Gleason score
18 consistent rate between the reread and the initial
19 read were about 83 percent.

20 Here are the Gleason score distribution
21 results from the reread. Compared to those from
22 initial read, the incidence rate of the Gleason 6

1 or less prostate cancers remains essentially
2 unchanged with a rate of 17.8 percent with placebo
3 versus a rate of 13.2 percent with dutasteride.
4 Similar findings were observed for the subgroup of
5 Gleason 7 to 10 prostate cancers.

6 However, there's now a more evident increase
7 in Gleason 8 to 10 prostate cancers, from 16
8 patients on placebo to 32 patients on dutasteride.
9 Simply, it was doubled with a nominal p value of
10 .02, suggestive of a 100 percent relative risk
11 increase for the high-grade Gleason 8 to 10
12 prostate cancer. The difference between the two
13 arms was 16.

14 These results verified the initial signal of
15 an increased risk for high-grade prostate cancer
16 using the original Gleason scoring and highly
17 suggests that treatment with dutasteride increases
18 the incidence of high-grade prostate cancer at men
19 at risk for the disease.

20 Based on the 16 increases with dutasteride
21 in Gleason score 8 to 10 prostate cancers from
22 approximated biopsy population of 3,300, as shown

1 on the previous slide, we estimated that for every
2 200 men treated with dutasteride for four years,
3 there would be one additional man diagnosed with
4 Gleason 8 to 10 prostate cancer.

5 As discussed earlier, the study allowed
6 unscheduled for-cause biopsy if clinically
7 indicated, for example, for changes in digital
8 rectal examination of the prostate or in PSA. We
9 wondered whether there was an increased risk for
10 Gleason 8 to 10 prostate cancers in the for-cause
11 biopsies because the for-cause biopsy resembles
12 clinical practice.

13 This slide shows the Gleason score
14 distribution in the for-cause biopsies based on the
15 reread results. The majority of the for-cause
16 biopsies were performed because of the increases in
17 PSA. As you can see, prostate cancer rates on for-
18 cause biopsies were increased with dutasteride for
19 both Gleason score 7 to 10 and Gleason 8 to 10
20 prostate cancers. For Gleason 8 to 10 prostate
21 cancers, the increase was about 2 percent.

1 In contrast, the positive for-cause biopsy
2 rate for Gleason score 6 or less tumors was reduced
3 with dutasteride; 8.1 percent with dutasteride as
4 compared to 9.9 with placebo. The difference of
5 the decrease was about 2 percent as well. Overall,
6 the percentage increases in the incidence of high-
7 grade tumors appear to counterbalance the benefit
8 of the percentage in reduction of Gleason 6 or less
9 tumors.

10 Although only a small portion of the men had
11 unscheduled for-cause biopsies in the study, these
12 paradoxical results raise a serious question as to
13 whether dutasteride could provide a clinically
14 meaningful reduction of prostate cancer in a
15 regular clinical practice setting for cancer
16 prevention.

17 Issue 2 concerns whether the biopsy-detected
18 Gleason 6 or less prostate cancers are clinically
19 meaningful or relevant to patients. As discussed
20 earlier, the overall risk reduction in the study
21 was driven almost entirely by the detection of
22 Gleason 6 or less tumors, which is likely due to

1 time-mandated repeated biopsies without a cause
2 that uncovered latent prostate cancers. Although
3 such tumors are generally considered at a low or
4 very low risk to men, some of them may be
5 clinically important.

6 To better evaluate the clinical relevance of
7 Gleason 6 or less tumors in the study, the Epstein
8 criteria were applied to distinguish between those
9 at sufficient risk that require immediate treatment
10 and those with sufficiently low risk to be followed
11 with active surveillance without immediate
12 treatment intervention.

13 Epstein criteria has the following
14 requirements; Gleason 6 or less without any
15 presence of Gleason pattern 4 or 5, fewer than 3
16 core involved with tumor, no core with more than 50
17 percent involvement of tumor, and a PSA density
18 equal to or less than .15.

19 Patients with tumors meeting the criteria
20 are considered to have very low risk of prostate
21 cancer, which most likely represents latent
22 prostate cancers. And according to the current

1 NCCN prostate cancer guidelines, these patients are
2 recommended to have active surveillance rather than
3 to undergo immediate aggressive treatment if their
4 life expectancy is less than 20 years.

5 Based on the pathological element of the
6 Epstein criteria, we examined all the Gleason 6 or
7 less tumors diagnosed in both reread and the
8 initial read in the study. We found that
9 approximately 80 percent of the tumors met the
10 Epstein criteria, representing very low risk of
11 disease and suggesting that the overall reduced
12 risk with dutasteride is highly related to the
13 detection of latent prostate cancers that would not
14 have been diagnosed if repeated biopsies without
15 cause had not been performed in the trial.

16 On the other hand, a minority of the Gleason
17 6 or less tumors, about 20 percent, did not meet or
18 missed the Epstein criteria, suggesting that this
19 small portion of tumors may be clinically
20 meaningful and that dutasteride may reduce
21 detection of clinically low-grade prostate cancer.

1 The difference between the two arms in those
2 not meeting or missing the criteria shown in the
3 right is 45. Please note that the size of the
4 biopsy population relative to that difference was
5 approximately 3,300 and was similar between the two
6 arms.

7 Based on the 45 decreases in possibly
8 clinically meaningful Gleason 6 or less tumors and
9 with the small decrease in Gleason 7 tumors, we
10 estimated a treatment to prevention ratio for
11 dutasteride for patients who had biopsies in REDUCE
12 trial. This estimated ratio is 60 to 1, meaning
13 that approximately 60 men would need to be treated
14 with dutasteride for four years in order to prevent
15 one man from being diagnosed with a possibly
16 clinically meaningful prostate cancer. Most of the
17 prevented tumors would be low-grade prostate cancer
18 with a Gleason score 6 or 5 that can also be
19 managed with active surveillance if their life
20 expectancy is less than 10 years.

21 Issue 3 concerns the generalizability of the
22 REDUCE trial results to clinical practice. I would

1 like to discuss this from two perspectives. The
2 main concern is the protocol-mandated scheduled
3 biopsies and the applicability of the results to
4 clinical practice.

5 Approximately 90 percent of the overall
6 results of the study mainly came from the protocol-
7 mandated scheduled biopsies at two and four years
8 of treatment in the absence of a clinical
9 indication. This is not consistent with clinical
10 practice where only for-cause biopsies are
11 performed in men at risk for prostate cancer when
12 clinically indicated.

13 The known high prevalence of latent prostate
14 cancer in men 50 to 80 years of age -- as we
15 mentioned earlier, about 40 to 70 percent
16 prevalence of latent prostate cancer -- were
17 without -- in a high detection of latent, very low
18 risk or low risk prostate cancer if the prostate is
19 biopsied repeatedly without cause. A decrease in
20 the detection of these latent tumors is clinically
21 irrelevant and is of limited clinical value to
22 patients. Therefore, the results from the

1 scheduled biopsies without cause in the trial are
2 considered not applicable to clinical practice for
3 prevention of prostate cancer. Nevertheless, we
4 wonder if there is any important difference in the
5 results of the scheduled biopsies between the two
6 treatment arms.

7 This slide shows the results from the
8 scheduled not-for-cause biopsies. As you can see,
9 these results are basically similar to the overall
10 results as discussed earlier. Again, the risk
11 reduction was limited to Gleason 6 or less tumors
12 with an increase in the incidence of Gleason 8 to
13 10 prostate cancers with dutasteride.

14 This increase in high-grade prostate cancer
15 from 14 with placebo to 24 with dutasteride was
16 apparently independent of the PSA values as of the
17 time of biopsies performed, thus argue against the
18 hypothesis that dutasteride may improve PSA
19 diagnostic performance for detecting high-grade
20 prostate cancers. Please note that the REDUCE trial
21 was not designed to investigate the utility of the

1 PSA for detecting high-grade tumors in men taking
2 dutasteride.

3 The other concern of Issue 3 is whether the
4 results are applicable to African-American men. As
5 mentioned earlier, only 2 percent of the men in the
6 study were black. This marked underrepresentation
7 is in contrast to the known high incidence of
8 prostate cancer in this population.

9 As shown on this slide, the overall age
10 adjusted incident rate of prostate cancer in black
11 men is about 60 percent higher than that in white
12 men. In addition, a subgroup analysis shows that
13 there was no risk reduction detected in black men
14 in the REDUCE trial. Instead, there was an
15 increase incidence of prostate cancer in black men
16 taking dutasteride. This may be due to chance
17 because of the small number of black men in the
18 study making interpretation of the results
19 difficult. Nevertheless, the applicability of the
20 overall result to African-American men remains
21 unknown. Taken together, the results of the REDUCE
22 trial may not be generalizable to clinical practice

1 for prevention of clinically relevant prostate
2 cancer.

3 Now, let us review the safety findings
4 briefly. First, I'd like to reiterate that the
5 major safety concern is the increased risk for
6 high-grade prostate cancer in men on dutasteride
7 therapy. This risk was demonstrated in several
8 analyses, as we just presented.

9 Aside from that risk, the toxicity profile
10 of dutasteride in the trial was consistent with the
11 toxicity profile detailed in the approved product
12 label. The most common recognized side effect
13 associated with use of dutasteride are reproductive
14 system disorders, specifically, impotency,
15 decreased libido, ejaculation, and breast
16 disorders.

17 This slide lists the most common treatment
18 emergent adverse events occurring more frequently
19 on the dutasteride treatment arm, which included
20 decreased libido, breast, and ejaculation
21 disorders, consistent with the known safety
22 information about dutasteride. Please note that

1 although these specific events were increased on
2 the dutasteride arm, overall rates of other common
3 adverse events, moderate and severe adverse events,
4 serious adverse events and fatal events, were
5 similar between the two treatment arms. There were
6 no additional specific safety concerns other than
7 an increased incidence of high-grade prostate
8 cancer.

9 In summary, treatment with dutasteride for
10 four years resulted in a statistically significant
11 reduction in the incidence of biopsy-detectable
12 prostate cancer when compared to placebo. The
13 overall risk reduction was approximately 23
14 percent.

15 The benefit-risk analysis shows that overall
16 risk reduction was limited almost entirely to the
17 decrease in incidence of Gleason 6 or 5 prostate
18 cancers. The majority of them would present very
19 low risk of disease as assessed by the Epstein
20 criteria or according to the NCCN prostate cancer
21 guidelines, and these very low-risk tumors pose

1 little threat to men with life expectancy of less
2 than 20 years.

3 For tumors not meeting the Epstein criteria,
4 which may represent clinically meaningful prostate
5 cancers, the estimated treatment to prevention
6 ratio is about 60 to 1, meaning that approximately
7 60 men would need to be treated with dutasteride
8 for four years in order to prevent a clinically
9 relevant prostate cancer in one man.

10 Most of the prevented clinically possibly
11 meaningful tumors would be low-grade Gleason 6 or 5
12 prostate cancers. In contrast, an notable increase
13 in Gleason score 8 to 10 prostate cancers was
14 detected with dutasteride treatment. This risk is
15 demonstrated using either the original or the
16 current Gleason scoring system and also shown in
17 several different analyses, highly suggesting that
18 this risk represent a true safety signal in
19 otherwise healthy men taking dutasteride.

20 The estimated treatment to increase the risk
21 ratio is 200 to 1, which means that for
22 approximately 200 men treated with dutasteride for

1 four years, there would be one additional man
2 diagnosed with Gleason score 8 to 10 prostate
3 cancer. Moreover, the results of the REDUCE trial
4 may not be generalizable to clinical practice for
5 prevention of clinically relevant prostate cancer
6 because the trial was conducted in a manner not
7 consistent with clinical practice and had a marked
8 underrepresentation of black men that makes the
9 applicability of the overall results to African-
10 American men unknown.

11 Taken together, the results of the
12 dutasteride REDUCE trial are similar to the
13 finasteride PCPT results, which also show that the
14 overall reduced incidence of prostate cancer by
15 finasteride was entirely limited to the decrease in
16 Gleason score 6 or less prostate cancer but with a
17 considerable increase in the incidence of high-
18 grade Gleason score 8 to 10 prostate cancers.
19 These similarities will be presented next by Dr.
20 Theoret with a comparison of the PCPT trial to the
21 REDUCE trial. Thank you.

22 DR. WILSON: Okay. Thank you.

1 Dr. Theoret?

2 **FDA Presentation - Marc Theoret**

3 DR. THEORET: I will now present the
4 comparison of the PCPT and REDUCE trial results
5 based on FDA's review of the two applications.

6 Finasteride and dutasteride are both from
7 the 5 alpha-reductase inhibitors class of drugs.
8 However, finasteride is different from dutasteride
9 in that it is a selective Type 2 5 alpha-reductase
10 inhibitor, whereas dutasteride inhibits both the
11 Type 1 and Type 2 of 5 alpha-reductase isoenzymes.

12 In general, the Prostate Cancer Prevention
13 Trial enrolled men believed to be at a low to
14 moderate risk for prostate cancer. These are men
15 who are age 55 years or older and who had a normal
16 PSA test and normal digital rectal examination at
17 the study outset.

18 In contrast, the REDUCE trial enrolled men
19 believed to be at an increased risk for prostate
20 cancer based on a prior negative prostate biopsy
21 performed for clinical concern and an elevated PSA.
22 Men enrolled in the REDUCE trial were required to

1 have a single prior prostate biopsy which was
2 negative for prostate cancer on central pathologic
3 review. However, both trials allowed men who were
4 at higher risk for a prostate cancer diagnosis,
5 based on having a first-degree relative with
6 prostate cancer. Both trials excluded men who had
7 a high-grade prostatic intraepithelial neoplasia or
8 who used 5 alpha-reductase inhibitors.

9 A comparison of the study design for both
10 trials are shown in this slide. Both trials
11 included a placebo run-in period, three months for
12 the PCPT, and four weeks for the REDUCE trial. Men
13 were randomized one to one to either their
14 respective 5 alpha-reductase inhibitor or a placebo
15 pill.

16 Men randomized on the PCPT underwent annual
17 digital rectal examinations and PSA testing from
18 years 1 through 7 on the trial. Unscheduled for-
19 cause biopsies were prompted by well-defined
20 parameters for elevations on PSA testing or for
21 abnormalities on digital rectal examination, both
22 performed annually. The protocol mandated that all

1 men undergo a scheduled prostate biopsy performed
2 at the end of their seventh year on study even in
3 those participants without an abnormality found on
4 PSA testing or digital rectal examination.

5 In comparison, men randomized on the REDUCE
6 trial had scheduled prostate biopsies performed at
7 their second and fourth years on study. Criteria
8 to prompt an unscheduled for-cause biopsy were left
9 to the discretion of the investigator to be
10 performed as clinically appropriate.

11 The primary endpoint was the cumulative
12 incidence of prostate cancer, either after seven
13 years or four years of treatment for the PCPT and
14 the REDUCE trials respectively. Notable
15 differences between the trials are apparent in the
16 method of assessing the primary endpoint. First, a
17 history of a negative prior prostate biopsy was
18 allowed in the PCPT but a confirmed single negative
19 prostate biopsy performed within six months of
20 study entry was required for the REDUCE trial. As
21 previously noted, the timing of protocol-mandated
22 scheduled biopsies and the criteria to prompt an

1 unscheduled for-cause biopsy were different on the
2 PCPT compared to the REDUCE trial.

3 In both trials, the report of PSA was
4 approximately doubled for men receiving 5 alpha-
5 reductase inhibitors. Importantly, the number of
6 prostate cores required in each trial differed. In
7 the PCPT, a six-core biopsy was recommended,
8 whereas a more extensive 10-core prostate biopsy
9 was required for the REDUCE trial.

10 Similar to each trial was the required
11 central pathologic grading of all prostate
12 specimens, but there is an important difference
13 between the grading systems used in each trial.
14 The PCPT, initiated in 1993, graded prostate cancer
15 specimens using a modified Gleason scoring system,
16 which is now the current standard for grading
17 needle biopsy specimens. The REDUCE trial,
18 initiated in 2003, graded specimens using the
19 original Gleason scoring system, which does not
20 include high-grade tertiary Gleason patterns in
21 score, as mentioned by Dr. Ning.

1 Please note at the request of the FDA,
2 nearly all prostate cancer specimens on the REDUCE
3 trial were submitted for a blinded reread using the
4 modified Gleason scoring system. Dr. Lucia, the
5 primary pathologist for the PCPT, is the same
6 pathologist who performed this reread.

7 As shown in this slide, the mean age, race
8 distribution and frequency of a positive family
9 history of prostate cancer are similar for men
10 randomized on PCPT and REDUCE trials. However,
11 based on the differences in the eligibility
12 criteria and desire to enroll a population of men
13 at increased risk for prostate cancer on the REDUCE
14 trial, the median PSA was higher for men on REDUCE
15 compared to the PCPT.

16 Only 9 percent of the men on PCPT had a
17 history of a prior negative prostate biopsy
18 compared to 100 percent of the men randomized on
19 the REDUCE trial, since this was an eligibility
20 requirement. In addition, fewer men had a
21 diagnosis of BPH at baseline on the PCPT compared
22 to men on the REDUCE trial.

1 The primary efficacy results are similar for
2 both trials. For consistency, the primary efficacy
3 analysis for the all biopsy population is shown on
4 this slide. The cumulative incidence of prostate
5 cancer on the 5 alpha-reductase inhibitor arm was
6 16.6 percent for the PCPT and 19.9 percent on
7 REDUCE. On the placebo arms, the cumulative
8 incidence of prostate cancer was 22.4 percent on
9 the PCPT and 25.1 percent for REDUCE.

10 The relative reduction in risk for a
11 prostate cancer diagnosis was consistent between
12 both trials for men randomized to the 5 alpha-
13 reductase inhibitor arms. This was a 26 percent
14 reduction for the PCPT and a 23 percent reduction
15 for the REDUCE trial.

16 Now, I will recapitulate FDA's concerns,
17 highlighting the results observed from the PCPT and
18 REDUCE trial. The first FDA concern is the
19 increase in high-grade prostate cancer observed on
20 the 5 alpha-reductase inhibitors arms compared to
21 the placebo arms on both trials. Please note that
22 in this figure and subsequent figures, the results

1 from two independently conducted, large,
2 randomized, placebo-controlled chemoprevention
3 trials comparing a 5 alpha-reductase inhibitor are
4 shown in the same graph for ease of demonstrating
5 similar issues identified within trials, not for
6 making cross-study comparisons between individual
7 arms. In addition, all results are based on the
8 prostate cancer grading using the modified Gleason
9 scoring system.

10 This figure shows the cumulative incidence
11 of high-grade cancer categorized by both Gleason
12 score 7 to 10 or Gleason score 8 to 10 tumors.
13 Placebo and finasteride arms of the PCPT are shown
14 in red, and placebo and dutasteride arms of the
15 REDUCE trial are shown in gray. As seen on the
16 left-hand side of the figure, Gleason score of 7 to
17 10 prostate cancer as a category were increased
18 only in the PCPT. However, high-grade modified
19 Gleason score 8 to 10 tumors were increased on the
20 5 alpha-reductase inhibitor arms in both trials.

21 The second FDA concern is that the risk
22 reduction in prostate cancer was limited to Gleason

1 score 6 or lower tumors. On this slide, the
2 relative risk of being diagnosed with prostate
3 cancer on the 5 alpha-reductase inhibitor arm
4 compared to placebo arm is shown for the PCPT in
5 red and the REDUCE trial in gray. Note that values
6 below 1 indicate a risk reduction of prostate
7 cancer, and values above 1 represent a risk
8 increase for prostate cancer on the 5 alpha-
9 reductase inhibitor arm compared to placebo arm.

10 Clearly demonstrated in this figure is that
11 the overall risk of prostate cancer is reduced in
12 men on the 5 alpha-reductase inhibitor arms.
13 However, this risk reduction is driven by the
14 significant reduction in lower-grade Gleason 6 or
15 lower tumors. On the far right of this figure, the
16 relative risk of Gleason score 8 to 10 prostate
17 cancer is increased on the 5 alpha-reductase
18 inhibitor arms, as previously noted. The
19 third concern with both trials discussed today
20 revolves around the generalizability of the
21 results. Most prostate cancer diagnoses on both
22 trials were prompted by a scheduled prostate biopsy

1 mandated by the protocol. In general, a scheduled
2 prostate biopsy for men without a prior prostate
3 cancer diagnosis, or concerning clinical criteria
4 such as elevated or rising PSA or abnormal DRE, is
5 not consistent with clinical practice. Based on
6 the design features of the PCPT, many more cancers
7 were diagnosed on for-cause biopsies, approximately
8 40 percent of all cancers diagnosed.

9 This is compared to the considerably smaller
10 9 percent of for-cause cancers diagnosed on REDUCE.
11 In addition, when considering only those prostate
12 cancer diagnosed in men who underwent the scheduled
13 biopsies, increased high-grade modified Gleason
14 score 8 to 10 tumors on the 5 alpha-reductase
15 inhibitor arms were observed in both trials.

16 As part of the risk-benefit analysis, FDA
17 analyzed the number needed to treat based on
18 potentially clinically meaningful cancers. For
19 PCPT, this was defined as a cancer detected by
20 biopsy prompted a PSA or DRE criteria. For REDUCE,
21 a possibly clinically meaningful cancer was
22 analyzed based on tumors not meeting Epstein

1 pathologic criteria. Also, calculated was the
2 number needed to treat for one additional Gleason
3 score 8 to 10 cancer to be diagnosed on the
4 5 alpha-reductase inhibitor arm for both trials.

5 To be clear, both studies were not designed
6 to collect information that would elucidate the
7 actual clinical significance of the prostate
8 cancers diagnosed, for example, time to metastatic
9 disease, prostate cancer specific survival, or
10 overall survival.

11 On this side, the results of the numbers
12 needed to treat analyses are shown. For otherwise
13 healthy men age 55 or older with normal PSA and
14 digital rectal examinations, the number of men
15 needed to treat to reduce one man from being
16 diagnosed with prostate cancer prompted for cause
17 ranged from 39 to 73, depending on the number of
18 men considered to be at risk for a for-cause
19 prostate cancer diagnosis.

20 For men age 50 years and older, believed to
21 be at increased risk for prostate cancer and based
22 on the prior negative prostate biopsy due to

1 clinical concern and an elevated PSA, approximately
2 60 men required treatment for four years with
3 dutasteride to reduce one man from being diagnosed
4 with prostate cancer. In contrast, approximately
5 200 men required treatment with seven years of
6 finasteride or four years of dutasteride for one
7 additional man to develop a high grade Gleason
8 score 8 to 10 prostate cancer.

9 In summary, the data from both large, multi-
10 center, placebo-controlled trials were intended to
11 establish the benefits of 5 alpha-reductase
12 inhibitors by a statistically significant reduction
13 in the cumulative incidence of biopsy-proven
14 prostate cancer, although the trials were conducted
15 in populations of men believed to be at different
16 risk for prostate cancer.

17 In the PCPT, otherwise healthy men age 55
18 and older were treated, while REDUCE men, age 50
19 and older without prostate cancer but believed to
20 be at increased risk for prostate cancer diagnosis
21 based on elevated PSA, were treated.

1 For efficacy, the benefit in reduction in
2 risk of prostate cancer with each 5 alpha-reductase
3 inhibitor is similar between both trials, the
4 relative risk reduction of approximately 25 percent
5 and an absolute reduction in prostate cancer of 5
6 to 6 percent. Also consistent between both trials
7 is the observation that the efficacy is driven
8 either entirely by or primarily by a reduction in
9 risk of Gleason score 6 or lower prostate cancer
10 for the PCPT or REDUCE trials respectively.

11 For safety, in both trials, there was the
12 unexpected increased detection of high-grade
13 Gleason score 8 to 10 prostate cancer among men
14 receiving 5 alpha-reductase inhibitors. This was a
15 0.8 percent increase on the finasteride arm in the
16 PCPT and a 0.5 percent increase on the dutasteride
17 arm in the REDUCE trial when using the modified
18 Gleason scoring system. This translates to a 70
19 percent relative increase for PCPT and 100 percent
20 relative increase for REDUCE.

21 The foremost consideration for risk-benefit
22 analysis is that the population studied in both

1 applications are men without a cancer diagnosis.
2 Therefore, only the highest level of evidence with
3 the greatest degree of certainty in that evidence,
4 demonstrating a clinically meaningful benefit in
5 the context of a favorable risk-benefit profile,
6 should support the use of a drug for cancer
7 prevention in a population of healthy individuals.
8 Based on trial design considerations similar to
9 both the PCPT and REDUCE trial, data on hard
10 clinical endpoints, for example, overall survival
11 or prostate cancer-specific survival, are not
12 available to help guide a risk-benefit analysis.

13 We have one question for the finasteride
14 application and one question for the dutasteride
15 application. For finasteride, is the finasteride
16 risk-benefit profile favorable for reduction in the
17 risk of prostate cancer in men age 55 years of age
18 or older with a normal digital rectal examination
19 and a PSA of less than 3?

20 For dutasteride, is the dutasteride risk-
21 benefit profile favorable for reduction in the risk
22 of prostate cancer in men at increased risk of

1 developing the disease defined as those who have
2 had a prior negative biopsy due to clinical concern
3 and have an elevated serum prostate specific
4 antigen?

5 DR. WILSON: Okay. I would like to thank
6 FDA, and at this point we're going to go ahead and
7 take a break for lunch. May I please remind all
8 members to please do not discuss anything that
9 we've gone over this morning among yourselves, and
10 we will reconvene at 1:00 p.m. sharp.

11 (Whereupon, at 11:50 a.m., a luncheon recess
12 was taken.)

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

(1:10 p.m.)

DR. WILSON: Okay. Let's go ahead and get started. I'd like to welcome all of the ODAC members back, and the sponsors. And we have two guest expert speakers who will be addressing issues related to the topic at hand, and I would like to first invite Dr. Scardino. Let me also remind all of these speakers that we're on a very tight time schedule, so please keep your talks to the 20 minutes. Thank you.

Guest Speaker Presentation - Peter Scardino

DR. SCARDINO: Thank you very much. I'm delighted to be here. So I've titled my remarks "Comments on Chemoprevention of Prostate Cancer" because it's not my full-time job at all to look at this field. I think my expertise largely derives from the fact that I wrote an editorial for the New England Journal of Medicine when the PCPT trial came out, cautioning the medical profession about prescribing finasteride at that time for chemoprevention for a variety of different reasons.

1 And I've followed the literature since then, and
2 I'm honored to be here and give you my thoughts on
3 the field.

4 I've learned a lot this morning, but my
5 slides were prepared before I had the benefit of
6 seeing all the presentations that were given today,
7 so I'll skip through some of the ones that are
8 really more redundant.

9 I also would like to speak from the point of
10 a doctor who takes care of men with prostate cancer
11 full-time, and it's pretty much what I've done for
12 most of my 30 years of practice. I see patients in
13 the office. I do surgery for prostate cancer. But
14 I counsel many men who are at high risk who are
15 undergoing biopsies and who are trying to make the
16 decision about what the right thing is to do for
17 prostate cancer. So many of the issues that we're
18 facing today are certainly issues that I face every
19 day in clinical practice.

20 I was asked by the FDA to particularly look
21 at several topics listed here. What is the
22 prognosis of prostate cancer based on

1 histopathology and what is the importance of
2 Gleason grade? We've heard a lot about that, and
3 I'd just make a few additional remarks. What
4 is the relevance of the Epstein criteria in
5 identifying the need for chemoprevention? What's
6 the clinical relevance of cancers found on
7 scheduled biopsies as opposed to for-cause
8 biopsies? And we've seen quite a bit of data
9 presented at this meeting that have not been
10 published and not available in the literature
11 before this, so I'm going to show you what has been
12 published and what I was able to glean, and try to
13 set that in a clinical context.

14 What is the future morbidity and mortality
15 from these tumors? I'll show you some long-term
16 data both from watchful waiting trials and from
17 treatment trials for patients with various grades
18 and various indications for -- various features of
19 prostate cancer.

20 Finally, the benefit of preventing Gleason 6
21 cancers, given the risk of increasing Gleason 8
22 through 10 cancers is the question I think we're

1 all trying to answer this morning. So I will give
2 my opinion, but I don't have any additional
3 information to add to the subject.

4 You've heard about the Gleason grading
5 system, and I won't reiterate the classic system
6 that's been used widely. Almost all of the
7 clinical data that I'll show you is based on this
8 classic system. I will just point out the long-
9 term prognosis associated with Gleason grade.

10 Gleason grading has consistently been the
11 most powerful or one of the most powerful, along
12 with PSA, prognostic factors for predicting
13 prognosis of patients with localized prostate
14 cancer, recurrence after therapy, and even long-
15 term survival.

16 This is from Peter Albertsen's work. It's a
17 modification just showing that for different
18 Gleason grades in a population-based study in
19 Connecticut in the 1970s, the increase in prostate
20 cancer mortality, which is in black, relative to
21 overall mortality or other cause mortality, which
22 is gray, showing the profound impact of Gleason

1 grade as it was assigned to those patients at that
2 time.

3 This is a series of patients treated with
4 radical prostatectomy at our institution, and this
5 is the likelihood that a patient's cancer would
6 recur, documented by a rising PSA after surgery by
7 biopsy Gleason grade. So it's clear that men with
8 low Gleason grade tumors grade 6 and less have a
9 very favorable prognosis, intermediate for Gleason
10 7, and a poor prognosis for Gleason 8 through 10.
11 But remember, this is biopsy diagnosis, and I just
12 point out that not all men with a low Gleason score
13 cancer who have surgery are cured of their cancer.

14 Many of these cancers turn out to be higher
15 grade and more extensive in the radical
16 prostatectomy specimen than they were. And even
17 those that are Gleason 6 in the radical
18 prostatectomy specimen are not totally benign. And
19 many patients with high Gleason score tumors 8
20 through 10 can be cured with a single modality
21 therapy of surgery. They're not an inevitable sign
22 of an incurable or metastatic cancer. So grade's

1 an important prognostic cancer, but it's only one
2 of many prognostic factors.

3 We've talked about the modification in the
4 Gleason grading system, and it's worth pointing out
5 that essentially the change in Gleason grading
6 that's come about that was approved by the WHO in
7 2005 did several things. One thing, it moved some
8 of the tumors that were previously classified as
9 Gleason pattern 3 into Gleason pattern 4. That
10 Gleason pattern 1 is basically nonexistent. You
11 virtually never see it anymore. Pattern 2 is
12 almost irrelevant. It's very rare. So
13 essentially, prostate cancers, from the time they
14 start out, the smallest, earliest cancers, are
15 considered 3. So as a result of that, Gleason 3
16 plus 3 is the dominant grade of biopsy cancers, and
17 they're now considered essentially well-
18 differentiated. You occasionally see a Gleason 2
19 plus 3, but that's very uncommon; 3 plus 4 would be
20 considered moderately differentiated; 4 plus 3,
21 moderate to poorly differentiated; and 8 through

1 10, that is Gleason 4 plus 4 or higher, would be
2 more so.

3 In addition, because of the work largely of
4 John Epstein looking at the prognostic significance
5 of tertiary patterns in the original Gleason
6 scoring system, any pattern representing less than
7 5 percent of the tumor on a biopsy or on a radical
8 prostatectomy specimen was ignored. If you
9 recognize those higher patterns and you use that to
10 change the Gleason score, you're shifting the
11 Gleason scores to higher levels. And the result of
12 that, it was well described by Peter Albertsen in a
13 paper entitled "Prostate Cancer and the Will Rogers
14 Phenomenon," the old idea that if you simply keep
15 reclassifying lower-risk patients into higher-risk,
16 the prognosis for every group gets better.

17 This was the results when a group of men who
18 were originally classified as Gleason 3 plus 3 were
19 reexamined. A number of the tumors were reassigned
20 to higher grades. They were taken out of this
21 category of Gleason 3 plus 3, and there were
22 therefore fewer deaths in patients originally

1 classified as Gleason 3 plus 3, a 24 percent
2 reduction in mortality. But that was also true for
3 Gleason 7 and Gleason 8, 9 and 10. As you shifted
4 these tumors into higher grades, the prognosis for
5 each category of grades gets better.

6 So I think that this cautions us to be
7 careful about extrapolating from simply Gleason
8 grade, particularly Gleason grade in a needle
9 biopsy, to what's going to happen to that patient
10 long term. And I'm reminded, for example, of
11 thyroid cancer, where if you look at the
12 pathological criteria for thyroid cancer when you
13 do thyroidectomies, you'll find many patients with
14 poorly differentiated tumor, extracapsular
15 extension, even lymph nodes, who have an extremely
16 good prognosis and do very well with therapy and
17 are at very low risk of dying of their disease.

18 So just because there's a shift in
19 pathologic parameters, that doesn't necessarily
20 translate into the survival curves that you see
21 that are 15 or 20 years old and were based upon a
22 different Gleason grading system. So I think we

1 have to take the grades into account and not focus
2 all of our effort on that.

3 We've heard about the systematic biopsies.
4 I think for those of you who do not treat patients
5 with prostate cancer, there's a fundamental
6 difference in the diagnosis of prostate cancer from
7 breast cancer, where the diagnosis is focused on a
8 target, a lesion, a palpable lesion or a lesion
9 seen on a mammogram. In prostate cancer, there is
10 very rarely a target. Most of the time, the cancer
11 is diagnosed by random, systematic biopsies taken
12 from defined areas of the prostate.

13 So there's a big sampling error in trying to
14 determine what have I seen on biopsy and how does
15 that relate to what's really there, and what does
16 it have to do with the trigger criteria for the
17 diagnosis of cancer in the first place.

18 It's not unusual to have a man with a
19 palpable nodule. You do a systematic biopsy, and
20 the cancer found on biopsy is remote in the
21 prostate from the area of the palpable nodule. We
22 know that men with palpable nodules, the positive

1 predictive of a palpable nodule is only about one-
2 third. So every patient with a palpable nodule
3 doesn't have a palpable cancer, and the same is
4 true with PSA, as I'll show you later.

5 This is a very typical prostate cancer where
6 each Gleason pattern is color coded. Gleason
7 pattern 2 is this favorable shade, 3, 4 and 5. You
8 can see that there's multiple patterns throughout
9 the prostate, and it's very easy to see how a
10 needle put into this area could come up with a very
11 different pattern of Gleason score and a different
12 Gleason score depending upon sampling error.

13 This is a whole mount histologic section of
14 a patient who we would consider to have indolent,
15 latent, clinically insignificant cancer. You can
16 see this patient had a biopsy, had a 3 plus 3
17 cancer. He had his prostate removed, and this is
18 all we could find in the prostate, a minute amount
19 of cancer. That's what we think of when we think
20 about insignificant cancer, but because of the
21 sampling error, that's not what's always there.

1 I'll skip through this and just again point
2 to one study. This is very typical and
3 representative. This was from our institution, 336
4 patients who had biopsy Gleason score and radical
5 prostatectomy Gleason score, showing that the
6 Gleason score on biopsy underestimated the grade of
7 the cancer in 39 percent but overestimated it in 15
8 percent.

9 Just statistically, the higher the Gleason
10 score on biopsy, the greater the likelihood that
11 there's going to be regression to the mean in the
12 prostate. The lower the Gleason score, the greater
13 likelihood there'll be regression to the mean with
14 a higher grade.

15 So it's not surprising to find these
16 differences, but I'd just point out, notice these
17 patients who had a Gleason score 8 through 10
18 tumor, that of a total of 19 Gleason 8 through 10
19 tumors, 12 of them were Gleason 7 or less in the
20 final radical prostatectomy specimen. So just
21 because you assign a patient an 8 through 10 score
22 on biopsy doesn't mean the patient has Gleason 8

1 through 10 in the radical prostatectomy specimen.
2 There's a fair amount of sampling error in all
3 these.

4 As we do more and more biopsies, the
5 sampling error decreases. This shows by the early
6 part of this decade, that the Gleason score on the
7 biopsy was accurate in 56 percent of the patients,
8 overestimated the cancer in about 15 percent, and
9 underestimated it in about 35 to 40 percent. And I
10 think that's still true pretty much today, although
11 the more biopsies you take, the more accurate the
12 grading.

13 This is the prognosis of the same group of
14 patients, radical prostatectomy patients, based
15 upon Gleason score in the radical prostatectomy
16 specimens. So this is supposedly the gold standard
17 or the final diagnosis and the most accurate
18 assignment of Gleason grade. Again, if you look at
19 this top line of Gleason cancer 6 or less, even
20 with surgical treatment, not every one of these
21 cancers is cured. Even when you have the whole
22 prostate and you know the Gleason score is 6, about

1 10 percent or 15 percent of the time, the cancer
2 progresses through initial surgical therapy,
3 arguing that these are not all benign lesions. And
4 the same thing is true if you look at the Gleason 8
5 through 10 in the radical prostatectomy specimen,
6 these patients have a significantly worse
7 prognosis, about one-third less likely to be cured
8 than those patients who were assigned Gleason 8
9 through 10 on the basis of biopsy.

10 So what is the relevance of the Epstein
11 criteria in identifying those at need for
12 chemoprevention? The Epstein criteria came out of
13 the era when we began to realize that grade alone
14 was not sufficient to explain the prognosis of a
15 patient with prostate cancer, that clinical stage
16 was important, serum PSA was important, and even
17 quantitative analysis of cancer and systematic
18 biopsy results all gave independent important
19 prognostic information that could be used for
20 predicting pathologic stage -- that's the Partin
21 tables -- or predicting prognosis.

1 It also led to simple classification schemes
2 now in wide use, like the AUA or D'Amico
3 classification into low-, intermediate- and high-
4 risk tumors. Low-risk tumors, as we've heard, or
5 low clinical stage, Gleason 6 or less and PSA under
6 10. Again, look at the patients with low clinical
7 stage, they do well, but not all of them are cured
8 by having their prostate removed. Again, about 10
9 or 15 percent of those patients will recur.

10 If we look at the long-term probability of
11 dying of cancer in men treated surgically by the
12 risk group, low, intermediate and high, certainly,
13 those men with low-risk cancers have a much less
14 likely chance of dying of cancer over 15 years than
15 intermediate or high risk. But because low-risk
16 cancers make up such a large proportion, nearly
17 half of all the patients, they're responsible for
18 14 percent of the deaths, even more deaths than in
19 the patients with intermediate cancer. Certainly,
20 most of the patients who die of cancer are in the
21 high-risk group, but pointing out that some men not

1 only develop recurrence but die of prostate cancer
2 who have low-risk disease.

3 Part of the reason is the inaccuracy of
4 biopsies. This is a group of patients, nearly
5 2,000, with low-risk prostate cancers who we had
6 the prostate and we looked at the pathologic
7 features of the cancer in these men with low-risk
8 disease. And while 70 percent of them were truly
9 Gleason 6 cancers, 30 percent were not; 14 percent
10 were extracapsular, and some patients had seminal
11 vesicle invasion or positive nodes.

12 So the Epstein criteria were developed
13 partly in response to that kind of understanding
14 that even when you identify somebody with low-risk
15 cancer, some patients will be within that group who
16 actually have higher-risk disease. Is there a way
17 we could identify those patients with very strict
18 criteria? And it was in that atmosphere that the
19 Epstein criteria were developed.

20 We all have known for years that more
21 patients will develop histologic evidence of cancer
22 in their prostate in their lifetime -- this is the

1 lifetime risk based on serially sectioned prostates
2 -- than will be diagnosed with cancer, about 17
3 percent, or die of prostate cancer, about 3.6
4 percent. So there are 11 or 12 men who develop
5 cancer in their prostate for every one who will die
6 of the disease. And we also sought ways to
7 identify who are these patients with histologic
8 cancer that appears to be latent or clinically
9 insignificant.

10 So the earliest work on this in terms of the
11 definition we use today was done by Stamey and
12 McNeal, and they did a remarkably simply study,
13 which you can draw your own conclusions about the
14 validity of it. They looked at the SEER incidence
15 back then in the early 90s and late 80s, and said
16 the lifetime risk of being diagnosed with cancer
17 was about 8 percent.

18 They went to cystoprostatectomy specimens,
19 prostates removed as part of a cystectomy for
20 bladder cancer. These were men with no suspicion
21 of having prostate cancer. They serially sectioned
22 and morphometrically determined the volume of

1 cancer in these specimens. Forty percent of the
2 patients had cancer in the prostate. They made an
3 assumption that 8 percent of the cystoprostatectomy
4 patients, had they lived, would have been destined
5 to develop a clinically diagnosed cancer. So they
6 took that 8 percent out of 40 percent, in other
7 words, the top 20 percent of the cancers by volume,
8 and said these must be clinically significant
9 cancers; cancers that were .5 to 6.1 ccs seemed to
10 be those destined to become clinically significant
11 if the patient had lived. And, therefore, they
12 proposed that cancers less than half a gram were
13 clinically insignificant. Most of these cancers
14 were low Gleason score. They didn't have any
15 Gleason 4 or 5, and they were confined to the
16 prostate.

17 That's really where the idea of a clinically
18 insignificant cancer in a radical prostatectomy
19 specimen developed. It's not necessarily a highly
20 robust database, but it has been widely used.
21 We've published studies classifying patients into
22 clinically unimportant or insignificant cancer,

1 which are less than half a gram, Gleason pattern 3
2 or less, confined to the prostate as opposed to
3 those that appear curable or those that are more
4 locally advanced. And when you look in
5 cystoprostatectomy patients, 78 percent of the
6 patients have an insignificant cancer by those
7 criteria, 22 percent are curable, none are
8 advanced.

9 In non-palpable cancers identified because
10 of an elevated PSA -- this is a paper written in
11 1994 -- 17 percent of the patients had a cancer in
12 the prostate that met clinical insignificance. And
13 of the palpable tumors, only 10 percent did. So
14 there seem to be quite a difference between
15 clinically detected cancers by PSA or DRE and
16 incidental cancers.

17 When we looked at the long-term outlook of
18 men with pathologically clinically insignificant
19 cancers, very few of them ever recur after radical
20 prostatectomy. It's almost an anecdotal case. So
21 these patients truly seem to have a disease that is
22 very low risk, extremely low risk.

1 Jonathan Epstein tried to develop criteria
2 for identifying such cancers in the prostate, and
3 he arrived at these potential definitions; a PSA
4 density less than 1 with fewer than three cores,
5 less than 50 percent of any core, no pattern 4 or
6 5, or a PSA density less than .15 with one core
7 less than 3 millimeters, and you've heard quite a
8 lot about that.

9 The accuracy of this in predicting the
10 presence of a pathologically insignificant cancer
11 is not, I think, clearly established. It's
12 certainly not fully accurate. The data suggest
13 that the positive predictive value is somewhere
14 between around 80 percent, the negative predictive
15 value, a little higher than 80 percent. The
16 sensitivity for detecting insignificant cancers is
17 about 50/50. It varies in different series, and
18 the specificity ranges from 68 to 98 percent; so a
19 reasonable predictive model but certainly not fully
20 accurate and certainly does not fully define the
21 prognosis of a patient.

1 So the next question was, what is the
2 clinical relevance of cancers found on scheduled
3 biopsies as opposed to for-cause biopsies? Well,
4 that data is difficult to come by if you analyze
5 the published studies from the PCPT and the REDUCE
6 trial. But I'll try to show you what data I have.

7 This is a slide from the PCPT investigators.
8 It was sent to me by them, and they've already
9 shown it today. Just to point out that using the
10 Epstein criteria, many of the patients who had
11 biopsy-proven cancers, end-of-study biopsies, with
12 a PSA less than 4 and a DRE that was not
13 suspicious, had cancers that would be considered
14 significant using the Epstein criteria. Going back
15 to the literature and trying to determine the
16 difference between for-cause and scheduled
17 biopsies, you can see Gleason score 7 was about
18 almost 30 percent of the for-cause biopsies in the
19 placebo arm, about 15.8 percent of the scheduled
20 biopsies, so few of these were higher-grade
21 cancers. Insignificant cancers were 39 percent of
22 the scheduled biopsies in the PCPT, as best I could

1 reconstruct, and 24.7 percent of all biopsies in
2 the PCPT. In the REDUCE trial, it appears that
3 Gleason score of 7 or greater was about 30 percent
4 in both arms of the trial.

5 If you look at screening studies done in the
6 United States and Canada and Europe, these are
7 systematic screening trials in which the biopsy
8 data was analyzed; 10 to 36 percent of patients
9 identified with cancer in screening trials have a
10 Gleason 7 or greater tumor, so it overlaps these
11 areas.

12 If you look at the cancers detected in
13 clinical practice, about 35 percent of cancers are
14 Gleason 7 or greater, so a little bit higher than
15 this. If you look at clinical practice cancers
16 today that would meet the Epstein criteria, these
17 are patients who are seen and have treatment for
18 prostate cancer, it represents about 20 percent.

19 So this data is difficult to come by. If you
20 look at the incidence of pathologically
21 insignificant cancer, where radical prostatectomy
22 specimens are available, in the PCPT trial, about

1 41 percent of the placebo patients had a Gleason
2 score 7 cancer compared to 39 percent in screening
3 studies in the United States, 50 percent in
4 prostates removed as a result of screening in
5 Europe, and anywhere from 35 to 63 percent of
6 prostates removed in large clinical practice
7 series. So this data comes from a four-institution
8 study with 12,000 patients and represents probably
9 a typical experience in the United States.

10 If you look at the likelihood that these
11 cancers are organ confined, 80 percent in the PCPT;
12 75 percent in screening in the U.S.; 61 percent in
13 screening in Europe; about 70 percent in
14 contemporary clinical practice; extracapsular
15 extension about 12; 14 percent in PCPT, 12 percent;
16 and 20 percent and relatively few patients in any
17 of groups have some seminal vesicle invasion or
18 positive nodes.

19 You come away from this experience feeling
20 that while , in general, patients in the PCPT and
21 probably in the REDUCE trial had more favorable
22 prognostic features by biopsy or by radical

1 prostatectomy when that was available, that they
2 weren't uniformly very low risk, insignificant
3 cancers.

4 So what is the benefit of preventing Gleason
5 6 cancers compared to Gleason 7? Just a few
6 thoughts on that. If you put patients in a
7 watchful waiting program who meet the Epstein
8 criteria for prostate cancer, and you follow them
9 closely -- this is from Ballentine Carter series at
10 Hopkins -- there's a steady progression rate over
11 time in men who will then develop more unfavorable
12 features and be reclassified as clinically
13 significant.

14 So you can see this reaches almost 50
15 percent by six years. So putting patients in
16 watchful waiting doesn't obviate the possibility
17 that they will be found on subsequent evaluations
18 to have a more serious cancer and end up having a
19 recommendation for treatment.

20 The same thing was true in this series,
21 which is a multi-institutional series that we
22 published. All these patients not only had an

1 initial biopsy that met Epstein criteria, they had
2 a second biopsy that had to meet those criteria
3 before they were put on the trial. So this was
4 very, very strict selection bias for these men, and
5 you can see at five years, 25 percent of them no
6 longer met the criteria and have gone on to
7 recommendation for further treatment.

8 Finally, I think you should be aware that
9 across the United States, even as recently as 2007,
10 watchful waiting is very rarely used to treat men
11 with prostate cancer. The CAPRA scores are a
12 composite prognostic score that incorporates stage,
13 grade, PSA and biopsy results, but these are the
14 very low-risk men. And you can see watchful
15 waiting is somewhere around 5 to 10 percent of
16 these men, in the most recent literature, in the
17 most recent study, 8.5 percent.

18 So watchful waiting is not a way of assuring
19 that a patient who's thought to have a low-risk
20 tumor will never be treated. Few men go into
21 watchful waiting, and when they do, many men come
22 out of watchful waiting for additional disease.

1 Just because you detect a cancer because of
2 an elevated PSA level doesn't make a clinically
3 significant cancer. PSA levels vary quite a bit.
4 We published this paper in JAMA in a 1,000 men
5 without prostate cancer showing that the
6 likelihood, if a man develops an abnormal PSA,
7 whether your threshold is over 4, over 2, age
8 specific reference ranges, many of those men, more
9 than half of them, their PSA on just follow-up with
10 no intervention returns to normal and below the
11 threshold.

12 So many PSA elevations are simply random
13 variations in the PSA produced by the BPH and have
14 nothing to do with the cancer that's found. So
15 many men found on, quote, "for cause" actually have
16 biopsies that would be no different than the
17 scheduled biopsies in the trials you've heard
18 about.

19 In fact, it's been shown that if your
20 prostate gland is a bit enlarged, over 30 grams or
21 50 grams in one study, and your cancer is less than
22 3 grams, which is a pretty big cancer, that the

1 effect of the large prostate confounds the
2 predictive accuracy of PSA to identify the presence
3 of cancer.

4 So, in summary, my take on the field now is
5 that 5 alpha-reductase inhibitors do prevent
6 prostate cancer. I think they seem to have little
7 effect on high-grade cancer. They're generally
8 safe. The performance characteristics of PSA and
9 digital rectal exam are better with men on these
10 drugs. That means that if the patient has a more
11 serious cancer, we're more likely to be able to
12 find it. These drugs could be given to a subset of
13 men at high risk as identified by elevated PSA
14 levels and have almost the same societal benefit as
15 giving them to all men.

16 It reminds me very much of the era before we
17 had medical therapy for BPH. Every man who went in
18 to see a urologist 30, 40 years ago would be told
19 you've got some symptoms, you might as well have a
20 TURP to treat them now. And the patient would say
21 do I really need it? Isn't there any medicine I
22 could take? And the doctor would say no, there's

1 no medicine. And you might as well have the
2 surgery now because if you wait five or 10 years,
3 you'll only be older and the surgery will be harder
4 to go through.

5 When medical therapy comes out for
6 preventing prostate cancer, many men who are found
7 to have prostate cancer, incidentally, because of
8 an elevated PSA or a digital rectal exam that might
9 not be relevant, will grasp for a medical therapy
10 that would prevent them from getting prostate
11 cancer. And I think it would largely change the
12 dynamics, and we'd see a much more wide embrace of
13 watchful waiting.

14 So as a clinician who treats patients, I'm
15 hopeful that we'll have a medication like this if,
16 in your judgment, it seems safe and appropriate.
17 Thank you very much.

18 DR. WILSON: Okay. I'd like to now invite
19 Dr. Walsh.

20 **Guest Speaker Presentation - Patrick Walsh**

21 DR. WALSH: Well, thank you for this
22 opportunity. I think I'll begin with just a little

1 background about myself. I have worked in the
2 field of 5 alpha-reductase for 42 years. It was 42
3 years almost this month when Jean Wilson published
4 his seminal paper in the Journal of Biological
5 Chemistry.

6 In 1974, I had the privilege, while I was on
7 the faculty at the University of Texas Southwestern
8 Medical School, of working with Jean Wilson, the
9 first author of the paper, on the 5 alpha-reductase
10 deficiency syndrome.

11 In the early 1990s, I had the privilege of
12 working with Merck on the successful study and
13 launch of their drug, Proscar.

14 So it has been with great interest that I
15 have followed the use of these agents and role of
16 dihydrotestosterone in prostate cancer, and today
17 I'll share with you some of my views. I have no
18 disclosures.

19 So let's talk first about the rationale for
20 the use of these agents. And I apologize for the
21 cartoon, but there may be people in this room that
22 really are not aware of what 5 alpha-reductase

1 inhibitors, which throughout this talk will be 5
2 ARIs, are.

3 Testosterone, the major circulating androgen
4 in men, enters the prostatic cell and is converted
5 by the 5 alpha-reductase enzyme to
6 dihydrotestosterone, which binds to receptors
7 translocated to the nucleus and activates messenger
8 RNA and protein synthesis.

9 When the 5 alpha-reductase enzyme is
10 blocked, testosterone accumulates in high
11 concentrations in the prostate. It binds to the
12 androgen receptor and is also translocated to the
13 nucleus. It binds with less affinity. So for this
14 reason, you need to understand the 5 alpha-
15 reductase inhibitors do not completely block
16 androgen action.

17 Similarly, if you deal with a tissue -- and
18 I will use the example of use prostate cancer --
19 that has very low 5 alpha-reductase activity,
20 again, the predominant intracellular androgen is
21 testosterone, and in that setting, 5 alpha-
22 reductase inhibitors wouldn't be very active.

1 Now, there are two types of 5 alpha-
2 reductase inhibitors, Type 1 and Type 2. Type 1,
3 its major location is the skin. Type 2 is the
4 prostate. I'm sure everyone in the room probably
5 knows that dutasteride, a dual blocker, blocks both
6 Type 1 and Type 2, whereas finasteride only blocks
7 Type 2.

8 I'm going to get into some commonsense
9 things that many people have heard. One of them is
10 because 5 alpha-reductase inhibitors should be
11 successful because men with congenital 5 alpha-
12 reductase deficiency syndrome do not develop
13 prostate cancer. And that's correct. And the
14 reason is why? For the same reason that women
15 don't, because they don't have a prostate.

16 In utero, under the influence of
17 dihydrotestosterone, the urogenital sinus develops
18 into the prostate. And in the absence of
19 dihydrotestosterone, the urogenital sinus develops
20 into the lower vagina. And so for this reason, men
21 with congenital absence of this enzyme cannot
22 develop either BPH or prostate cancer.

1 The other thing is while tamoxifen prevents
2 breast cancer, why don't 5 alpha-reductase
3 inhibitors prevent prostate cancer? Well, first,
4 tamoxifen is an antagonist of the estrogen receptor
5 that prevents prostate cancer and most importantly,
6 is very effective in treating breast cancer. The
7 comparable agent on the androgen side is
8 bicalutamide, which is an antagonist of the
9 androgen receptor that's effective in treating
10 advanced prostate cancer. However, because it
11 causes impotence and gynecomastia, it is not an
12 appropriate agent for prevention. 5 alpha-
13 reductase inhibitors are not androgen receptor
14 antagonists and are not effective in treating
15 prostate cancer.

16 Let's talk about the mechanism of action.
17 In 1993 when the PCPT trial was launched, we were
18 told that we know that dihydrotestosterone promotes
19 the growth of prostate cancer and finasteride
20 decreases levels of dihydrotestosterone. Thus,
21 with lower levels of dihydrotestosterone, perhaps
22 prostate cancer won't develop.

1 But the real question is, does
2 dihydrotestosterone promote prostate cancer.
3 Number one, the level of the Type 2 5 alpha-
4 reductase enzyme, which is the predominant 5 alpha-
5 reductase enzyme in the prostate, the level of that
6 enzyme is low in prostate cancer. Here you see on
7 the left, messenger RNA, and on the right,
8 enzymatic activity, and you can see that both the
9 messenger RNA and enzymatic activity are lower in
10 cancer.

11 Secondly, when men with BPH are treated with
12 a 5 alpha-reductase inhibitor, if their PSA does
13 not fall by 50 percent, we strongly suspect cancer.
14 Next, as you will learn later in this talk, and
15 you've heard also from Peter, when men are treated
16 with 5 alpha-reductase inhibitors, there is no
17 reduction in high-grade tumors. When men with
18 metastatic disease are treated with finasteride,
19 there is no clinical response. And in the Merck
20 package insert dated August 2010, it states, "No
21 clinical benefit has been demonstrated in patients

1 with prostate cancer treated with Proscar," which,
2 of course, is the trade name for finasteride.

3 These and other data indicate that
4 testosterone itself, not dihydrotestosterone, is
5 the major androgen that promotes the growth of
6 significant prostate cancers. And if inhibition of
7 dihydrotestosterone synthesis does not adversely
8 affect the growth of prostate cancer, why should we
9 expect these inhibitors to prevent it?

10 Now I'm going to turn to some clinical
11 observations, and Peter's already talked about the
12 importance of Gleason score and I'll skip that.
13 And I know that you know the details of both
14 trials, the PCPT trial, which used finasteride,
15 lasted seven years; the REDUCE trial used
16 dutasteride, was a four-year trial. It's
17 been said that the patients in the REDUCE trial
18 were at increased risk. They were high risk. Why?
19 Because they'd already undergone a biopsy, it had
20 to be a negative biopsy, and because the PSAs were
21 higher than in the PCPT trial. Now, were they
22 actually at higher risk? In this study, in men

1 with PSAs of 2.5 to 10 and a prior negative biopsy,
2 their risk of developing a subsequent diagnosis of
3 cancer was lower, only 17 percent than men who have
4 not had a prior biopsy was 29 percent.

5 Indeed, if we look at the placebo groups in
6 terms of the percent of patients who had a positive
7 biopsy and the percent with Gleason 8 to 10, you
8 can see the percent with the positive biopsy was
9 the same in the two trials. But the chance of
10 having Gleason 8 to 10 disease was four times
11 higher in the PCPT trial than in the REDUCE trial.
12 So I conclude that men in the REDUCE trial are not
13 a high-risk group for being diagnosed with prostate
14 cancer.

15 I'm going to talk next about the effect of
16 inhibition by 5 alpha-reductase inhibitors on
17 prostate cancer detection in three settings:
18 Number one, what is their effect in men with an
19 abnormal digital rectal examination or PSA, the
20 setting where we would use the drugs clinically?
21 What about their effect in men with no indication
22 for a biopsy, men who would never undergo a biopsy

1 in a clinical setting? And finally, what is their
2 effectiveness in preventing men from undergoing a
3 biopsy in the first place?

4 Let's take the first setting, the clinical
5 setting, and this was the first seven years of the
6 PCPT trial. This was the primary endpoint; and
7 that is, in patients with a placebo or finasteride
8 who are diagnosed with prostate cancer. So during
9 the first seven years, participants underwent an
10 annual digital rectal examination and PSA
11 measurement, which was corrected for the effect of
12 the drug by multiplying by two for the first three
13 years and thereafter, 2.3. And a biopsy was
14 performed if the rectal exam was abnormal or the
15 PSA corrected for the drug was greater than 4. And
16 we have been told that finasteride reduced the
17 number of cancers by 25 percent.

18 However, in the first seven years, 15
19 percent fewer men on finasteride, who had an
20 abnormal PSA or rectal exam, actually underwent a
21 biopsy. And this alone reduced the number of
22 cancers by 15 percent. Therefore, you cannot look

1 at the total number of cancers. You need to look
2 at the percent positive biopsies. In men on
3 finasteride, it was 26.5 percent; in placebo, 29.5
4 percent; a 10 percent difference, not 25 percent.
5 Therefore in a clinical setting, the reduction in
6 cancers would be only 10 percent, a reduction that
7 is not statistically significant.

8 Now, we've learned from the FDA's reanalysis
9 of this data that it's not 25 percent; it's
10 actually a 14 percent reduction. And if 15 percent
11 fewer patients underwent a biopsy, then that's a 14
12 percent reduction in number of cancers. Well, if
13 you reduce that by the number of people that didn't
14 undergo a biopsy, I think it's a total wash.

15 Therefore, finasteride has no primary effect
16 on preventing prostate cancer. It only prevents
17 biopsies in men who have an indication for them.
18 And the effect in the PCP trial lasted only seven
19 years. On the right, you can see the number of new
20 cases in the placebo and finasteride group, and the
21 number of high-grade cases at that point was twice
22 as high.

1 I'm going to make one more point, and I will
2 follow that up later in my talk on two occasions.
3 However, at four years, the number of cancers at
4 that time, of high-grade cancers, in the placebo
5 and finasteride group are the same.

6 Now, we've been told that the high-grade
7 disease is an artifact. And this is the way the
8 story goes. The amount of high-grade disease in
9 the prostate of men on placebo and finasteride was
10 exactly the same. However, because finasteride
11 shrinks the prostate, it's easier to find high-
12 grade disease with a needle biopsy in a smaller
13 prostate. Now, if this were true, you could look
14 at the amount of cancer in the entire prostate, not
15 just the needle biopsies, to prove this. And that
16 actually was done in this nice study by Dr. Lucia.
17 This study compared Gleason scores on the biopsy to
18 the Gleason score on the radical prostatectomy
19 specimen in men in this trial who underwent
20 surgery.

21 If shrinkage explained the high grade
22 disease, then in the placebo men with larger

1 prostates who are Gleason 6 on biopsy, you would
2 expect that in the radical prostatectomy specimens,
3 you'd find more Gleason 7. And what did you find?
4 There was no difference. When you looked at the
5 biopsy to radical prostatectomy, Gleason scores,
6 the number of upgrading was the same.

7 So that makes me conclude that shrinkage
8 does not make it easier to detect high-grade
9 disease. More high-grade disease is found because
10 there is more high-grade disease to find.

11 Now, why is that? Well, does it cause the
12 cancer or does it just improve the ability of PSA
13 to find high-grade disease? I'm not going to argue
14 that here in the few minutes I have left, but the
15 fact remains that men on finasteride are more
16 likely to be diagnosed with high-grade disease.

17 Let's take a look at the REDUCE trial, the
18 protocol-independent biopsies done between years 2
19 and 4. These were for-cause biopsies performed
20 either for an abnormal digital rectal examination
21 or an increase in PSA from the nadir, as described
22 here. And, again, when you take a look at the

1 placebo- and dutasteride-treated groups, there was
2 no difference in the percent positive biopsies.

3 So, in summary, in men who have an abnormal
4 digital rectal examination, or PSA, the clinical
5 setting, 5 alpha-reductase inhibitors, if the PSA
6 is corrected for the effect of the drug, there is
7 no reduction in the risk of being diagnosed with
8 cancer, and with longer use, there is the higher
9 risk of being diagnosed with high-grade disease.

10 There's an interesting observational study
11 that was carried out by the Finnish Prostate Cancer
12 Screening trial, where they looked at prostate
13 cancer incidence among finasteride users in that
14 screening trial. And they were able to carry this
15 study out because they were able to link pharmacy
16 records with the screening trial and they were able
17 to not only know what drugs they were on but how
18 long they were on it.

19 In this trial, men on finasteride had no
20 significant decrease in prostate cancer incidence.
21 However, men who took it for longer than four years
22 -- that's where that four-year mark comes up I

1 spoke about earlier - had a 2.6 fold increased risk
2 of being diagnosed with high-grade disease. Now,
3 because prostate shrinkage occurs within six months
4 of treatment, yes, this effect was not seen for
5 four years, one cannot attribute this to the
6 improved ability to detect a high-grade disease in
7 a smaller prostate.

8 Now, let's take a look at biopsies in men
9 who had no indications, men who would never have
10 undergone a biopsy in a clinical setting. In the
11 PCPT trial, these were the end-of-study biopsies.
12 These men had been screened for seven years, they
13 had a negative digital rectal examination, they had
14 a PSA less than 4, and in this select group of
15 people, there was a 33 percent decrease in Gleason
16 6 disease, but there was no effect on patients with
17 high-grade disease.

18 The REDUCE trial, of course, this was the
19 primary endpoint. These patients had one or two
20 prior negative biopsies and more than two to four
21 years of screening. And you can see there was a 22
22 percent decrease in Gleason 6 and no decrease in

1 Gleason 7 to 10. Although there was no overall
2 increase in high-grade disease at year 4, 12 men on
3 dutasteride versus one on placebo had Gleason 8 to
4 10. And I understand now, using the modified
5 Gleason scoring system, the number is 14 versus
6 zero.

7 So what can we make of this? Why is there
8 increased high-grade disease at Year 4? Well, the
9 investigators attribute the 12 high-grade tumors to
10 a reduction in the 141 low-grade cancers at year 2,
11 reasoning that 8 percent progressed to Gleason 8 to
12 10 two years later. However, Roehl found, in a
13 similar group of men who had a negative biopsy, on
14 the second biopsy, only 1 percent had Gleason 8 to
15 10, and on the third biopsy, 2 percent. Neither of
16 these projections reach 8 percent.

17 These tumors cannot be explained by an
18 artifact. Prostate shrinkage, there was no
19 decrease in the size of the prostate in men on
20 dutasteride over those two years, and when you
21 compare them to the placebo group, there was only a
22 7 percent change. And, again, you cannot blame it

1 on an improved performance of PSA because these
2 were not PSA-driven biopsies.

3 So the curious question, a serious question,
4 is what would have happened had the study been
5 longer and biopsies had been performed at years 6
6 and 8. Would there have been even more high-grade
7 tumors? This is of concern because, based upon
8 what we know with the longer use of 5 alpha-
9 reductase inhibitors, high-grade disease becomes
10 more prevalent. And to err on the side of safety,
11 I think we should strongly consider this
12 possibility. Indeed, I think a trial of prevention
13 for four years, looking at the 20-year or 30-year
14 natural history of prostate cancer, is far too
15 short to commit someone to a lifetime treatment.

16 So, in summary, in patients who have no
17 indication for a biopsy, there is a 22 to 33
18 percent decrease in Gleason 6 disease with no
19 decrease in life threatening tumors.

20 Now, what are these tumors? At autopsy,
21 about half of men have small indolent tumors in
22 their prostates. These tumors do not elevate PSA

1 and are not palpable. I believe that these are the
2 tumors that were reduced by 5 alpha-reductase
3 inhibitors.

4 What about preventing men from under-doing a
5 biopsy? The only study that sheds light on that is
6 the Prostate Cancer Prevention Trial, and in that
7 trial, finasteride reduced the number of men who
8 would be candidates for a for-cause biopsy in the
9 first seven years by only 9.6 percent.

10 So what are my recommendations? First of
11 all, what is the value of inhibiting Type 1? Well,
12 you can see that reduction in PSA with dutasteride
13 and finasteride is the same. Reduction in prostate
14 size is the same. The reduction in a positive
15 biopsy for an abnormal DRE and PSA, there is no
16 reduction. The reduction in random biopsies of
17 what I would call autopsy cancers, 22 to 33
18 percent. Reduction in Gleason 7 to 10 in those
19 patients, zero. And had I seen the FDA's
20 reappraisal of the data, I would add to this line
21 now an increase in Gleason 8 to 10 in those

1 patients is significantly increased with both
2 drugs.

3 So what is their value? Well, in prostate
4 cancer, 5 alpha-reductase inhibitors are weak
5 androgen antagonists because there's less 5 alpha-
6 reductase to block. Their major effect is the 50
7 percent reduction in PSA arising from benign
8 disease. Their treatment effect, which is really
9 weak early hormonal therapy, causes a 23 to 25
10 percent reduction in small Gleason 6 tumors that
11 would have only been detected by autopsy, and the
12 muted effect last less than seven years.

13 What is their danger? Because 5 alpha-
14 reductase inhibitors lower PSA arising from benign
15 disease -- again, this is the PSA arising from
16 benign disease -- they give men a false sense of
17 security. Men will interpret their decrease in PSA
18 like their decline in lipids after taking a statin.
19 Look, my PSA was elevated, but it fell 50 percent.
20 This drug really works. It's preventing me from
21 getting prostate cancer. And you can hear that as
22 a sound bite on the television at night in an ad

1 directed to laypeople. These men will really need
2 to understand what their PSA is.

3 In this study by Dr. Thompson in men on
4 finasteride, if their PSA ever goes up at all,
5 their risk of having cancer is threefold higher and
6 their risk of high-grade disease is sixfold greater
7 than men without an increase.

8 I wasn't here this morning, so I don't know
9 anyone's talked about Dr. Andriole's nice article
10 that just came out in the Journal of Urology,
11 looking at how you might use PSA in monitoring
12 people on dutasteride. And he suggested that if you
13 look again for an increase from nadir to trigger a
14 biopsy, and you place that at the very lowest
15 level, which isn't really realistic, at .1 --
16 that's within the assay variation, but we'll use
17 that number -- 43 percent of men with high-grade
18 disease will be missed.

19 But I think this is also an underestimation
20 because all of these men had a prior biopsy before
21 entering the study. Most Gleason 8 to 10 tumors
22 were identified and eliminated. So, actually, this

1 is a population of patients from which you cannot
2 generalize to an unbiopsied population.

3 Well, if the goal of 5 alpha-reductase
4 inhibitors, as Dr. Scardino nicely said and I agree
5 100 percent, is to reduce biopsies and side effects
6 of treatment, why don't we focus on improving PSA
7 testing? And Dr. Scardino and his group have come
8 up with an excellent approach using a four
9 kallikrein panel. Application of this panel to a
10 thousand men with an elevated PSA would reduce the
11 number of biopsies by 513 and would only risk 12 of
12 100 high-grade cancers.

13 What kind of advice are we being given as
14 clinicians about what to do? Well, these are the
15 clinical practice guidelines that the American
16 Society of Clinical Oncology and the American
17 Urological Association have promulgated.
18 Asymptomatic men with PSA less than 3 who are
19 regularly screened or are anticipating undergoing
20 screening for early detection may benefit from the
21 discussion of both the benefits and side effects.
22 However, the panel cannot recommend a specific cut

1 point to trigger a biopsy for men taking 5 alpha-
2 reductase inhibitors because no specific cut point
3 or change in PSA has been prospectively validated.
4 And that is incorrect. This was the primary
5 endpoint for the PCPT.

6 So this is the kind of advice that we as
7 physicians are being given today; and that is, only
8 use it in men who are being screened but we can't
9 tell you how to screen. Is that because it only
10 works when you fool the patient into believing his
11 PSA is low? I believe that's the only way it
12 works.

13 So in summary, for the patient who is
14 worried about dying from prostate cancer, treatment
15 with a 5 alpha-reductase inhibitor is absolutely
16 the last thing he should do. It does not prevent
17 the disease but gives him the false sense of
18 security that it does, and in doing so may delay
19 the diagnosis until he has aggressive disease that
20 may not be curable. For the patient who doesn't
21 want to be diagnosed, why not advise him just to

1 stop PSA testing or something we're working on,
2 improving PSA testing?

3 I'll finish with this slide from The Medical
4 Letter, the respected Medical Letter, where they
5 commented on the REDUCE trial and said, "In
6 clinical practice, taking dutasteride would
7 probably decrease the number of prostate biopsies
8 and subsequent radiation treatments and
9 prostatectomies, but it might also increase the
10 number of deaths from the disease."

11 Thank you for the opportunity of addressing
12 you.

13 **Questions to Presenters**

14 DR. WILSON: Thank you very much.

15 So I would like to now open the floor up to
16 the members of the committee to ask questions to
17 the presenters.

18 Yes, sir, Dr. D'Agostino.

19 Dr. D'AGOSTINO: We have read all this
20 material very carefully and heard the discussions
21 and appreciate all the wonderful discussion and all
22 our wonderful presentations, and I must admit that

1 I'm struck with the fact that the potential for
2 high risk is really there.

3 In the first presentation by Merck, the PCPT
4 study, I don't buy into any of the sort of
5 potential detection biases. I think that the FDA
6 has addressed it, the fact that they probably
7 weren't there.

8 With the REDUCE study, there's one
9 presentation piece that keeps bothering me, where
10 the sponsor is saying that we see more high disease
11 because of the two year biopsy. And hearing Dr.
12 Walsh's presentation and trying to put that
13 together, has the drug reduced the chance of
14 getting -- or the chance of being diagnosed with a
15 Gleason less than 6 only to save you later on for a
16 much higher disease?

17 So I'm saying that they're claiming that the
18 placebo group and the ones who had cancer were
19 removed, but by doing that, they've said that they
20 missed the higher disease they would have seen
21 later on had they kept everybody in. But the fact
22 is that the drug does seem to be reducing it less

1 than 6. And when you got to four years, all of
2 those individuals who weren't less than 6, or a
3 number of them who weren't less than 6, are now in
4 the high grade.

5 Am I interpreting in the same way, Dr.
6 Walsh, that you are interpreting the results?

7 DR. WALSH: Yes, I think that's where
8 Dr. Scardino and I probably -- where the pedal hits
9 the metal. And that is, do you want to have people
10 benefit from not having Gleason 6 or do you want
11 people with Gleason 8 to 10 disease not even know
12 about it until it's too late to cure it? I think
13 that's the trade-off.

14 DR. D'AGOSTINO: And just one last comment
15 or question, in using the REDUCE numbers that the
16 FDA came, the 60 to 1, in terms of the reduction in
17 the disease and the 200 to 1 in terms of the high
18 grade possibly coming, then I would say like if you
19 take the 60 and you multiply it by 3, you get
20 approximately 200, 180. So I look at 200
21 individuals, three of them will be saved from the

1 less than 6, but one of them will go on to the 8 to
2 10.

3 Is that a right interpretation? That might
4 the FDA to answer that. If you put that 60 to 1
5 together with the 200 to 1.

6 Dr. NING: Right. Mathematically, you could
7 do that, but we are not clear whether when
8 increasing high-grade tumor, would it be trade-off
9 with one decrease in --

10 DR. D'AGOSTINO: I'm not trying to trade it
11 off. I'm just trying to say that the 60 to 1 and
12 the 200 to 1 look like.

13 DR. NING: Yes. That's yes.

14 DR. ANDRIOLE: May I clarify something?
15 Because I think there is some confusion about the
16 numbers needed to treat in the REDUCE trial. In
17 the REDUCE trial, the number needed to treat was
18 19, and we got to that, based on the 5.2 percent
19 absolute risk reduction over four years for cancer.
20 Now, we considered all cancers we found meaningful,
21 and I realize that when the FDA looked at it, you
22 excluded the Epstein criteria cancers from the

1 denominator, and, hence, your number needed to
2 treat was higher.

3 But I think it's valid to consider all the
4 cancers we found in the REDUCE population
5 significant. Why? Because these are men who had
6 elevated PSAs, and as we've heard from numerous
7 speakers today, men like this, with elevated PSAs,
8 frequently undergo repeated biopsies of the
9 prostate. We know that from the SEER database. We
10 know that from the PLCO cancer screening trial,
11 which some have criticized for not biopsying
12 patients enough. So it's very, very common for
13 these men to undergo repeated biopsies, and when
14 they're found to have cancers, they are generally
15 treated. And that means it's a significant cancer.

16 One semantic point I would also like to make
17 is that it is true that we call the biopsies in the
18 REDUCE trial a study-mandated biopsy, but for many
19 of those men, it was merely a substitute for what
20 would have been a for-cause biopsy. And we know
21 that because the majority of the men in the placebo
22 arm had rising PSAs and would have met the NCCN

1 criteria to undergo biopsies if they had not
2 already been scheduled to undergo a protocol-
3 mandated biopsy.

4 DR. WALSH: Could I make one comment to
5 Dr. D'Agostino's question?

6 DR. WILSON: Yes, sir.

7 DR. WALSH: Stewart Justman wrote a very
8 interesting book, "Do No Harm." And it's a very
9 interesting historical walk through all the
10 different things that we have done as physicians
11 which have caused harm. And he speaks about the
12 presence of high-grade disease with these drugs.
13 He makes the point like the FDA made the point; and
14 that is, if you're going to take perfectly normal
15 people and treat them with a drug, there can be no
16 side effects.

17 So I don't think we can even use a trade-off
18 necessarily in numbers. I mean, I understand it
19 gives you -- that number is pretty astounding you
20 came up with. But the fact that if you're going to
21 give anything to someone who's perfectly healthy
22 and put them at risk for a complication such as

1 fatal disease, I think any small number of that, as
2 Stewart Justman pointed out, he felt was
3 unacceptable.

4 DR. D'AGOSTINO: Yes, I was going for the
5 meaningful cancers, but even if you enlarge it to
6 the more broad case, I still see that there's a --
7 I wouldn't call it a trade-off. I'm just trying to
8 get a sense of what the numbers are saying, and it
9 is like 1 to 200, 3 to 200.

10 DR. WILSON: May I please remind everyone,
11 do not speak without being recognized by the chair
12 first? And I do want to also address what the
13 sponsor just said. We must distinguish between a
14 meaningful cancer that leads to metastatic prostate
15 cancer and death from one that leads simply to a
16 prostatectomy. Let's not confuse the two, and I
17 believe that's just what we heard from the sponsor.

18 So meaningful cancer, as we are trying to
19 prevent deaths from prostate cancer here; that's
20 what this drug is being looked at for. It is not
21 being looked at to prevent having a prostate
22 biopsy.

1 So I have a question that I would like to
2 ask Dr. Walsh because I'd like to understand a
3 little bit more about the biochemistry of the 5
4 ARIs.

5 In your schematic, I thought I heard you say
6 that by interfering with it, that the amount of
7 testosterone rises within the prostate.

8 DR. WALSH: That's right. It rises actually
9 50-fold. Whether that goes to super-physiologic
10 levels -- I mean, there have been some people who
11 have speculated that the high levels of
12 testosterone may be one of the reasons there is
13 high-grade disease because testosterone is the
14 intracellular androgen that appears to most affect
15 prostate cancer growth. I don't know the answer to
16 that.

17 It certainly must go up to the level of a
18 plasma. So it goes to very high levels, and that's
19 why it's not a complete androgen blockade. And
20 that's why if you treat patients with prostate
21 cancer, like the Merck insert says, it doesn't
22 work.

1 DR. WILSON: So I think that we know from
2 the studies that treatment of prostate cancer that
3 has spread beyond the prostate with 5 ARIs has no
4 effect. So this drug does not affect at least what
5 we would consider to be clinically meaningful
6 prostate cancers that lead to patients' death, plus
7 we also have some evidence that testosterone may be
8 an important hormone for actually driving prostate
9 cancer.

10 Would you not say that's a true statement?

11 DR. WALSH: I would. And that's my whole
12 argument about prevention. And that is, in the
13 for-cause setting, all I see is it's lowering PSA,
14 and so men aren't getting biopsies. It's not
15 because those cancers are having a significant
16 suppression.

17 DR. SCARDINO: Mr. Chairman?

18 DR. WILSON: Yes, sir.

19 DR. SCARDINO: Just a couple of comments, I
20 think the physiology has to be distinguished
21 between the effects of these 5 alpha-reductase
22 inhibitors on metastatic prostate cancer or large

1 prostate cancers and their effect on early, small
2 prostate cancers. We've got lots of evidence that
3 taking these drugs reduces the incidence of atypia,
4 it reduces the incidence of high-grade PIN, it
5 reduces the incidence of low Gleason grade prostate
6 cancer. So the physiology of low-grade cancer may
7 be quite different, and the rationale may be
8 totally different.

9 Secondly, we're talking about these Gleason
10 6 and Gleason 8, 10 cancers as if a Gleason 6
11 cancer can never threaten your life and a Gleason 8
12 through 10 cancer always threatens your life is
13 tantamount to metastatic disease and death. And
14 that forgets the long effects of time on these
15 tumors. We don't know, but we have lots of
16 evidence to suggest many men with Gleason 6 cancer
17 will develop higher-grade cancer. They are at risk
18 of dying of cancer. So I don't think it's the
19 equivalent to substitute the present biopsy results
20 for the long-term clinical outcome. That's why we
21 do surgery and radiation for these asymptomatic men
22 with cancers found because of slightly elevated or

1 slightly rising PSAs or an abnormal digital rectal
2 exam today.

3 DR. WILSON: So I would agree with
4 everything you said, and I think what we don't know
5 and what is lacking from these trials is we have no
6 evidence from these trials that this drug is
7 preventing the progression, or the rate of
8 progression, of low-grade Gleason cancers that can
9 be treated with this to a higher grade. And I
10 guess that is the piece that we are lacking in
11 terms of being able to say that this drug will
12 actually prevent clinically meaningful tumors that
13 lead to patients' deaths.

14 Let me turn to Dr. Kelly.

15 DR. KELLY: Thank you. I just want to carry
16 on that theme a little further. One of the
17 concerns we have is we always try to extrapolate
18 from one disease state of prostate cancer to
19 another, and sometimes that can be a very dangerous
20 thing, just like Dr. Scardino said.

21 But one of the big things that I want to
22 understand and if either of you know it is, is

1 what's the natural history of high-grade cancers
2 treated with these 5 alpha-reductase inhibitors?
3 Do they act the same as any other Gleason 8, 9 or
4 10? Do we know that data? Is there any data on
5 that?

6 DR. SCARDINO: I think that there's very
7 little data on that. But 5 alpha-reductase
8 inhibitors, as you know, Kevin, are used for
9 advanced prostate cancer in combination with anti-
10 androgens. And while it's still not a proven
11 indication and there have been no randomized
12 trials, there's no evidence of activation.

13 Are you aware of any data, Pat?

14 DR. WALSH: I think maybe his question is
15 different, and it's a key question. And that is,
16 if it's possible that the 5 alpha-reductase
17 inhibitors by treating the low Gleason score in
18 these tumors, then made it more apparent these were
19 Gleason 8 tumors, whereas, if in fact, if they had
20 not been treated, they might have been Gleason 3
21 plus 4 rather than 4 plus 4. I think that's the
22 question.

1 So we should know whether these are tumors
2 that have been made more aggressive or tumors that
3 just appear more aggressive if we have follow-up
4 and we could compare people who had Gleason 8
5 disease who had been treated with 5 alpha-reductase
6 inhibitors to patients who did not. And we do not
7 know that data. It's just too bad that the PCPT
8 trial did not have the follow-up because we might
9 have that answer seven years later.

10 DR. KELLY: So just to carry on that theme
11 then, one of the concerns is there's major safety
12 issues because of these high-grade tumors. The
13 question is, is what are those major safety issues
14 if we don't know the natural history of these high-
15 grade cancers?

16 DR. WALSH: I would assume, using Stewart
17 Justman's thing, that you have to err on the side
18 of safety.

19 DR. KELLY: So there is no data, and we
20 don't know those safety concerns then; is that
21 correct?

1 DR. SCARDINO: No, I think that's true. I
2 don't think we really have any systematic data on
3 the follow-up of men with these tumors. I am
4 impressed that the pathologic features of the high-
5 risk cancers in the PCPT that were on the drug
6 seemed to be more favorable than the pathologic
7 features of the high-grade cancers in the people in
8 the placebo arm. But I think that's a teaser and
9 not definitive.

10 DR. WILSON: I just wanted to follow up on
11 that. I think that that's a worthwhile topic for
12 hypothesis, but I think it is a red herring. If
13 you have somebody that has Gleason 8, we have to
14 assume that it's going to have the natural history
15 of other Gleason 8 tumors until proven otherwise
16 for consideration of the current issue.

17 Yes, Dr. Kelly?

18 DR. KELLY: I don't agree with that, and I
19 think that as we treat higher-grade tumors with
20 hormonal therapy, the natural history of those on
21 hormonal therapy is different. So I don't agree
22 with that point one bit because we have no data on

1 that, and you can't assume that you take data from
2 one disease state and apply it to another, it's
3 going to pertain to it. And I think that that is
4 an unknown, and we need further follow-up and
5 longer studies to actually study this.

6 So how can you say there's increased risk
7 when you do not know the natural history of this
8 cohort?

9 DR. WILSON: No, Dr. Kelly, I think you
10 misunderstand what I said. What I said is that
11 within the context of approval of a drug such as
12 this, one has to err on the side of assuming that
13 the 8s are going to act like other 8s. You cannot
14 throw out the idea that they may not, and,
15 therefore, we just disregard it. It is a matter of
16 a study. I would laud the companies to study it,
17 but for the consideration of what we're dealing
18 with here, I do not think that we should begin to
19 make suppositions that the high-grade disease we're
20 seeing is somehow more indolent. You may be right,
21 but I don't think it should be part of the
22 consideration.

1 Dr. Curt?

2 DR. CURT: Thank you, Dr. Wilson. We've
3 been talking about whether or not long-term
4 exposure to this agent leads to high-grade disease,
5 and I thought GSK was able to give us some
6 reassuring safety data in the setting of low-grade
7 prostate cancer and in the setting of BPH, where,
8 in fact, there was no increased incidence of high-
9 grade disease.

10 We have to remember that these are drugs
11 where there are millions of years of safety data.
12 And I was wondering if either sponsor, either Merck
13 or GSK, had any data on risk of prostate cancer in
14 the setting of BPH where this drug has been used
15 for years, where both of these drugs have been used
16 for years.

17 DR. PAOLETTI: A general comment,
18 Mr. Chairman. If this is a debate where we are
19 allowed to participate as well to the debate?
20 Okay. Because there are many experts that would
21 like to add their point of view.

1 DR. ROEHRBORN: Claus Roehrborn speaking for
2 GSK. I want to just discuss for a moment the trial
3 that was mentioned or the study that was mentioned
4 by Dr. Walsh by Roehl. And he stated that in this
5 serial biopsy group of men, the Gleason 8 to 10
6 yield was 1 and 2 percent at the second and third
7 biopsy round in patients who had a prior negative
8 biopsy.

9 Now, this is exactly the situation in the
10 dutasteride arm in REDUCE because those men in the
11 dutasteride arm had a negative biopsy at baseline
12 and at year 2. And if they were found to have
13 Gleason 8 to 10 in a subsequent biopsy, let's say
14 at year 4, it would be the precise situation what
15 the Roehl study describes.

16 If we review the Gleason 8 to 10 rate in
17 these patients, in the dutasteride arm in REDUCE,
18 it is 0.5 percent at two years and it is 0.5
19 percent at four years. It does not increase. It
20 is also half of what was reported by Roehl in his
21 serial biopsy study, and there are other serial
22 biopsy studies that show similar data.

1 So we should be careful when talking about
2 increasing in Gleason 8 and 10. This is lower than
3 the expected rate of 8 to 10 in a serial biopsy
4 population in which the first and the second biopsy
5 may have missed the cancer. This is the first
6 argument.

7 I will ask Dr. Logothetis, who will now talk
8 about the placebo arm in the REDUCE trial, because
9 the Roehl paper does not apply to the placebo arm.
10 In the placebo arm, positive biopsy patients were
11 removed from consideration because they were found
12 to have cancer, taken out of the study, and could
13 not possibly be rebiopsied later on. The profound
14 effect that this has on the placebo arm and the
15 imbalance at the four-year end-of-study biopsy will
16 now be discussed by Dr. Logothetis.

17 DR. LOGOTHETIS: There are a couple of sort
18 of explicit and some implicit concerns that I heard
19 in this discussion for two sides of this coin. The
20 first side is the low-grade patients. The second
21 side is the potential for missing or accelerating
22 the development of high-grade cancers.

1 I'd actually like to look both sides of
2 those coins. I think just as we're very cautious
3 in redefining the importance of the high grade, we
4 should also be very cautious in not modeling and
5 redefining or diminishing the importance of low
6 grade. I think Dr. Scardino did a good job to say
7 that all these are not benign even from the
8 potential for lethality, and the endpoint of this
9 study was to reduce the frequency of cancer under
10 the assumption that that's a favorable event for
11 patients. And actually, it did show that, and it
12 showed that in a group of diseases that were
13 prospectively defined as being significant because
14 the community has agreed and the patients can't
15 deal with this uncertainty, and they get
16 interventions. And that uncertainty is often well
17 justified, as Dr. Scardino showed.

18 So when we sit in the clinic and we decide
19 on individual patients, can we observe, it's no
20 surprise that the minority of patients accept
21 observation because that uncertainty drives
22 treatment, and that uncertainty is justified.

1 The second issue is the challenge of dealing
2 with this do no harm, which we are certainly very
3 sensitive to. And now I'll put my sort of hat for
4 being considerate of the whole community of
5 patients that may get exposed to the risk of this
6 drug.

7 There is this observation that can't be
8 ignored, that there are some high-grade cancers
9 that are enriched or maybe even increased in
10 frequency that are present there. Leaving aside
11 the preclinical studies, because there's
12 preclinical data on either side of this coin, the
13 reality is that these occur at a very low rate.
14 The principal difference within the group of
15 patients in the prospective study is not the
16 increase in the rate of high grades, it's .5
17 percent, as was repeated, in the first half of the
18 study and in the second half of the study. It's
19 explaining the surprising and puzzling observation
20 of sudden disappearance of disease in the placebo
21 group.

1 That whole event is what drives this
2 difference, that puzzling decline may be from an
3 imbalance in these groups of patients where the
4 tumors were removed from this operation. That's
5 the puzzling issues.

6 So I challenge the notion that there's
7 progressive increase in Gleason score 8. I'll
8 challenge the notion that there's increase over
9 time, based on the data. I'll challenge the notion
10 that these are insignificant cancers based on
11 prospective definition of what was significance at
12 the time and now by the community. And I'll
13 actually challenge the issue that we're certain
14 that there is an increase in high grades, although
15 all of us are alarmed by that and all of us would
16 expect to be very careful. And I think when you do
17 the calculations up there, you can see that the
18 differences are not increasing over time.

19 DR. WILSON: Okay.

20 DR. WALSH: May I respond, Mr. Chairman, to
21 that?

22 DR. WILSON: Yes.

1 DR. WALSH: I don't understand the argument
2 that in the placebo group the 18 were removed. In
3 dutasteride group, the 17 were removed. And you
4 have a 12-fold increase at the next biopsy
5 interval. What I want to see is I want to see this
6 film running, and I want to see what it is in two
7 years. And that is the concern. But the idea that
8 the placebo 18 were removed, well, the 17
9 dutasteride were removed, too.

10 DR. ANDRIOLE: May I clarify something
11 because it is not the 18 and the 17 that are
12 considered to be removed. It's the Gleason 5 to
13 7s, the 558 and the 417 that were removed from the
14 study.

15 DR. WALSH: And I addressed that saying that
16 that --

17 DR. ANDRIOLE: And we know from a rebiopsy
18 study by Chu in Toronto that 8 percent of men who
19 have Gleason 5 to 7 prostate cancer, who undergo a
20 repeat biopsy on a watchful waiting program, will
21 be found to have Gleason 8 prostate cancer on their
22 first follow-up biopsy.

1 DR. WALSH: Those are people who are
2 diagnosed with cancer. These men were not
3 diagnosed with cancer. That's a whole different
4 setting.

5 DR. ANDRIOLE: No, no. We're referring to
6 the difference, the 141 cases, excess cases of
7 Gleason 5 to 7 cancer found in the placebo group
8 during the first round of biopsies in the REDUCE
9 protocol. If those 141 men had stayed in the
10 protocol, had they undergone a repeat biopsy of the
11 prostate, we would anticipate, like Chu, that about
12 8 percent of them would have been upgraded to
13 Gleason 8.

14 DR. WALSH: Let me --

15 DR. ANDRIOLE: -- 8 percent of 141 is about
16 11 or 12 more cancers. So the number of Gleason 8
17 cancers would have been identical.

18 DR. WALSH: Let me give the audience
19 something to chew on. And that is, you said Chu's
20 study is of patients in expectant management.
21 Those people already have a diagnosis of cancer.
22 These other people don't have a diagnosis of

1 cancer. That's a whole different group, Gerry. I
2 mean that's --

3 DR. ANDRIOLE: Dr. Walsh, I'm not making
4 myself clear.

5 DR. WILSON: Wait, wait.

6 DR. PAZDUR: Okay. Folks, order in the
7 court here.

8 DR. WILSON: Order, please; please.

9 DR. PAZDUR: Everybody sit down and let's
10 get two chairs for those gentlemen there, and we'll
11 call on them when it's necessary.

12 DR. WILSON: I agree.

13 DR. PAZDUR: Okay. Just sit down; sit down.

14 This is supposed to be for people in this
15 group that are sitting at the table to ask the
16 sponsor and everybody else questions. We realize
17 that there are widely held beliefs with a lot of
18 emotion here, but let's control the emotion, and
19 let's ask the questions of the people around the
20 table, and not have a debate between the different
21 urology people in the different companies and the
22 experts that we brought forth here.

1 So, Nicole, please get a chair for the two
2 doctors that are there. And, gentlemen, please sit
3 down, and when you're called on, we'll ask your
4 opinion. And please state your name when you
5 address the table here.

6 DR. WILSON: Let me just say that your names
7 are being put on a list. If you've held your hand
8 up once, you don't need to hold it up again and you
9 will be called on in the order.

10 Now, Dr. Curt asked a question, and
11 unfortunately, nobody responded. So, Dr. Curt,
12 would you ask your question?

13 DR. CURT: I just wanted to say with this
14 issue of whether or not there is an increased risk
15 of high-grade disease with a long exposure. I
16 thought GSK did give some interesting data in the
17 setting of BPH and early prostate cancer, where
18 there's actually not an increase in high-grade
19 disease. And I wanted to remind the committee that
20 these are both agents with long clinical exposure.
21 GSK has more than 5 and a half million patients
22 years of exposure for this drug.

1 I'm just wondering, is there any evidence,
2 either in the setting of clinical trials with BPH,
3 early prostate cancer, or the clinical use of these
4 agents in BPH, that what we're talking about is in
5 any way real in terms of millions of years of
6 patient exposure? So are there safety data is what
7 I'm asking.

8 DR. WILSON: So can I ask the sponsor or
9 either of our two distinguished speakers if they
10 have any data that addresses Dr. Curt's question.

11 One at a time. You would like to answer
12 that? Okay. Go ahead.

13 DR. KAUFMAN: In response to Dr. Curt's
14 question, the data --

15 DR. WILSON: Thank you. Could you please
16 state your name.

17 DR. KAUFMAN: Keith Kaufman, clinical
18 research at Merck Research Laboratories.

19 So in addition to the data that you've seen
20 from PCPT, we have two large studies that were
21 conducted in men with BPH, approximately 3,000
22 patients each, treating men for about four years

1 with randomization one-to-one to Proscar or
2 placebo.

3 So in the PLESS trial, which was the first
4 that I'll speak to, this was 3,040 men randomized
5 one-to-one to Proscar or placebo for four years.
6 And in that study, as you see, for men randomized
7 to finasteride, there were 72 total prostate
8 cancers diagnosed in the finasteride group, 77 in
9 the placebo group, for a diagnosis rate for
10 finasteride of 4.7 percent and placebo 5.1 percent;
11 not significant.

12 If we look just at the for-cause biopsies
13 that were generated; that is, prostate cancer
14 diagnoses, based during the study on a PSA or an
15 abnormal digital rectal, it was 2.5 percent on
16 finasteride and 3.4 percent on placebo.

17 The second study is MTOPS, the medical
18 therapy of prostatic symptoms. This was a full-
19 factorial study of over 3,000 men randomized on
20 1-1-1 (ph) to placebo, the alpha blocker doxazosin,
21 finasteride 5 milligrams, or the combination. And

1 this is the cumulative percentage of incidence of
2 prostate cancer events in the trial.

3 DR. WILSON: So the issue at hand is high
4 grade. We know that it reduces low grade. What
5 about high grade?

6 DR. KAUFMAN: We have Gleason score data
7 from PLESS that we can share with you here. So of
8 the 72 total cancers in the finasteride 5 milligram
9 group and the 77 total cancers in the placebo
10 group, this was the distribution of Gleason scores
11 out of a total of 149. There were 12 high grade in
12 the finasteride and 17 in the placebo group.

13 DR. WILSON: Okay. Thank you.

14 Dr. Sekeres.

15 DR. SEKERES: Thank you, Dr. Wilson.

16 These are two extraordinary studies that
17 have enrolled tens of thousands of men to receive
18 these drugs, and I think both arguments about the
19 potential for biases are valid on both sides of the
20 fence. But at the end of the day, we have two
21 well-designed prospective studies, both of which
22 have shown an increase in high-grade prostate

1 cancer in patients who are treated with these
2 drugs. And other studies can be shown to say,
3 well, it didn't show it here, but these weren't
4 necessarily the same patients who were eligible for
5 the studies we're discussing here, and they
6 wouldn't necessarily fit the label that's being
7 discussed here as well.

8 So I think the crux for this part of the
9 argument that we're discussing right now, and I'm
10 focusing just on the high-grade prostate cancers,
11 is what happened to them afterwards. And I don't
12 think anybody's asked the companies directly for
13 follow-up. We've all heard that there isn't any
14 follow-up, but I'd actually like the companies to
15 say for the record is there follow-up on these
16 patients with high-grade prostate cancers.

17 Did they respond to subsequent hormonal
18 therapy, which really gets at the theory that Dr.
19 Walsh advanced earlier, of whether or not it's even
20 rational to try to prevent prostate cancer with
21 this class of drugs.

1 So could I have somebody from both companies
2 comment, is there follow-up on how these patients
3 were treated subsequently and whether or not they
4 were treated successfully subsequently?

5 DR. THOMPSON: My name is Ian Thompson. I'm
6 the principal clinical investigator of the Prostate
7 Cancer Prevention Trial. When the trial was
8 unblinded, we asked the question whether or not it
9 would be possible to continue the follow-up of all
10 these individuals, and we had an extended follow-up
11 period to follow the individuals with a prostate
12 cancer diagnosis, understanding that because they
13 were unblinded, subsequent prostate cancer events
14 themselves in the non-prostate cancer patients
15 would be uninterpretable.

16 During that period of time - I don't know if
17 we have the slide -- I believe it was five prostate
18 cancer deaths over the course of the trial, 6 in
19 finasteride (unclear); 6 in placebo. It may be the
20 other way around. We had prolonged follow-up of
21 these individuals for death.

1 Here are the data coming up. From the long-
2 term follow-up, the total number of prostate cancer
3 deaths were 3 and 3 in the two groups out of 18,880
4 men that had actually been enrolled.

5 The challenge with survival is when you have
6 numbers like that, we asked ourselves the question
7 would it be even feasible to follow these
8 individuals for another 5, 10 or 15 years, and the
9 decision was made that the resources for that were
10 --

11 DR. SEKERES: I understand that. I --

12 DR. THOMPSON: I'm sorry. To answer your
13 other question with regards to response to hormonal
14 therapy, we don't have those data. As the patients
15 were subsequently -- they had met the primary
16 endpoint and many of the study sites had closed.
17 We don't have the data with regards to the
18 response.

19 DR. SEKERES: Ian, I am a member of SWOG,
20 also. I understand what it's like to try to get
21 data from a cooperative group after a study has
22 ended.

1 So just for the record, if you could answer
2 the question directly. In patients who were
3 diagnosed with high-grade prostate cancers, who
4 were treated with finasteride, do you have any data
5 on how they were treated subsequently and whether
6 that treatment was successful?

7 DR. THOMPSON: No, we don't.

8 DR. SEKERES: Okay. Thank you.

9 DR. PHILLIPS: From GSK, I'd like to ask
10 Dr. --

11 DR. WILSON: Excuse me. Would you please
12 ask to be recognized?

13 DR. PHILLIPS: Could I be recognized?

14 DR. WILSON: Yes. Please state your name
15 and ask to be recognized.

16 DR. PHILLIPS: My name is Anne Phillips.
17 Could I be recognized?

18 DR. WILSON: Yes.

19 DR. PHILLIPS: To give you data from GSK,
20 I'd like to ask Dr. Castro to come to the podium.

1 DR. CASTRO: Thank you. My name is Ramiro
2 Castro. I'm an urologist working in clinical
3 research in GlaxoSmithKline.

4 So I want to address a couple of questions
5 from the chairman and the speakers.

6 DR. SEKERES: I asked a specific question,
7 and I'd like you to answer that question; could
8 you, please?

9 DR. CASTRO: Yes. So we have information
10 from the Extension study, which is a study
11 involving, 2,700 patients that previously
12 participated in the REDUCE. The vast majority of
13 them are not in the current medical therapy that
14 were given at the trial. We have identified 14
15 cancers during the extension study, nine in
16 dutasteride, five in placebo, one Gleason 9 in
17 dutasteride, four Gleason 7s in dutasteride.

18 The other source of information is coming
19 from how many cancers are diagnosed after
20 discontinuing the therapy in the 30 days after
21 discontinuing the therapy. There were nine in
22 placebo, six in dutasteride.

1 The final comment is, of those Gleason 7 to
2 10 that were diagnosed in the trial, the
3 information about the stage is 19 were 3 to 4 in
4 placebo, 14 to 3-4 in dutasteride. This is the
5 information we have.

6 DR. SEKERES: That isn't the question I
7 asked, though. I can repeat it for you, if you'd
8 like.

9 Among the patients diagnosed with high-grade
10 prostate cancers, who were treated with drug, how
11 were they treated subsequently and were they
12 treated subsequently successfully? Do you have
13 that data or no?

14 DR. CASTRO: This information, we haven't
15 collected.

16 DR. SEKERES: Thank you.

17 DR. WILSON: I'd like to recognize
18 Dr. Garnick.

19 DR. GARNICK: Thank you. I have two
20 questions relating to the non-prostate cancer
21 adverse side effects from both studies. In the
22 briefings materials that we were presented as

1 committee members, if one takes a look at the death
2 rate from hematological cancers on finasteride
3 versus placebo -- and I'm specifically referring to
4 the FDA pages 34 to 35 in their document -- I
5 calculate that there were 36 deaths secondary to
6 acute leukemia, acute myelogenous leukemia,
7 lymphoma or multiple myeloma on finasteride versus
8 placebo. If one collectively takes a look at the
9 gastrointestinal cancers on finasteride versus
10 placebo, it includes esophageal, gastric,
11 colorectal cancer, I calculate 73 deaths for GI
12 cancers on finasteride versus 51 on placebo.

13 Then if one takes a look at the dutasteride
14 data, the nonfatal SAEs of blood in lymphatic
15 system was 18 for dutasteride versus 6 for placebo.
16 I'm just wondering if that was sort of
17 epiphenomenon or do we think there's an issue
18 there. And my question is, what do the
19 carcinogenicity studies show for both finasteride
20 and dutasteride, and are there any post-marketing
21 surveillance studies to indicate whether this is
22 just sort of anecdotal or a trend? And that's my

1 first question. I also have a second question as
2 well.

3 DR. WILSON: Why don't you just go ahead and
4 answer your first question? Would someone from the
5 sponsor like to address that? Please state your
6 name into the record.

7 DR. PHILLIPS: Anne Phillips, may I be
8 recognized? I'd like to ask Dr. Harmony Garges,
9 our safety physician, to respond to the question.

10 DR. GARGES: Hi, I'm Harmony Garges with
11 GlaxoSmithKline. In terms of the question, there
12 isn't any evidence from preclinical data to support
13 carcinogenesis or direct carcinogenic effect with
14 dutasteride. Additionally, from the post-marketing
15 arena, we haven't had any signal for any
16 malignancies, whether it be hematologic
17 malignancies or other in post-marketing data.

18 DR. WILSON: Dr. Garnick, did you have a
19 second question?

20 DR. GARNICK: Yes. The second question
21 relates to a concern that I have on really the
22 determination of the sexual side effects on all

1 arms of both studies, whether it be finasteride,
2 dutasteride or placebo. I assume that in the --
3 and this is an assumption -- finasteride, the
4 sexual function data was prospectively collected
5 versus the dutasteride, in which the sexual
6 function was probably just patient reported.

7 So, for example, if you take a look at the
8 incidence of impotence on the dutasteride, it was
9 12.1 percent versus 8.1 percent on placebo. And in
10 the finasteride study, the numbers were 68.9
11 percent versus 63.1 percent.

12 So my question to the sponsor is I assume
13 that these were either self-reported or
14 prospectively reported to account for such a huge
15 discrepancy. And, certainly, the numbers of 12
16 percent and 8 percent are not compatible with
17 what's seen in clinical practice.

18 DR. WILSON: Would the sponsor like to
19 respond?

20 DR. PHILLIPS: Anne Phillips from GSK. I'd
21 like to ask Dr. Garges to respond.

1 DR. GARGES: So then speaking for GSK, what
2 we reported in the REDUCE trial specifically was
3 incidence. So these were new events. So if a man
4 entered the trial and had a history of sexual
5 dysfunction at baseline, continued to have that
6 sexual dysfunction while on the trial, that was not
7 counted as an event because it was present at
8 baseline. So our data reflects new cases, incident
9 cases.

10 DR. WILSON: Would Merck like to comment?

11 DR. THOMPSON: Thank you, Mr. Chairman. Ian
12 Thompson, Southwest Oncology Group.

13 Two comments with response to that,
14 Dr. Garnick. If at any one point in time, a
15 participant reported a sexual event, it was counted
16 over the seven-year period of time. So an
17 individual may have had a sexual adverse report at
18 one point in time and then later on it was the
19 cumulative numbers. I'd like to show you a
20 slide. We had a prospective evaluation of sexual
21 function over time in these men. Dr. Carol
22 Moinpour published this in JNCI. And as you can

1 see, this was using a sexual function score that
2 works very similar to the current IPSS. It
3 correlates quite closely. And you can see, over a
4 period of time, the sexual function score changed
5 over time. So we had both an instrument measuring
6 it as well as self-report.

7 But the reason for the higher numbers is
8 most likely due to the opportunity over a seven-
9 year period of time, multiple telephone calls,
10 every six-month visits, and the opportunity for a
11 man to say whether or not he had a sexual AE. I
12 hope that answers your question.

13 DR. GARNICK: Thank you. It does.

14 DR. WILSON: I would like to recognize
15 Dr. Steers.

16 DR. STEERS: Thank you, Mr. Chairman.

17 The fact of the matter is these drugs are
18 already approved for use, or this particular drug,
19 and we're asked to consider, or the FDA is, the
20 specific labeling indications that are before us,
21 and that's where my questions will be directed,
22 based on the data that we saw today and has been

1 given to us previously, especially when marketing
2 direct to consumers and physicians are going to
3 trigger off this label.

4 So for the sponsor I have two points of
5 clarification.

6 Number one, for the first part of the
7 indication, where it states reduction in prostate
8 cancer, if the sponsor truly believes this is
9 clinically significant cancer, why was this not
10 stated, or if they think it should correlate with
11 the data, why was not low-grade cancer placed in
12 this indication to help clarify what I think is
13 evident to everyone here, the heterogeneity and the
14 complexity of prostate cancer.

15 Second, as indicated by Dr. Walsh, the
16 second part of the label, those men at increased
17 risk. Well, obviously, increased is not stated
18 compared to who. And these men have all had a
19 previous biopsy and still an elevated PSA. So is
20 it compared for men with just elevated PSA, and is
21 there any data that men who've had one negative
22 biopsy with persistent elevated PSA are more likely

1 to die of prostate cancer or have a greater amount
2 of significant prostate cancer?

3 So for both the sponsor, experts, first the
4 indication or why so generic a label for prostate
5 cancer, realizing not all prostate cancer is
6 created equal. And number two, increased, why is
7 there not clarification, and do the experts in this
8 room believe these men are at increased risk who
9 have had a negative biopsy and still PSA?

10 DR. WILSON: Would the sponsor like to
11 respond?

12 DR. PHILLIPS: Yes, it's Anne Phillips. In
13 terms of the indication for reduction of prostate,
14 the wording was chosen specifically because that is
15 the purpose of the study, to look at reduction in
16 risk of detection of prostate cancer in men at
17 risk. So that was why that wording was there.

18 In terms of defining if the men were at
19 risk, they were at increased risk defined by having
20 a prior negative prostate biopsy for clinical
21 concern and also having an elevated PSA. The men
22 were at increased risk, we believe, as is evidenced

1 by the fact that in the placebo arm, 72 percent of
2 the men in the placebo arm actually continued to
3 have a rising PSA.

4 But I'd like to ask Gerry Andriole, the
5 principal investigator, to discuss this from his
6 clinical experience.

7 DR. ANDRIOLE: Yes, thank you. I continue
8 to believe that these men are at elevated or
9 increased risk for prostate cancer because their
10 PSA is elevated, and we know from many data sources
11 -- and I'll mention two, the community-based
12 screening that occurs in the PLCO cancer screening
13 trial, and a report in the Journal of National
14 Cancer Institute looking at SEER Medicare datasets
15 of men with elevated PSAs and the rate and
16 frequency of which they undergo repeat biopsies,
17 that these men are at substantial risk to undergo a
18 repeat biopsy and to have clinically-detected
19 prostate cancer because of an elevated PSA.

20 As Dr. Phillips was saying, in the placebo
21 arm of the REDUCE trial, although many of the
22 biopsies were called protocol-dependent or

1 protocol-mandated biopsy, in fact, a large majority
2 of the men in the placebo arm had rising PSAs and
3 would have met criteria to undergo a for-cause
4 biopsy. The fact that they're called protocol-
5 mandated biopsy is more a semantic difference than
6 a real one.

7 DR. WILSON: Okay. I would like to
8 recognize Dr. Logan.

9 DR. LOGAN: I have two questions. The first
10 is for the sponsor of the dutasteride study. This
11 revisits a little bit the issue that was raised
12 previously about the cancers diagnosed in the year
13 2 biopsy versus the year 4 biopsy. Maybe if the
14 sponsor could bring up Slide A-45; this is showing
15 the mean PSA levels of the placebo versus the
16 dutasteride over time. The question that I had
17 was, it appears that the high-risk cancers are
18 showing up sooner, as early as the six-month time
19 point in the placebo arm, whereas the drop in the
20 PSA levels is perhaps masking that.

21 Could you comment on whether any additional
22 analysis of this has been done, possibly in terms

1 of separating out these profiles for those that are
2 diagnosed with high-risk disease at two years
3 versus those that are diagnosed at four years?

4 DR. PHILLIPS: It's Anne Phillips at GSK. I
5 would like to ask Dr. Chris Logothetis who
6 presented this part of the presentation.

7 DR. LOGOTHETIS: That's an interesting
8 question. The answer is that there's been no
9 detailed analysis, given the relatively small
10 numbers, to try to link any subtle changes with any
11 of these groups. So the answer is there's been no
12 further analysis done on the PSA in this here.

13 DR. LOGAN: And I raise the issue because of
14 it suggests that there's possibly a shift in the
15 timing of the occurrence of the cancers, and that
16 may be an explanation for why you're not seeing as
17 many in the second time period in the placebo
18 group.

19 DR. LOGOTHETIS: Let me get Dr. Rittmaster
20 here. Maybe he can --

21 DR. RITTMASER: Roger Rittmaster from GSK.
22 So I wasn't entirely sure of your question in terms

1 of the dutasteride responses. One of the things we
2 learned from this trial is the initial fall at six
3 months does not predict whether a patient has low-
4 grade, high-grade, or no cancer at all. And I
5 think that was an a-ha moment in terms of the
6 understanding in the urology community.

7 In terms of the rise in the placebo group,
8 we haven't actually correlated zero to six months
9 in the placebo group with the eventual occurrence
10 of prostate cancer. It's something that could be
11 done, but it hasn't been done, specifically.

12 DR. LOGAN: So the second question I had is
13 related to the issue of potentially approving this
14 as a chemopreventive agent, either of these drugs.
15 In terms of implications of compliance, of the
16 compliance of patients with the drug and for a
17 general population of patients that are possibly
18 not at real high risk, and so they may or may not
19 be very rigorous about taking the drug, we've seen
20 that both of these agents affect the PSA levels.
21 They may affect monitoring for prostate cancer,
22 incidence of biopsy.

1 So the question is, have either of the
2 sponsors looked at compliance issues and whether
3 that impacts monitoring of PSA levels?

4 DR. PHILLIPS: Anne Phillips from GSK. We
5 haven't looked at monitoring obviously in the real-
6 world situation because we have only looked at this
7 in terms of prostate cancer risk reduction in the
8 REDUCE trial itself. And in that artificial
9 situation, compliance was very high. However, I do
10 understand the concern about how men would be
11 taking this in the real-world setting. And we
12 certainly want to ensure that they and the
13 prescribers clearly understand what the drug does,
14 how PSA should be followed, the importance of
15 compliance, and that any confirmed rise from nadir
16 of a patient's PSA, that should give pause for
17 thinking is there a high-grade cancer there that is
18 not being suppressed by dutasteride.

19 If this indication is approved, we certainly
20 would work closely with the FDA to ensure that
21 appropriate education and support for prescribers
22 and also for patients is in place.

1 DR. WILSON: I would like to make a comment
2 and ask the sponsor something, and I want to try to
3 do this slowly because this is a very, I think,
4 complicated subject.

5 In the Proscar study, I think it's
6 unequivocal that there were more high-grade 8 to
7 10s in the treatment arm than in the placebo arm.
8 And so that's obviously what we're all worried
9 about.

10 Now, in the REDUCE trial, the analysis also
11 showed at the end that there were more Gleason 8 to
12 10 in the treatment arm. Now, the company has
13 stated, and I think it may well be true, that the
14 placebo arm had fewer cases because there were more
15 prostate cancers, Gleason 6s, that were diagnosed
16 in the first round and, therefore, removed, and,
17 therefore, they weren't there to contribute to the
18 next round. And this is where my issue lies.

19 Are we simply putting our head in the sand
20 and reducing the diagnosis of Gleason 6, by
21 reducing them 26 percent, such that we are missing
22 a subset of those cases that will, in fact, have

1 high grade because it is the detection of Gleason 6
2 or higher that activates therapy. And we know that
3 that if you -- we don't know this, but the data
4 would indicate that if we reduce the 6 and we don't
5 find it, that some of those patients will still
6 have 8. So in many ways, that 6 may be an increase
7 biomarker of there being tumor there. And so we
8 simply may be delaying diagnosis of the higher-
9 grade disease, and that is the last thing you want
10 to do when you're trying to cure patients with
11 prostate cancer.

12 So I would like to hear from the sponsors
13 and also Dr. Walsh what their take is on this.

14 DR. PHILLIPS: So it's Anne Phillips from
15 GSK. I would like to have Dr. Koch and then
16 Dr. Logothetis respond to your concerns.

17 DR. KOCH: Gary Koch, biostatistics
18 department of University of North Carolina. All of
19 my activity for GSK is through a cooperative
20 agreement between GSK and the university. That
21 agreement pays part of my regular university salary

1 and has a structure for travel reimbursement. I
2 have no other financial ties.

3 So what I'd like to do is to try to
4 re-explain Slide A-44. This was part of the main
5 presentation. So in years 1 and 2, there were 18
6 and 17 Gleason 8 to 10s in the two arm, a rate of a
7 half of a percent in each of the two arms. And in
8 years 3 and 4, you also had a half of a percent in
9 the dutasteride arm, but there was a very low rate,
10 .04 percent, in the placebo arm.

11 One explanation for the very low rate in the
12 placebo arm was that this study had informative
13 missing data with respect to the outcome of 8 to
14 10s during years 3 to 4 because the patients that
15 are in the dark blue met the primary endpoint
16 during years 1 and 2, which was any grade that was
17 6 or higher or 5 or higher, as you will. So they
18 were then considered to have met the endpoint, and
19 they were then removed from risk.

20 What we did as a hypothetical exercise was
21 to assume that had they not been removed from risk,
22 had they not been removed from the study and

1 managed with their status known but actually had
2 remained in the study, 5 percent in each of the two
3 arms would have at years 3 and 4 progressed to a
4 Gleason 8 to 10. My understanding is there's
5 literature that suggests that percent might be as
6 high as 7 percent. And when we do that, we would
7 then have imputed 28 additional events for the
8 placebo group in years 3 and 4 and 21 for the
9 dutasteride group, which would have meant that had
10 we not removed those patients from risk in years 3
11 and 4, we would have seen 29 on placebo, 33 on
12 dutasteride. And then if we wanted to then know
13 what the total number would be, it would be 18 plus
14 29 or 47 on placebo, 17 plus 33 or 50 on
15 dutasteride.

16 But it was very important to try to clarify
17 here that we have what is known as informative
18 censoring. Those patients who probably are the
19 ones that are at the greatest risk for progressing
20 to an 8 to 10 by having already become a 5 to 7
21 were by study design and by the ethics of the trial
22 removed from risk. And, thereby, one could not

1 observe what their 8 to 10 status would have been
2 for years 3 and 4.

3 DR. WILSON: So maybe you said exactly what
4 I said, which is that the placebo group, you pulled
5 them out, and, therefore, they weren't there to be
6 diagnosed later on, because if they still had, they
7 might well have had the 8 to 9, but you simply
8 don't pick them all up; because in the dutasteride
9 arm -- you were pulling more of them out in a
10 placebo arm because they were coming out with the
11 low-grade Gleasons that weren't being cleared out
12 by this ARI.

13 DR. KOCH: Yes, they were pulled out from
14 both groups.

15 DR. WILSON: I understand.

16 DR. KOCH: There were 140 more pulled out
17 from the dutasteride group.

18 DR. WILSON: Right.

19 DR. KOCH: I'm sorry, from the placebo
20 group.

21 DR. WILSON: Exactly.

1 DR. KOCH: There were 140 more pulled out
2 from the placebo group.

3 DR. WILSON: So one hypothesis is that when
4 you pull somebody with Gleason -- if you take 20
5 people with Gleason 6 and you biopsy them, you have
6 a certain rate. But if you then take that 20 and
7 you artificially hide the fact that -- you take out
8 five or six because you've simply hidden the fact
9 that they have higher-grade disease because the
10 Gleason 6 is no longer there, I think what's
11 happening is you may then delay the diagnosis of
12 the high-grade disease because you don't always get
13 it on your first biopsy. In fact, we know you
14 don't get it on any of your biopsies 50 percent of
15 the time, because prostatectomy specimens in some
16 series have shown upgrading as high as 50 percent.

17 So my concern is that you are basically
18 putting your head in the sand, the patients are, by
19 having Gleason 6 fall, and, therefore, not
20 triggering definitive therapy. So some of those
21 may have a artificial sense of being well when, in

1 fact, they're walking around with higher-grade
2 tumor.

3 DR. KOCH: I think that one of the clinical
4 colleagues can explain what happened when those 5
5 to 6s were pulled out.

6 DR. WILSON: Let me just have Dr.
7 D'Agostino.

8 DR. D'AGOSTINO: An alternative explanation
9 is that in the individuals that didn't have grade 5
10 to 7 in the treatment group, they were being
11 positive effects on the -- or the drug was
12 positively affecting them. They didn't have grade
13 below 5, and then they went on to develop grades
14 between 8 and 10. It doesn't necessarily have to
15 be that they -- and so when you start hypothesizing
16 all sort of alternatives or explanations, it could
17 be that the drug is really holding them off and
18 then suddenly hitting them with the 8 to 10, or it
19 could be that it's grading up. Both of those
20 explanations fit the data.

21 DR. WILSON: That's true. My concern,
22 though, is that having Gleason 6 on a biopsy is a

1 trigger for therapy in most folks, and when you do
2 prostatectomy, half of those people will have
3 higher grade disease.

4 DR. D'AGOSTINO: I agree 100 percent.

5 DR. WILSON: You've now taken out 25 percent
6 of those folks. You're taking out that trigger,
7 and the whole question is, is this also preventing
8 the higher grade disease. And at least in the
9 Proscar study where there were end-of-therapy
10 biopsies, the answer was no. There was more high-
11 grade disease, leaving me concerned that you are
12 delaying definitive therapy by taking out this
13 important biomarker.

14 Now, there's no doubt that some of those
15 people will have low-grade disease, and you will be
16 over-treating folks. But that's what we're here to
17 look at, what are the risk-benefit lies.

18 Yes, sir?

19 DR. THOMPSON: Mr. Chairman, let me respond
20 to that, because one of the things we oftentimes
21 miss is that we assume that the current methodology
22 of detection of prostate cancer is acceptable,

1 using a threshold of 4, which was the study design
2 to begin with. We've seen the results of that in
3 the PLCO clinical trial that showed that using that
4 threshold of 4, there is no relative risk reduction
5 in mortality. The European trial used a lower
6 threshold in many circumstances. Our biggest
7 problem is that there are probably -- because 92
8 percent of the American population who are risk of
9 prostate cancer have a PSA less than 4, and so our
10 biomarker performs very poorly for the detection of
11 the disease that you're concerned with.

12 I think the evidence -- I've not heard any
13 evidence to the otherwise that the evidence is very
14 clear that detection of cancer, high-grade cancer,
15 is substantially improved, vis-a-vis PSA, by its
16 performance characteristics. And the other
17 observation is our biggest problem -- in fact,
18 today it was published in the Journal of the
19 American Medical Association, a study on active
20 surveillance. And we are seeing increased interest
21 in active surveillance. And my personal concern as
22 a urologic oncologist is that patient with a

1 Gleason 6 tumor that wants to go on active
2 surveillance who's actually harboring a high-grade
3 tumor. And the evidence to me is compelling, the
4 no increase in hazard rate, the significant
5 improvement in sensitivity of detection of prostate
6 cancer.

7 Now, we're not talking about the positive
8 predictive value, as Dr. Walsh pointed out. We're
9 talking about if you actually have high-grade
10 disease in your prostate, if you have on a 5 ARI,
11 specifically finasteride, it substantially
12 increases the likelihood and it's intuitive. It's
13 intuitive, the prostate is smaller, higher
14 likelihood you'll detect it, and it's been
15 documented in patients who are not on 5 ARIs. The
16 larger the prostate, the greater the likelihood
17 you're going to miss it.

18 Those patients who are interested in active
19 surveillance, the potential risk is we may be
20 missing these high-grade tumors. And so in
21 balance, what you have is the potential for
22 reducing the likelihood of detection of

1 inconsequential cancers. And it's not trivial.
2 There may be people in the audience who have had
3 radical prostatectomies or had radiotherapy. We as
4 urologic oncologists manage those patients. Their
5 lives are profoundly affected by the disease. But
6 also the individual with low-grade disease who
7 actually has high-grade disease, that because we
8 can't find the disease, we place them on active
9 surveillance and put them at risk by virtue of what
10 Dr. Scardino showed earlier, by the failure rate of
11 these people active surveillance. So actually, I
12 think it goes both ways.

13 DR. WILSON: I just wanted to make one
14 comment. An analysis by the FDA about prostate
15 volume and frequency of finding high-grade disease
16 did not bear out that the smaller prostate volume
17 is the reason why there was a higher rate of 8 and
18 higher. I also think from first principles, unless
19 we are affecting 8 to 10, we are likely delaying
20 the diagnosis of high-grade patients because we're
21 reducing the ability to see low-grade disease that
22 may be a biomarker for higher-grade tumor. And so

1 I think that's a worry, and I just think that
2 that's just what the data would raise as concerns.

3 Let me turn to -- the FDA had a statement.

4 DR. THEORET: So we just wanted to point
5 out, in terms of the high-grade disease, there's
6 definitely a difference when you look at the
7 grouping of Gleason scores 7 to 10 and Gleason
8 score 8 to 10. I'm going to ask our statistician,
9 Dr. Zhang, to comment.

10 DR. ZHANG: Thank you. My name is Jenny
11 Zhang. I'm the statistical reviewer for the
12 Proscar application. This slide summarizes the
13 results from the post hoc analyses that were
14 conducted or referenced by the applicant for
15 Gleason score 7 to 10 versus 8 to 10 cancers.

16 All the analyses have their own caveats and
17 limitations, some of which were discussed in
18 Dr. Theoret's presentation. However, in the
19 interests of time, I'm not going to go into those.
20 I just want to focus on the discrepancy between the
21 results for GS 7 to 10 versus Gleason score 8 to 10
22 cancers.

1 The first analysis fits logistic regression
2 models, and this was published in Cohen in 2007,
3 one adjusting for baseline covariates only, denoted
4 as Model A, and the other adjusting for additional
5 post randomization covariates of prostate volume
6 and number of biopsy cores.

7 The applicant claims that since the odds
8 ratio for the latter model decreased from the
9 former to be close to 1, then detection bias due to
10 finasteride-induced prostate shrinkage could
11 account for the increase of the Gleason 7 to 10
12 cancers that we're seeing on finasteride. However,
13 we see that for Gleason score 8 to 10s this was not
14 the case, and the odds ratio do not decrease for
15 the latter model.

16 The second analysis uses the relationship of
17 prostate volume and high-grade cancer seen on the
18 placebo arm to predict the number of high-grade
19 cancers on finasteride. And this was also
20 published in Cohen, et al.

21 The hypothesis here is that if the observed
22 and the predicted number of high-grade cancers on

1 finasteride was similar, then the increase in the
2 high-grade on finasteride could be explained by
3 detection bias. However, again, we see that the
4 observed and predicted numbers of the Gleason score
5 8 to 10 cancers were not similar. Observed was 73,
6 and the predicted was only 47.

7 The third analysis was shown in the main
8 presentation. This analysis looked at the 25
9 percent of biopsy-detected cancer patients who also
10 underwent a prostatectomy. The risk of Gleason 7
11 to 10 cancers on finasteride was 20 percent for 7
12 to 10 and close to 80 percent for Gleason 8 to 10s.

13 Another exploratory analysis evaluated the
14 sensitivity of biopsy as compared to prostatectomy,
15 which is what Dr. Thompson's point was, and claimed
16 that there was a high rate of under-grading by
17 biopsy on finasteride for Gleason 7 to 10 cancers.
18 However, when you look at the Gleason 8 to 10
19 cancers, the sensitivity of biopsy was similar
20 between the treatment arms.

21 The last set of analyses were already
22 discussed in Dr. Theoret's presentation and again

1 shows the inconsistency of the results between the
2 Gleason 7 to 10 and 8 to 10 results. Thus, this
3 inconsistency can be seen across the post-hoc
4 analyses in questions of robustness of the Gleason
5 7 to 10 results.

6 So one other point I wanted to make, if
7 that's okay, was that I know that some people may
8 say that looking at the Gleason 8 to 10 results are
9 not reliable because there are much fewer cancers
10 on the Gleason 8 to 10. However, I wanted to
11 remind you that 75 percent of the increase in the
12 Gleason 7 to 10 cancers were driven by an increase
13 in the Gleason 8 to 10 cancers.

14 Although the confidence intervals for the
15 Gleason 8 to 10 results are wider, however, that
16 does not necessarily mean that the Gleason 8 to 10
17 results are less reliable. On the contrary,
18 defining high-grade cancers more stringently as
19 Gleason 8 to 10 should actually reduce the noise in
20 the data and allow the true treatment effect to
21 emerge more clearly. An analogy may be a clinical
22 trial with loose eligibility criteria that results

1 in a low magnitude of treatment effect compared to
2 the same clinical trial with more stringent
3 eligibility criteria that would result in a higher
4 magnitude of effects.

5 Just really quick, as a simple graphical
6 illustration of what I just said, the red lines in
7 this graphic denote the real information within the
8 data, while the black lines denote the noise. The
9 goal is obviously to differentiate between the
10 information and noise in the data.

11 So categorizing the Gleason 7 to 10 tumors
12 as high grade, there's still a fair amount of noise
13 mixed in with the true information, making it more
14 difficult to tease out the real treatment effect.
15 However, using the more stringent categorization of
16 Gleason score 8 to 10 cancers as high grade, the
17 noise should be reduced and the true information
18 more clearly isolated.

19 Thus, Y confidence intervals do not
20 necessarily take away from the reliability of the
21 Gleason 8 to 10 results. In fact, the Gleason 8 to
22 10 results should be more likely to reflect the

1 true treatment effect due to an expected reduction
2 in noise. And as shown before, all Gleason 8 to 10
3 results favor the placebo. Thank you.

4 DR. WILSON: Yes, sir.

5 DR. WALSH: I think that the point you make
6 is very good, and the Finnish observation study, or
7 the Finnish prostate cancer screening trial, showed
8 that on men on finasteride, there was no decrease
9 in cases over time, but there was a 2.6-fold
10 increase in high-grade cases after four years,
11 which would be perfectly consistent with your
12 observation.

13 The problem with that, and I've got to
14 emphasize, is that general practitioners have 12
15 minutes to spend with a patient. I don't know how
16 many of them are going to be able to give this drug
17 to a patient and explain all of the complexities of
18 the lowering his PSA and the false sense of
19 security. This is not a statin. I don't think
20 they'll have that conversation. And secondly, if
21 they use, as GSK suggested, a rise in PSA to

1 trigger a biopsy, they will miss at least half of
2 the high-grade cases.

3 DR. WILSON: Okay. Thank you.

4 I would like to now recognize Dr. Penson.

5 DR. PENSON: Thank you, Mr. Chairman. I
6 have two questions. One is actually to you as the
7 chairman, the other is to the SWOG investigators.
8 My question to you is a comment you made earlier
9 about focusing on disease-specific mortality and
10 deaths from prostate cancer. The question that is
11 put to us is the risk benefit, and one of the
12 benefits that I would see to reducing Gleason 6
13 disease is the tremendous over-treatment of
14 prostate cancer. And that is a public health
15 burden.

16 So please clarify for me if we're looking at
17 general public health burden or specifically
18 disease-specific mortality.

19 DR. WILSON: Well, I guess my response to
20 you would be that, according to the analyses we've
21 seen, the use of these drugs reduces one case in
22 every 60 patients that are exposed to it, so that's

1 very small. We're not talking about a large impact
2 on terms of reducing unnecessary surgeries.

3 Having said that, I think that a much
4 greater weight, in my view, should be placed on
5 risk when you're dealing with a preventative agent.
6 And we don't know whether or not this drug may
7 increase the incidence of high-grade disease. We
8 don't know if this is all an artifact. We don't
9 know whether or not it is simply delaying the
10 diagnoses of high-grade disease, and we don't know
11 if the high-grade disease we see, as Dr. Kelly
12 points out, is the same biology.

13 All we can do is go with what we have.
14 Number one, we know that high-grade disease has a
15 very poor outcome. I think we have to assume it's
16 something we don't want to delay until we prove
17 otherwise that somehow it's different. And number
18 two, I think we do not want to delay high-grade
19 disease diagnosis because when you delay diagnoses,
20 PSA goes up, tumor volume goes up, invasion
21 happens, and those are some of the many risk
22 factors associated with this then becoming an

1 incurable state. And that's the basis for how I
2 think we ought to be looking at the risk versus
3 benefit here. I think survival is something
4 we're not going to see. This is a disease that's
5 measured in decades for patients with TC-1 if
6 that's what they have. And so I think one of the
7 reasons even why PSA screening hasn't become
8 positive, because the follow-ups have just been way
9 too short.

10 DR. PENSON: Thank you. That's helpful. I
11 think when you put it in that frame of reference,
12 then we really come down to the risk and benefits.
13 I might disagree with the number of 60 to 1, based
14 on the Epstein criteria, but, clearly, the question
15 now becomes the risk. And this is my question to
16 the SWOG group and Dr. Thompson, I think
17 specifically, which is I'm a little concerned with
18 the FDA's analysis where they look at the relative
19 risk for Gleason 8 to 10 disease in the
20 prostatectomy specimen and also the slides which
21 were just shown. It seems to me that we've seen
22 Dr. Scardino and Dr. Walsh basically acknowledge

1 that there probably is an increased risk of high-
2 grade risk disease. The GSK group has called it an
3 uncertainty, which in my mind implies that they
4 think there is a possibility.

5 So what I'd ask you, Dr. Thompson, is to
6 comment on the FDA's last slide, and, specifically,
7 is it simply the testing characteristics now
8 carrying over to the prostatectomy that increases
9 the relative risk to 1.78? Am I missing something
10 here? Is it just more detection bias or could this
11 be real?

12 DR. THOMPSON: I'm not sure, Dr. Penson.
13 But one thing I think all of us understand is that
14 the difference between a Gleason 7 and a Gleason 8
15 tumor is not -- they are not two different
16 diseases. It is a spectrum of disease, and biopsy
17 is a poor characterization of the actual presence
18 of disease.

19 While it is indeed true that all of these
20 subsequent analyses suggest that there may be a
21 higher risk of high-grade disease, we have to
22 acknowledge it's based on very small numbers as

1 opposed to the 7 through 10s, thus the wide
2 confidence intervals. And just like that may be
3 inconsistent with the finding of the start Gleason
4 3-4s, the Gleason 7s, the explanation for the
5 Gleason 3-4s is pretty consistent across the range,
6 that when you incorporate the biases, the risk does
7 not appear to be there.

8 I'm not saying that it's lower in the
9 finasteride group, because I think that all of us
10 would agree the primary benefit of finasteride, or
11 perhaps the 5 ARIs as a group, is the prevention of
12 that so-called inconsequential disease that is
13 truly consequential if it's you. But the
14 consistency across the observations in the 3-4s,
15 when you incorporate these substantial biases, if I
16 had a biomarker that shifted that RLC curve for
17 PSA, we would have substantial benefits across the
18 population. That's just PSA alone, not including
19 DRE and the detection bias.

20 So I would contend that indeed you see
21 those, those red numbers there on the right, to the
22 right, very wide confidence intervals because

1 they're very small numbers as opposed -- because
2 those Gleason 3-4s, we treat those, as urologic
3 oncologists, as high-grade disease. Those are
4 patients who get hormones in addition to
5 radiotherapy. Those patients are generally not
6 offered active surveillance. They have radical
7 radiation and radical surgery. So the concept that
8 those may be reduced and in the same time, you may
9 be enhancing their detection by improving your
10 detection methodologies, may have substantial
11 public health benefit.

12 DR. WILSON: Yes, sir?

13 DR. LOGOTHETIS: Chris Logothetis and
14 speaking in this case from GSK. So I'd like to
15 bring up a slide describing the performance, which
16 I think is central to this, is PSA as a predictor,
17 as a biomarker for disease, because I think we've
18 all acknowledged and we've heard about the
19 uncertainties and the crudeness of our test and the
20 fact.

21 All I want to point out here in these
22 studies, when looking at both the Gleason score 7

1 to 10 and the enriched group, the 8 to 10 group,
2 the performance of PSA for predicting and detecting
3 these does not prejudice against the dutasteride
4 arm. There's no evidence to suggest that. There's
5 some evidence, but it hasn't been prospectively
6 studied. I agree with completely with the FDA
7 here. There's some evidence to suggest that
8 performance will even be better. But there's
9 really no evidence that we're prejudicing our
10 patients, who are on dutasteride, with proper
11 follow-up to have an adverse outcome.

12 Using low-grade cancer as a predictor to
13 find high-grade cancer, we all worry about that
14 because there's mixed diseases, but that speaks to
15 the uncertainties of the biopsies, and that vexes
16 our daily practice and is not specific to these
17 patients.

18 So all I'd like to point out is that these
19 patients are not prejudiced by any data that we
20 have available, and it may even be that they're a
21 little better at performance in predicting outcome.

1 DR. WILSON: Actually, I'm not really sure
2 that's how I would look at this data. At the end
3 of the day, these biopsies are surrogates, and what
4 matters is what is in the prostate. So you're
5 showing us surrogates, okay? And so if you are
6 affecting the surrogacy of one group, and you're
7 not taking them to prostatectomy, and you only have
8 your trial going on four years, it may be that
9 there is a group of patients that is cooking 8s
10 that you've not found because you've reduced one of
11 the surrogates, which is Gleason 6, only to find in
12 7, 8 years, that patient gets another biopsy and,
13 bang, he's got much more advanced disease.

14 So I just want to point out that the
15 performance of this is against the surrogacy of
16 these random biopsies and not the gold standard of
17 what is actually in the prostate itself, which you
18 only find out if it is triggered by having a
19 Gleason 6 and the patient decides to move forward.

20 DR. ROEHRBORN: Can I be recognized to
21 comment on this? Dr. Roehrborn.

22 DR. WILSON: Yes.

1 DR. ROEHRBORN: I'd like to get back to two
2 issues. First of all, the serial biopsy study by
3 Roehl. I think these are very valid data to
4 consider. Let's reflect. If you take a series of
5 500 men, let's say, with elevated PSA, you biopsy
6 and the biopsy's negative; you biopsy them again
7 and again and maybe a fourth time. As we heard,
8 the yield of Gleason 8 to 10 cancers in those
9 patients is between 1 and 2 percent at the third
10 and fourth biopsy.

11 Now, if you now translate that into the
12 REDUCE study in the dutasteride population and you
13 look at the yield of Gleason 8 to 10 at years 2 and
14 4, it is 0.5 percent. So we're talking a lot about
15 the increase and the odds ratios and the relative
16 risk of an increase, but we're forgetting that
17 there really is not an increase and that the
18 numbers observed, actually observed, are less than
19 expected from such a serial biopsy series.

20 One explanation we offered and you keenly
21 pointed to the very heart and soul of the matter is
22 the removal of those 141 excess cancers. And you

1 stipulated that this might actually be a risk
2 because by removing them early, we are inducing a
3 bias and we are perhaps breeding higher-grade
4 cancers. But then we have to remember that the FDA
5 has clearly told us that they don't like the random
6 mandated protocol-driven biopsies. And let's
7 remember, in the placebo group, these men were
8 removed because of this biopsy, which is not
9 clinical practice, will never be done in clinical
10 practice, and, in fact, if such drug would be used
11 in the population, there would not be a placebo
12 group.

13 DR. WILSON: Right, but that still does not
14 address the issue of 25 percent reduction in
15 Gleason 6, which may trigger a surgery. which then
16 may find up to 50 percent higher-grade disease, and
17 that is the elephant in the room, in my view.

18 Dr. Freedman?

19 DR. FREEDMAN: I think in the GSK in their
20 study and the other study, clearly, you met the
21 primary objective. And as we mentioned, the
22 discussion here is about benefit, benefit to a

1 population of individuals who are essentially
2 normal, excluding the fact that they're part of a
3 clinical trial and have undergone certain tests. I
4 would be interested to know, since Gleason 6 is the
5 predominant group there, how much consensus is
6 there amongst the urology community with regard to
7 the management of Gleason 6. That's the major
8 component that's been reduced here and reduced in
9 the treated population.

10 Also, what happens when the patients come
11 off treatment? We know that when you remove the
12 suppression, then some of the factors come back
13 that stimulate the hypertrophy in the prostate.
14 What effect does that have on the biology of the
15 neoplastic process, particularly for the lower
16 grade lesions? And that's where I think long-term
17 follow-up is very important, and we need to know
18 more about the biology of this disease. And we've
19 heard from Dr. Scardino that even the 6s over a
20 period of years can progress to a higher grade.

21 What factors can influence that?

1 DR. WILSON: So I think that these are very
2 interesting scientific issues, and so I'd like our
3 two expert speakers, Dr. Scardino and Dr. Walsh, to
4 see if they have any responses to Dr. Freedman's
5 concerns.

6 DR. SCARDINO: Just explain again your
7 concern. You made a comment, but I don't know if I
8 understood your concern.

9 DR. FREEDMAN: The first point was about the
10 grade 6 lesions. How much consensus is there
11 across the urologic community about the management
12 of those lesions? Because this is a critical group
13 where the drop occurred and the treatment was aimed
14 -- the success of the treatment was based upon the
15 lower grade lesions, particularly the grade 6
16 group.

17 The second question was, in those patients
18 who come off the suppression, do we know --
19 especially for low-grade lesions that might be
20 present within the prostate where the biology is
21 altered to any degree -- I think you mentioned in
22 some of your data that these lesions can change

1 from low grade to high grade over a period of time.
2 And it's important for us, if this is a drug that
3 patients are going to be using over a long period
4 of time, to know what biological changes it may
5 have with the use or discontinuation of that drug.

6 DR. SCARDINO: So to answer your second
7 question first, I don't think there's any good
8 information out there about what might happen to
9 someone with prostate cancer who's taking the drug
10 for that kind of suppression, who then comes off
11 the drug; would that trigger a change in the
12 biology of the tumor. I don't think there's any
13 information I know of that could address that
14 question.

15 As far as do some Gleason 6 cancers become
16 Gleason higher Gleason score in the future, I think
17 we don't know that. There have been some
18 tantalizing studies that suggest that, with serial
19 biopsies over time in men untreated, you see a
20 higher proportion of men developing high-grade
21 cancers. But we don't know whether that's because
22 they had small high-grade cancers initially that

1 were missed that grow larger over time and are
2 finally detected by biopsy or whether the Gleason 6
3 cancer present turns into a higher-grade cancer.

4 It's my belief, based upon all we know about
5 prostate cancer, that there is an evolution of some
6 Gleason 6 cancers into higher-grade cancers over
7 time. It would only make sense. There's no reason
8 why they shouldn't be able to. If a normal
9 prostatic cell can evolve into a high-grade cancer,
10 it's even more likely that a low-grade cancer can
11 evolve into a high-grade cancer, but proving that
12 is difficult.

13 As far as the consensus in the urology
14 community about Gleason 6 cancers, I think the best
15 information we have is that the overwhelming
16 majority, 90 to 95 percent of men with Gleason 6
17 cancer, even in the lowest-risk category in the
18 United States today are treated with radical
19 therapy. It's a small proportion of men, even low
20 risk men who are monitored.

21 Certainly, very few young men; that is men
22 below age 55, with a very low-risk cancer would be

1 recommended for monitoring, and only certain high-
2 grade elderly men, is there a general consensus
3 that low-grade cancers can be watched. So the
4 overwhelming majority of tumors are treated.

5 Now, should they be treated? I think
6 there's a great intellectual debate about that,
7 but, in fact, these patients are virtually all
8 treated today.

9 DR. WALSH: The reason for treatment, of
10 course, is clear; and that is, it's monetary. If
11 you look at the NCCN guidelines, I think you will
12 find clear guidelines about the way patients should
13 be treated. For men who fulfill the Epstein
14 criteria and have a lifespan less than 20 years,
15 they recommend expectant management. For patients
16 with a lifespan of greater than 20 years, or
17 patients with more criteria, that is, more cores,
18 more percent of cores and a higher PSA density,
19 then there are the other options expectant
20 management, surgery and radiation. So what goes on
21 and what should go on and are really answers to two
22 different questions.

1 DR. WILSON: I'm sorry. We're going to have
2 to move on.

3 Dr. Tempero.

4 DR. TEMPERO: Thank you. Margaret Tempero,
5 UCSF. I have two questions. The first is kind of
6 a general question. It seems to me that everyone
7 around the table agrees that men with prostate
8 cancer are over-treated, and there's a lot of
9 controversy about testing with PSA and screening
10 with PSA. And yet it's hard to deny that there's a
11 remarkable decline in prostate cancer-related
12 mortality.

13 So I'd like Dr. Scardino and Dr. Walsh to
14 tell us why that is.

15 DR. SCARDINO: This is Dr. Scardino. I
16 think the reduction in prostate cancer mortality is
17 partly due -- and a very significant part of it is
18 due to the early detection of potentially lethal
19 cancers and the effective treatment of those
20 cancers with surgery or radiation therapy with
21 definitive local therapy.

1 Having said that, it's also true that the
2 diagnosis of prostate cancer has shifted more and
3 more and more over time to earlier and earlier
4 lesions, that most of these earlier and earlier
5 lesions when they're found are treated, and that
6 there is a role for active surveillance in these
7 patients with early disease, but it's recognized
8 more in theory than in practice.

9 So I think that it calls for us to be more
10 discriminatory about who we treat, and I think this
11 would include high-grade cancers. A high-grade
12 cancer in and of itself is not necessarily a lethal
13 lesion, and it doesn't necessarily have to be
14 identified and treated the day it arises. There's
15 very good data that when a high-grade tumor is
16 discovered in a man with a relatively low PSA, a
17 relatively low clinical stage, that treatment is
18 extremely effective. So I think some delay in
19 diagnosis in high-grade cancers is not necessarily
20 a bad thing and is essential unless we continue
21 with the policy of treating everybody.

1 DR. WALSH: To add just two small points,
2 the fall in deaths from prostate cancer over the
3 last 10 years has been 4 percent a year, 40 percent
4 over the last 10 years. And one of the major
5 reasons is that 30 years ago, men with prostate
6 cancer weren't treated at all. They didn't undergo
7 surgery and radiation was too underpowered to cure.
8 So we really have a tumor here that was never
9 treated. As Dr. Scardino points out, in the 1990s,
10 a way to diagnose it at a curable stage came along
11 and better treatments came along.

12 The impressive study that I found in the
13 last year or so has been from Gutenberg. It's
14 their extension of the European study of screening,
15 and they found a 42 percent reduction in mortality
16 at 14 years in men that were screened and a number
17 of needed to treat of 1 to 12, in a population of
18 patients where 40 percent of them were initially
19 treated with expectant management.

20 So they don't use number needed to treat;
21 they say number needed to diagnose. And that's
22 where we need to be headed. What it's going to

1 take to get us there, I don't know, unless the
2 Medicare pays high rates for expectant management.

3 DR. WILSON: Yes, please, go ahead.

4 DR. TEMPERO: And my second question is
5 actually to GSK. Dr. Walsh mentioned the Finnish
6 cohort that had patients who were treated with
7 finasteride. Is there a similar cohort with
8 dutasteride that could be informative to us, either
9 now or in the future?

10 DR. PHILLIPS: It's Anne Phillips. I'd like
11 to ask Dr. Roehrborn to come to the podium to
12 answer you.

13 DR. ROEHRBORN: There are several biases
14 with the Finnish study, obviously. It's not a
15 randomized study. It's a study in which a very
16 small number of patients were diagnosed with high-
17 grade cancer, and we know very little about the
18 actual background of the patients, the treating
19 physicians. I read the study, and I failed to see
20 the study as a significant foundation for a
21 critical argument.

1 DR. TEMPERO: My question, though, is
2 whether there's a dutasteride cohort that could be
3 informative.

4 DR. LOGOTHETIS: The closest thing to a
5 dutasteride cohort are actually on the two trials
6 that I had presented, the CombAT and the REDEEM,
7 where there were patients who you could look at the
8 influence of the drug in patients with established
9 disease and they were observed time. And there,
10 there was a reduction in the frequency of all
11 grades of cancer, and then CombAT, the BPH study on
12 it, which there was an appended endpoint. So if
13 you were to ask for a controlled study that
14 differed from the current study, it would be those
15 two that would offer the best data.

16 DR. WILSON: Okay. I would like to now
17 recognize Dr. Sesterhenn.

18 DR. SESTERHENN: I have a simple question.
19 This is a chemoprevention trial, and during the
20 presentations, I was sometimes confused. Do you
21 mean you will prevent the development of cancer in
22 these patients who are 50 or older or do you want

1 to modulate the growth of the tumors and intercept
2 their growth? What do you want?

3 DR. WILSON: Would the sponsor like to
4 respond?

5 DR. PHILLIPS: Anne Phillips from GSK. I'll
6 ask Dr. Logothetis to respond to your question.

7 DR. LOGOTHETIS: So central to that dilemma
8 is the comment made by Ian Thompson, that in breast
9 cancer, you biopsy the cancer; in prostate cancer,
10 you biopsy the prostate. So even when you take
11 patients at risk for the disease, you acknowledge
12 in a prevention strategy that there's a subset of
13 patients who already have the established cancer.

14 So in reality, it's probably a mixture of
15 both. It's inhibiting progression, as is reflected
16 in some of the putative premalignant lesions that
17 have gotten better, in addition to the fact that we
18 enrich for cancers that are probably further along
19 in their progression state and not sensitive to
20 DHT. That's how I interpret that. That's purely
21 speculative. But by definition because of the
22 vagaries of biopsies, we have a mixture of patients

1 with early cancers and without cancers, and we're
2 both delaying and preventing. We're delaying the
3 detection or preventing the detection.

4 DR. WILSON: Sorry for being -- but I want
5 to be precise. There's no evidence that you are
6 delaying progression. What you're doing is you are
7 reducing what's already there, but progression
8 implies going on to a higher grade. There's no
9 evidence for that. I just want to make that clear
10 to everybody.

11 DR. LOGOTHETIS: Just accurately, what we're
12 delaying is reducing the detection rate.

13 DR. WILSON: That's right, but I'm just
14 saying progression is not the right word. Thank
15 you.

16 DR. SESTERHENN: Can I say something?
17 Because it seems to me the way it is presented,
18 that the patient will understand he will be
19 prevented from developing cancer, and I think that
20 is not good.

21 DR. THOMPSON: Dr. Sesterhenn, that's a very
22 good question. Are we actually truly preventing

1 the disease or eliminate or reducing the risk a
2 patient will be diagnosed with the disease? And
3 certainly, the only way to answer that question is
4 somehow to ascertain the entire prostate to begin
5 with, to make sure the patient has no prostate
6 cancer to begin with, which we know is not a viable
7 alternative, that one could imagine how one would
8 do so, and then to ascertain the entire prostate at
9 the end.

10 But the thing that we forget -- and you
11 certainly are one of the world's experts at
12 this -- is that the volume of the disease is one of
13 the very, very important predictors of the natural
14 history. And the volume of the disease is directly
15 related to the likelihood that a biopsy needle will
16 strike it.

17 So if you reduce the likelihood of detection
18 with the same biopsies in people who are taking a
19 5 ARI, you are inherently reducing the volume,
20 which is a surrogate for disease risk over time,
21 not to exclude the reduction in the likelihood that
22 the patient ultimately receives treatment.

1 DR. WILSON: The volume probably reflects
2 the length of time the tumor's there, which is
3 probably in some people related to the time that it
4 had to progress to a higher grade, and so there's
5 no evidence that reducing the low-grade volume will
6 have any impact on the clinical outcome because
7 they all may be surrogates for something else.

8 DR. SESTERHENN: The question I have is, if
9 you look at the absolute volume of a tumor, or the
10 percent of the prostate involved by a tumor, it's a
11 different horse, too. So you can't assume that a
12 large tumor in a large prostate has the same effect
13 as a small tumor in a small prostate, see, the
14 percentages. But I believe also when you give these
15 drugs, what Dr. Walsh indicated is, you might get a
16 heterogenic selection of a tumor cell type you
17 don't want to be treated with a 5 alpha-reductase
18 inhibitor.

19 DR. WILSON: Okay. Let's move on.
20 Dr. Loehrer?

21 DR. LOEHRER: I'm going to change the topic
22 a little bit.

1 Dr. Thompson, in the prevention trial,
2 40 percent of the patients did not complete
3 therapy. I'm not quite sure on the Avodart study
4 there. But do you have any data about the -- and
5 again, it's not fair to do that, but I'm just
6 curious about the outcomes of those patients who
7 had shorter amount of therapy versus completing the
8 seven years of therapy, whether or not there were
9 differences in the outcomes of the biopsies.

10 DR. THOMPSON: Could you hold that question
11 for a second? Let us think for a second? I don't
12 think that we do, but let me just take a look.

13 DR. LOEHRER: Okay.

14 DR. THOMPSON: The answer, we don't. Sorry.

15 DR. WILSON: May I recognize FDA for an
16 answer to that question?

17 DR. THEORET: Yes, I'm Marc Theoret. We do
18 have one slide that looked at patients that
19 discontinued treatment, and if you look at their
20 treatment discontinuation date, and we essentially
21 looked at their end-of-study biopsy prostate cancer
22 rate, after they had discontinued treatment at

1 least one year before that end-of-study biopsy,
2 small numbers, but I'd like to show this slide.

3 So like I mentioned, recorded for 18,600 men
4 were off treatment notice forms. And essentially
5 these forms were filled out when a patient
6 discontinued treatment, either temporarily or at
7 the end of this seven-year study; they would have a
8 treatment completed.

9 So what we did was look at all the patients
10 who had a treatment discontinuation form filled
11 out, and on that treatment discontinuation form was
12 the last date that those patients had taken the
13 study drug. That was what was recorded on the
14 form.

15 If you look at the treatment discontinuation
16 date compared to the end-of-study biopsy date,
17 which diagnosed that last end-of-study biopsy date
18 was performed, and we looked at all the patients
19 that had an end-of-study biopsy date greater than
20 or equal to one year after treatment
21 discontinuation -- as you can see here, if you look
22 at the all cancer group, 93 patients on finasteride

1 and 57, very similar, essentially the same or
2 similar cumulative incidence of prostate cancer for
3 a relative risk of 1. But, once again, very small
4 numbers, so it's difficult to say. We didn't have
5 a large group to look at for this analysis.

6 DR. WILSON: Does the sponsor have a
7 response?

8 DR. THOMPSON: Guess not. Sorry.

9 DR. WILSON: Okay. Thank you.

10 Last question, and then we're going to
11 finish this session. Dr. Majumder?

12 DR. MAJUMDER: Mary Majumder, consumer
13 representative. I wanted to follow up on Dr.
14 Walsh's concern that widespread use of these agents
15 for prevention or modulation of prostate cancer may
16 create a false sense of reassurance because PSA
17 levels are so low. And I know the BPH context is
18 different, but it might give us some insight into
19 whether confusion is a real concern. And I
20 wondered if either the sponsors or the FDA have any
21 data, any reports of confusion created among
22 patients because their PSA levels have dropped, and

1 so whether that has caused any problems with
2 monitoring for prostate cancer.

3 DR. WILSON: Would the sponsor like to
4 respond or either of our distinguished lecturers?
5 Dr. Walsh.

6 DR. WALSH: The package insert claims how to
7 correct for PSA was only recently corrected this
8 summer. I came two years ago and asked for it, and
9 it was in response to two patients I saw who were
10 on Propecia. There was nothing in the Propecia
11 package insert that really suggested the danger.

12 These two men, one man had a PSA that just
13 went up to 4, the other 3.5. One was a professor
14 of medicine at Hopkins. He had been on Propecia
15 for 10 years. If you've been on -- that's
16 finasteride, 1 milligram. If you've been for
17 greater than seven years, you have to multiply your
18 PSA by 2.5. So the patient with the PSA of 4
19 really had a PSA of 10. Both of them had extensive
20 Gleason 8 disease. One of the patients,
21 unfortunately, had positive margins and needed
22 surgery and radiation.

1 So there is certainly a danger for people
2 not understanding it. Whether the new package
3 insert, I'm very concerned about the combination of
4 not knowing you have cancer and the risk of high-
5 grade disease.

6 DR. WILSON: Would Dr. Scardino like to
7 comment?

8 DR. SCARDINO: Yes, just to note, I think
9 not providing information is different than asking
10 whether patients and doctors can understand
11 information. Certainly, we've been using, as we've
12 heard, more than 5 million man years with these
13 drugs for BPH, and I think those patients who are
14 under the care of a doctor are aware of the effect
15 of the PSA and it has not been a source of
16 confusion.

17 DR. THOMPSON: Just an observation with
18 regards to PSA. Today it's generally understood
19 that PSA is not a positive or elevated or a normal
20 test, that there's a range of risk. And it also is
21 modulated or modified by other risk factors,
22 African-American ethnicity, age, family history and

1 so forth. And so, generally speaking, a person's
2 assessment of risk is no longer based on an
3 elevated or normal PSA. And most folks when they
4 incorporate this decision-making will incorporate
5 all of these risk factors, and there are ways to
6 actually do so.

7 When you do so, the evidence would suggest,
8 as I pointed out earlier, our biggest problem is
9 that doing so in many individuals leads to a
10 decision not to biopsy a man who has high-grade
11 disease, the opposite of what we've been talking
12 about. If a man is on finasteride, 5 alpha-
13 reductase inhibitor, the performance of that test
14 is improved. And if he has a high-grade tumor,
15 there's a greater likelihood that the physician
16 will actually recommend a biopsy.

17 So it's a bit counterintuitive. It suggests
18 that there may actually be a benefit, is the
19 performance of the test is improved. And one of
20 our biggest problems, as I said earlier, in those
21 men whose PSAs are less than 4, there are far more

1 high-grade cancers in them because there are more
2 of those men than the men whose PSAs are elevated.

3 DR. WILSON: We actually have to finish this
4 session, but I do want to say again in response to
5 that, is the performance may be improved because
6 you're, in fact, delaying diagnoses. So it is a
7 double-edged sword. So I think it's important for
8 people not to think that this may be making the
9 performance higher because it may not be making the
10 performance higher in terms of the absolute number.

11 So I'm now going to turn to statements, and
12 I'd like to invite Ms. Morrow.

13 DR. VESELY: Excuse me, I'm sorry. I have a
14 statement to read first. Thank you.

15 DR. WILSON: Sorry, long day.

16 **Open Public Hearing**

17 DR. VESELY: Both the Food and Drug
18 Administration and the public believe in a
19 transparent process for information gathering and
20 decision-making. To ensure such transparency at the
21 open public hearing session of the advisory
22 committee meeting, FDA believes that it is

1 important to understand the context of an
2 individual's presentation. For this reason, FDA
3 encourages you, the open public hearing speaker, at
4 the beginning of your written or oral statement to
5 advise the committee of any financial relationship
6 that you may have with the sponsor, its product,
7 and, if known, its drug competitors.

8 For example, this financial information may
9 include the sponsor's payment of your travel,
10 lodging or other expenses in connection with your
11 attendance at the meeting. Likewise, FDA
12 encourages you at the beginning of your statement
13 to advise the committee if you do not have any such
14 financial relationships. If you choose not to
15 address this issue of financial relationships at
16 the beginning of your statement, it will not
17 preclude you from speaking.

18 The FDA and this committee place great
19 important in the open public hearing process. The
20 insights and comments provided can help the agency
21 and this committee in their consideration of the
22 issues before them. That said, in many instances

1 and for many topics, there will be a variety of
2 opinions. One of our goals today is for this open
3 public hearing to be conducted in a fair and open
4 way, where every participant is listened to
5 carefully and treated with dignity, courtesy and
6 respect. Therefore, please speak only when
7 recognized by the chair. Thank you for your
8 cooperation.

9 DR. WILSON: Ms. Morrow.

10 MS. MORROW: Thank you, Mr. Chairman, and
11 members of the committee. I appreciate the
12 opportunity to speak with you today. My name is
13 Theresa Morrow, and I'm cofounder of Women Against
14 Prostate Cancer. I have no financial relationships
15 to disclose.

16 I'm speaking today on behalf of wives,
17 partners, mothers, daughters, friends and loved
18 ones because, as you know, women often play a
19 crucial role in encouraging the men in their lives
20 to seek out regular and preventative healthcare,
21 including appropriate screenings for prostate
22 cancer. And when a man is diagnosed with prostate

1 cancer, the disease can have a devastating effect
2 on the entire family.

3 We are optimistic that your review of the
4 clinical research and the benefits of finasteride
5 and dutasteride will lead to the approval of these
6 drugs for use in the risk reduction of prostate
7 cancer. The approval of these drugs would be an
8 added tool in the continuing battle to improve
9 men's health, particularly when it comes to
10 prostate cancer, a disease that will be diagnosed
11 in over 220,000 men this year alone, 32,000 of whom
12 will lose their lives. We must take steps to lower
13 these numbers.

14 Encouraging results from the PCPT and REDUCE
15 and other trials demonstrate an important
16 opportunity to help men at an increased risk of
17 developing the disease. We have joined with other
18 leading organizations in the prostate cancer
19 community to stress the important role that your
20 recommendations today will play in the lives of
21 thousands of men and their families who are at
22 increased risk. Thank you.

1 DR. WILSON: Thank you very much.

2 Now I would like to invite Ms. Fadich.

3 MS. FADICH: Thank you, Mr. Chairman, and
4 members of the committee for allowing me to speak
5 before you today. I have no financial
6 relationships to report.

7 My name is Ana Fadich, and I'm speaking
8 today on behalf of the Men's Health Network, a
9 national nonprofit organization whose mission is to
10 reach men and their families where they live, work,
11 play and pray. Prostate cancer continues to strike
12 one in six American men, with African-American men
13 having an incidence rate up to 60 percent higher
14 than white men. Dutasteride offers hope for
15 men to reduce the risk of prostate cancer in those
16 who are genetically predisposed. Dutasteride has
17 demonstrated a 23 percent reduction in the risk of
18 developing prostate cancer. And although 23
19 percent may not seem like a great feat, it speaks
20 wonders to those men and their families who could
21 avoid suffering with it. Therefore, there is value
22 in reducing low-grade cancers.

1 There is an immense need for innovative
2 treatment options like these mentioned today, of
3 reducing the risk of prostate cancer in high-risk
4 men. Shrinking the prostate may make it easier for
5 patients and their healthcare provider to diagnose
6 prostate cancer, which may give us an opportunity
7 to cut down on surgeries, prostatectomies and other
8 serious issues. We believe dutasteride for
9 prostate cancer risk reduction is a step forward in
10 the battle against prostate cancer.

11 Members of the prostate cancer roundtable, a
12 group of 12 independent not-for-profit
13 organizations and two other partners have issued a
14 statement, which is available on the table outside
15 for all interested parties. We have come together
16 as a prostate cancer community to foster the
17 development of policies that support the early
18 detection of clinically significant prostate
19 cancer, the effective treatment of men with this
20 disease, and the appropriate education of all men
21 at risk. Thank you.

1 DR. WILSON: Thank you very much. The
2 public hearing comes to a close. We have one more
3 statement to be read.

4 DR. VESELY: The open public hearing portion
5 of this meeting has now concluded, and we will no
6 longer take comments from the audience. The
7 committee will now turn its attention to address
8 the task at hand, the careful consideration of the
9 data before the committee as well as the public
10 comments.

11 DR. WILSON: So it has been a very long
12 afternoon, so I would like to take break. It's now
13 3:45, and let's meet back here at 3:55. Thank you
14 very much.

15 (Whereupon, a recess was taken.)

16 **Questions to ODAC and ODAC Discussion**

17 DR. WILSON: So over the next 30 to 50
18 minutes, we have an opportunity to discuss further
19 among ourselves. If there are any pressing
20 questions that you want to ask the sponsor, please
21 ask me first. But generally this time is meant for
22 the board to discuss the issues, and, specifically,

1 at the end, we will be voting on the two questions.
2 However, right now, let me just open it up because
3 I know a number of you had questions and comments.

4 Dr. Curt, I believe you had one.

5 DR. CURT: It's a comment, Wyndham, not a
6 question.

7 DR. WILSON: That's fine.

8 DR. CURT: I just wanted to set these two
9 studies in the context of the only other trial
10 that's led to the approval of a drug for the
11 prevention of cancer, and that's, of course, the
12 use of tamoxifen in breast cancer. And as an
13 aside, I think it's very interesting that some of
14 the discussions that occurred during that process
15 we've had today, including tamoxifen was only
16 treating biologically irrelevant disease and
17 causing selection of ER-negative bad-acting tumor
18 cells.

19 But having said that, if you look at the
20 number of patients who were treated to prevent
21 breast cancer in the context of the NSABP-P1 trial,
22 that was a study that had 6,000 patients on each

1 arm, 6,000 on placebo, 6,000 on tamoxifen. And
2 there were 120 cancers in the placebo arm and 60 in
3 the tamoxifen arm. So you had to treat 6,000
4 patients to prevent 60 cancers, so that's about 100
5 patients treated to one patient who's prevented.
6 So that's pretty much in line with what we've seen
7 from the agency.

8 I would submit that tamoxifen is a drug that
9 has a worst safety liability than the drugs we're
10 talking about here today. And also, as we've heard
11 just recently, the cancers that are being prevented
12 are the cancers which are managed with aggressive
13 local therapies, which do have morbidities.
14 Thanks.

15 DR. WILSON: I think it's always worthwhile
16 looking at historical approvals like that. I think
17 what is of primary concern is whether or not this
18 drug may actually be leading to a worse grade, and,
19 hence, that may, based on everything we know about
20 grade, have a worse outcome. So I think that's a
21 fundamental difference between the tamoxifen study

1 and this one. I don't think there was any evidence
2 that you were possibly making things worse.

3 Dr. Garnick?

4 DR. GARNICK: I have a question for the
5 sponsor and the FDA. I didn't see anything in the
6 GSK's risk management program in which they were
7 going to ensure that the indicated population
8 actually is the treated population if this drug
9 ever gets the indication.

10 A second issue relates to how does the FDA
11 envision assessing efficacy; if this product were
12 ever to get commercially approved, how are you
13 actually going to measure the effectiveness of the
14 intervention in either a phase 4 study or post-
15 marketing studies.

16 DR. WILSON: Would the sponsor like to
17 answer that?

18 DR. PHILLIPS: Yes, it's Anne Phillips.
19 With the risk management plan, it doesn't have a
20 lot of details. Certainly, that is something that
21 we would be very willing to discuss and partner

1 with the FDA around, ensuring that the appropriate
2 population is treated.

3 DR. PAZDUR: The efficacy of the drug has to
4 be demonstrated before it is approved. Let's make
5 that clear.

6 [Laughter.]

7 DR. GARNICK: I fully appreciate that, but
8 given the ambiguities about some of the efficacy
9 issues that have come up --

10 DR. PAZDUR: Here again, that's the point.
11 And I want to touch on that point, and I'll
12 reiterate this point before the question comes.
13 We're asking you your clinical judgment, not to
14 make a regulatory decision based on what we did for
15 tamoxifen or whatever. We're asking you as
16 clinicians that are sitting around this table, with
17 the information that has been provided to you in
18 this disease, what is your opinion regarding the
19 favorable risk-benefit decision. Has safety and
20 efficacy been demonstrated that allows you to make
21 a definitive conclusion on risk-benefit in a
22 favorable light here?

1 I will emphasize to you repeatedly, as has
2 been through the FDA presentations, we are not
3 talking about the same applications as we generally
4 do in this committee about advanced disease,
5 metastatic disease, end-stage disease. We are
6 talking about really the diametrically opposed
7 situation, a population of people, not patients,
8 people, men, that don't have a disease here.

9 So your level of certainty, both from an
10 individual perspective, of treating an individual
11 perspective, has to be heightened, as well as from
12 a public health perspective. We're treating
13 potentially hundreds of thousands of people here,
14 not a small cohort of people that have a terminal
15 disease here, that need therapeutic options, et
16 cetera.

17 There's been a lot of noise, as you could
18 hear, and a lot of emotion, since these studies
19 have been published, with recommendations that
20 people need options here or considerations for
21 treatment. When we approve an indication, you have
22 to have proof, and you have to make a decision.

1 This is where the rubber meets the road, so to
2 speak; has safety and efficacy been demonstrated
3 that allows you to make a favorable risk-benefit
4 decision in the context of this clinical situation
5 here.

6 DR. WILSON: I would like to recognizes
7 Mr. Kiefert.

8 DR. KIEFERT: Thank you. I'm Jim Kiefert, a
9 patient representative. Listening to the
10 discussion this afternoon reminds me of the
11 testimony about our inadequacies of doing biopsies
12 when we compare it to breast cancer where they can
13 see the tumor clearly. We have image-guided
14 biopsies, and I remember the statement made that
15 one needle biopsy represents one-three-hundred-
16 thousandths of the volume of that prostate gland.
17 So the probability of missing some significant
18 cancer in that gland is significant. We just don't
19 have the ability to have good image-guided
20 biopsies. And biopsies are painful, and we've
21 heard about the risk involved with them. And if
22 there was anything we could do to reduce the amount

1 of biopsies necessarily to determine whether
2 someone has prostate cancer or not, it would be of
3 great benefit to men with prostate cancer.

4 The question that we have to address is that
5 risk-benefit, whether or not it, in fact, does
6 reduce the risk of prostate cancer. And I listened
7 to the data, and when the patients were taken out
8 who were having a biopsy and having treatment, and
9 then I heard the discussion about how it became
10 more comparable data, and then the FDA has that
11 same kind of data but looks at it a little bit
12 differently, it gets a little bit confusing.

13 I'm not sure if the bottom line is going to
14 be the risk-benefit profile on reducing prostate
15 cancer, is there definitive data. And maybe the
16 FDA or the sponsors could come up with one
17 statement about it so that we could wade through
18 all the complex data we heard to answer the
19 question that's put before us. I would appreciate
20 that as briefly as possible.

21 DR. WILSON: Well, let me ask the sponsor to
22 reiterate what they said before, which is that they

1 are concerned and cannot rule out that there's an
2 increased incidence of high-grade tumors in the
3 treatment arm.

4 Would the person who said that please stand
5 up and let me know if I said that statement
6 properly?

7 DR. LOGOTHETIS: Chris Logothetis. Okay. I
8 have been asked to represent GSK in this. There's
9 a 23 percent reduction in detected cancer --

10 DR. WILSON: No, no, please. High-grade
11 disease; what is the effect on high-grade disease?
12 That's the question.

13 DR. KIEFERT: Excuse me. That wasn't my
14 question. He was answering my question.

15 DR. WILSON: Well, there's no question that
16 low-grade disease is down. The only confusion has
17 been regarding the high-grade.

18 DR. LOGOTHETIS: Mr. Chairman, I believe the
19 question that was framed was, what is the evidence
20 that we reduced the cancer? And he was linking it
21 to how patients were benefitted. And the answer to
22 that, based on the results of the trial, is there's

1 a 23 percent reduction in detected cancer, which is
2 currently being treated in the overwhelming
3 majority. There's no evidence that it
4 proportionally affects high-grade cancers and that
5 high-grade cancers are represented at a bigger
6 difference in the dutasteride versus the control
7 arm. We don't know for certain -- we have not
8 excluded the effect on high-grade cancers as a
9 total group. We just don't have the data in our
10 study.

11 DR. WILSON: So let me just apologize to
12 Mr. Kiefert. I thought he was asking about the
13 confusion. There has been no confusion about the
14 low-grade cancers; confusion has regarded the high-
15 grade cancers.

16 So, once again, may I ask the sponsors, I
17 heard it before that they cannot rule out that
18 there is a real -- that there may be a real
19 increase in high-grade cancers in the treatment
20 arm. Can somebody please address that?

21 DR. KOCH: This is Gary Koch. As the
22 sponsor had previously shown, there is no evidence

1 of excess high-grade cancers in the first two years
2 of REDUCE, where randomization has an equal way of
3 having the two groups assessed. There was no
4 excess in CombAT or REDEEM as well.

5 In the last two years of REDEEM, there is an
6 ascertainment bias because of the informative
7 censoring, where one took away from risk a
8 substantial number of patients who were 5 to 7s.
9 And based upon a reasonable adjustment for taking
10 into account that excess of 141 patients, there was
11 no excess risk of high-grade cancers.

12 There's also a meta-analysis the sponsor
13 did, combining all of the data sources, which
14 basically shows all of the different sources of
15 information, the first two years of REDUCE, the
16 last two years of REDUCE, CombAT, REDEEM in its
17 first 18 months, which is supported by
18 randomization as well as its last 18 months. The
19 only outlier is the last two years of REDUCE.

20 Here is a combination or integration of the
21 randomized phases of all of the studies producing
22 an odds ratio of .74, which is bracketed by one.

1 And then if we throw all of the studies together,
2 all of the sources of information together, the
3 odds ratio is 1.07 with a confidence interval for
4 .68 to 1.69. And this is including years 3 and 4
5 of REDUCE as observed, even though there's a
6 substantial bias against dutasteride because of the
7 attrition, removing those 5 to 7 patients.

8 So to the best that we can understand,
9 taking into account the loss of randomization for
10 those last two years, there's not an excess of
11 high-grade cancers in the dutasteride studies.

12 DR. WILSON: FDA, please.

13 DR. NING: I would like to make a few
14 comments here. This is regarding whether there was
15 increasing high-grade tumors in BPH CombAT study of
16 dutasteride. I think that the sponsor initially
17 showed you that there was a decrease. That was not
18 100 percent right. They're only showing you the
19 absolute number.

20 If you look at the positive biopsy read by
21 Gleason score distribution, you see that even in
22 the CombAT study, that treat prostate cancer as an

1 adverse event, you still see kind of an increase in
2 percentage of high-grade tumor in Gleason score 7
3 to 10 from 11 percent to 14 percent; Gleason 8
4 through 10, 4 percent to 5 percent. And I think
5 this is different. Another comment I want
6 to make is about the REDEEM study. The sponsor
7 said that there wasn't any increase in high-grade
8 tumor. But if you look at the time period, if you
9 split that -- this is a small study, only about 300
10 patients. If you look at first year 1.5 within
11 that protocol-mandated biopsy, you don't see an
12 increase. But if you look at a second time period
13 from year 1.5 to year 3, then you would see that
14 actually Gleason 7, and more than Gleason 7
15 actually, increased from 6 percent to 11 percent,
16 and the Gleason 8, from 1 to 2 percent.

17 But overall, you don't see there was
18 significant increase, but this would suggest that
19 there is a treatment-related increase in high-grade
20 tumor.

21 Could I have my backup slide? This is one
22 thing I would like to make clear, that in

1 addressing this applicant's hypothesis, that the
2 exercise removal of that 141 low-graded tumors
3 during the year 1 and 2 in the REDUCE trial
4 contributed to the observed absence of high-grade
5 Gleason 8 to 10 prostate cancer, diagnosed during
6 years 3 and 4. As you can see, placebo basically
7 is zero, the overall group in scheduled biopsy
8 group and for-cause biopsies group.

9 So I just wanted to remind you that after
10 that 141 patients were moved, you still had like
11 280 patients who were diagnosed with prostate
12 cancer at a second time period from year 3 to 4.
13 So how could you have the kind of luck to remove
14 all of the high Gleason grade that potentially
15 detected in that 141 patients and not in other 280
16 patients?

17 DR. KOCH: I'm sorry. May I reply, sir?

18 So if you bring back the slide, I think it's
19 45, where we try to show what the calculation was.
20 By the way, the second year and a half of REDEEM is
21 also not protected by randomization because
22 patients diagnosed at a year and a half were again

1 removed from risk. So it has the same issue as
2 REDUCE.

3 So we did not remove any patients. All we
4 did was to say the 558 patients on placebo and the
5 417 patients on dutasteride discontinued the study
6 at two years because they had the primary event of
7 the study. If 5 percent of them, under the paradigm
8 of continuing the study, had continued and been
9 biopsied at four years, we would have expected 28
10 Gleason 8 to 10s in the 558 placebos and 21 in the
11 417 dutasteride.

12 DR. WILSON: Okay. Thank you.

13 DR. NING: Well, I understand, but how could
14 you explain that 273 patients who had prostate
15 cancer diagnosed during years 3 and 4 did not have
16 that potential, that their tumor wouldn't progress
17 to high grade? How could you --

18 DR. KOCH: Because --

19 DR. NING: -- 141 patients that were
20 basically diagnosed with prostate cancer during the
21 first time period carry all the potential of

1 developing the high-grade tumor. I just could not
2 understand that.

3 DR. KOCH: No, no. The 273 and the 211 are
4 having a transition from normal status to 5 to 7
5 during the two years represented by 3 to 4. We're
6 arguing that had the 558 and the 417 continued,
7 they would have had a transition of 5 to 7 to 8 to
8 10.

9 DR. WILSON: Okay. Let me move on.
10 Dr. Logan, our statistician, I think has a comment
11 about this.

12 DR. LOGAN: Yes. I just want to point out
13 there's a lot of assumptions in those imputed
14 additional cases that may have come out of those 5
15 to 7s that were moved from the study at years 1 and
16 2. There are assumptions that the rates of
17 conversion from 5 to 7 to 8 to 10 in the following
18 years are the same between those two groups, and
19 that may not be the case because we have
20 differential upfront diagnosis. And then we're
21 assuming, of course, that it's 5 percent. That's

1 based on an external study. We don't know if
2 that's generalizable to this particular dataset.

3 So those are really unobserved, and there's
4 a lot of assumptions in that kind of imputation.
5 So I just wanted to point that out.

6 DR. WILSON: Let me just be very simple
7 because I'm just a clinical guy, and I see you have
8 a randomized study up there. And we're looking at
9 the incidence of Gleason 8 to 10, and you're trying
10 to add -- you have a higher -- you've pulled a
11 bunch of 6s out of -- you've pulled a bunch of 5s
12 to 7s out at year 1 to 2.

13 Okay? Well, that's the clinical setting
14 here. And what you may have done is you may have
15 been pulling the 8s with them. And if this was, in
16 fact, true, if this was a cohort, if these are
17 people out there that are getting this therapy,
18 3,345 are getting nothing and 3,239 are getting
19 something, what your clinical trial says is that at
20 year 4, you're going to have more high-grade
21 tumors. And you can hypothesize as much as you
22 want, but what your study says is very clear. At

1 year 4, in a randomized study, you have more high-
2 grade tumors.

3 It's not even an equivocal question, and
4 you're trying to make all kinds of hypotheticals.
5 And the problem is that when you start reducing the
6 6s, which triggers pulling people out, you are
7 therefore basically putting your head in the sand
8 for people that may have higher-grade tumors. And
9 that is what may be operating here, and you're
10 trying to come up with all these what-ifs and
11 calculations. The bottom line is randomized study
12 at year 3 to 4, a much higher rate of Gleason 8 to
13 10. It is unequivocal; unequivocal.

14 DR. KOCH: One more sentence. The argument
15 simply is based on the 558 and 417 being at higher
16 risk to be an 8 to 10 in year 4 --

17 DR. WILSON: It's a randomized study. It is
18 a randomized study, period. That's why we do
19 randomized studies.

20 DR. PAOLETTI: May I add a comment? I am a
21 clinician as well and not a statistician. If we
22 remove together with the 5, 6, also the 7 and 8,

1 something wrong with that? We are still reducing
2 the risk of cancer overall at the first pass.

3 DR. WILSON: What matters, as best we can
4 tell, is trying to reduce high-grade tumors because
5 those are the ones that all of the clinical data
6 shows are most likely to die from prostate cancer.
7 We're trying to prevent prostate cancer deaths.
8 We're not trying to prevent a histological
9 diagnosis. We're trying to prevent prostate cancer
10 deaths, and we've got these surrogates. And the
11 best we can say right now is high-grade tumors, you
12 want to get at and you want to get it out. And
13 your data shows that at year 3 to 4, unequivocally
14 and in a randomized study, you have a higher rate
15 of high-grade tumors among patients getting
16 therapy. That's clear.

17 DR. PAOLETTI: And we agree completely.

18 DR. WILSON: You agree? Okay. Good

19 DR. PAOLETTI: But there is still the
20 possibility to detect this tumor using the tools
21 that we have today.

1 DR. WILSON: I understand that you agree
2 what the data shows, but you're trying to
3 rationalize, justify, statistically analyze it
4 away. And we are faced with patients that have no
5 medical problems, and we're being asked to take
6 this data, see it clearly, and then try to accept a
7 bunch of post-hoc analyses to try to rationalize
8 and justify why the data isn't showing what it's
9 showing. And that's got me very concerned, and you
10 can probably tell from my voice.

11 DR. THOMPSON: May I be responsive to your
12 question?

13 DR. PAZDUR: Can I make a point here?

14 DR. WILSON: Please.

15 DR. PAZDUR: The purpose of this session is
16 for the committee to have a discussion here. It's
17 not be an argument and a debate with the sponsors,
18 so let's direct it to the committee and limit the
19 interactions with the sponsor, because really what
20 we're interested in hearing is all of the
21 committee's viewpoint. And I really haven't heard
22 a lot from the other people here, so to speak.

1 DR. WILSON: So let me turn to Dr. Loehrer,
2 who's next on our list.

3 DR. LOEHRER: This is a question for you,
4 Rick. In the ODAC briefing document, in the first
5 page it says, "Merck does not request a new
6 indication for the supplement." And, yet, it seems
7 like the first question we're going to come to is -
8 -

9 DR. PAZDUR: Yes, and here again, I'm going
10 to make that real clear. We wanted both of these
11 applications presented because we think that this
12 is a comprehensive picture of two trials that were
13 very similar, okay? And it doesn't make sense to
14 answer one question without the other one.

15 Our questions, as I mentioned before, we're
16 not asking you whether the drug should be approved
17 or not. We're asking you a clinical decision in
18 your mind, your mind, not based on any other past
19 regulatory decisions or anything else, is there a
20 positive risk-benefit relationship here with each
21 of these drugs here?

1 We will take care of all of the regulatory
2 issues as far as the labeling and post-marketing
3 commitments. We want you to focus on one central
4 issue here that has been entirely confused in the
5 past outside of this committee. And that's why we
6 brought both of these applications to the
7 committee. It's not about physicians having a
8 consideration of various therapeutic choices, et
9 cetera. It's has safety and efficacy been
10 demonstrated that allows a favorable risk-benefit
11 decision to be made. And that's what we're after
12 with both these applications.

13 DR. WILSON: Okay. Thank you.

14 Dr. Sekeres.

15 DR. SEKERES: Thank you, Dr. Wilson.

16 I reflect back to residency a little bit
17 when we're taught, when you're in a code blue --
18 and I think part of these proceedings can be
19 likened to a code blue today.

20 [Laughter.]

21 DR. SEKERES: If you're opening too many
22 ampoules of a drug, you don't know the dose. You

1 don't know exactly what you're doing. And what
2 I've heard today in discussing these high-grade
3 prostate lesions is that we're opening a lot of
4 ampoules of drug. We're struggling to come up with
5 an explanation for it, and the companies have come
6 up with very logical explanations for it, and the
7 FDA has come up with very logical counter-
8 explanations as well. And at the end of the day,
9 we just have to accept the fact that there were
10 more higher-grade prostate cancers that developed
11 as a result of patients treated on the arms of
12 these drugs.

13 So then my next step is to reflect on also
14 what I've learned as being a member of ODAC, and
15 that is that when we have a patient with cancer,
16 we're ready to accept a certain amount of risk of
17 treatment because the risk of their disease is so
18 overwhelming. But here we're talking about people
19 who don't have cancer, and I think our bar has to
20 be very different in what risk we're willing to
21 accept. And it appears that a risk of .5 percent
22 even of people developing a high-grade prostate

1 cancer that has a lower likelihood of being cured
2 is unacceptable.

3 DR. WILSON: Dr. D'Agostino.

4 DR. D'AGOSTINO: I have a couple of comments
5 from various things. I agree wholeheartedly with
6 the chair in terms of the interpretation. The
7 clinical trials were the clinical trials, and one
8 can impute, and I can come up with a scenario, that
9 would put all those cases that they were imputing -
10 - I would have still kept them in the below 6 range
11 and pull out the high-grade from the other, from
12 the people who didn't show anything. So I think we
13 have to look at the clinical trials as they stand.

14 The other thing that is another issue, which
15 is my real question, is that in terms of what we're
16 being asked by the FDA, there is the whole issue
17 here of, if we say the risk benefit, we're looking
18 at the high grade, and I think it's very important.
19 But we also have the -- this is a lifetime
20 commitment to the drug. We spent a lot of time in
21 the cardiovascular field worrying about the effect
22 of lipids. Was it going to ruin livers? Was it

1 going to do this and that? I remember working with
2 Merck back in the early 90s on are people going to
3 go blind with the drug, and we don't know any of
4 those questions. So in terms of the risk-benefit,
5 it's more than just the study.

6 Then also, the clinical practice, I sit on
7 the New England Journal of Medicine editorial
8 board. We talk about how is this going to affect
9 clinical practice. And even though we're asking
10 about the efficacy, I think we still have to keep
11 in the back of our mind how does this get
12 translated. And again, I don't want to get into
13 the effectiveness because we were asked not to, but
14 there's still this lingering thing, what does this
15 study really show and how we do think about it in
16 terms of what it's going to do in the general
17 public and how we're going to extrapolate it. And
18 I think we have a lot of problems.

19 DR. WILSON: Dr. Penson?

20 DR. PENSON: Thank you.

21 I want to ask a question of Dr. Pazdur and
22 the FDA, and I want to basically make a comment

1 couching it in a question, as people are known to
2 do. It's interesting because Dr. D'Agostino's
3 comments made me think. As a urologist, I write
4 this drug routinely for patients with benign
5 prostatic hyperplasia all the time. We've been
6 using this drug for 20 years, and one could argue
7 that a lot of men with BPH and LUTS, lower urinary
8 tract symptoms, are effectively normal men. So
9 this has been out here before. So in certain
10 respects, when I start to look at this, the safety
11 profile is okay. I'm not worried about people
12 going blind on this drug.

13 In the end, if we accept the fact the
14 numbers that the FDA has given us, that for every
15 200 patients that you treat, you'll get one
16 additional case of high-grade disease. We have to
17 balance that against, I think in a worst case
18 scenario, 60 patients treated to get sort of one
19 decrease in what they call low-risk cancers. So
20 that, to me, is the question we're asked.

21 In my office, where I'm following patients
22 and I'm doing the PSA, I'm frankly comfortable with

1 that risk profile. But what we're not talking
2 about here is what's going to happen when we vote
3 on this. And what I mean by that is that this is
4 going go out there, and it's going to get out of
5 the specialist office, out of the people who do
6 PSAs office. We're going to have direct-to-
7 consumer advertising. We're going to have patients
8 who are taking this drug on their own. They're not
9 going to necessarily have their PSAs followed or
10 followed properly.

11 So the question I have for you, Dr. Pazdur,
12 is when you ask me this question about the risk-
13 benefit profile, am I going to account for the fact
14 of the, quote, unquote, "real world." what's really
15 going to happen when we have marketing or what just
16 happens in my office?

17 DR. PAZDUR: You better believe it.

18 DR. PENSON: So better believe it, the real
19 world. Thank you.

20 DR. WILSON: Yes, sir.

21 DR. D'AGOSTINO: The first thing I asked
22 when we had the session, when we were asking

1 questions, was exactly this 60 versus 1, 200 versus
2 1. And we're basically at, for 200 individuals,
3 we'll prevent the cancer in three, lower grade, but
4 meaningful, and we'll have one in the higher grade.
5 And I think that that is there. That's what's
6 really on the table.

7 DR. WILSON: I do think that this is in the
8 real world probably a major problem because
9 internists and general medical doctors will be
10 giving this. They're checking PSAs. And I think
11 that if this is delaying diagnosis, if, let's just
12 assume it's not making it worse. Let's just assume
13 that it's simply delaying; because of all the
14 things we have talked about, I think it's going to
15 get magnified far worse when it's not being handled
16 right. But I think that's obviously --

17 DR. PAZDUR: This is the issue that I was
18 bringing up in my opening comments of a risk-
19 benefit issue being addressed from a public health
20 perspective in a large number of people. We're
21 talking about, unlike our oncology indications,
22 which may have a few thousand patients, literally

1 hundreds of thousands of people being exposed to
2 this drug with many different practitioners having
3 the right to prescribe this drug. This is not an
4 oncology drug that is only going to be prescribed
5 by a select group of board certified medical
6 oncologists.

7 DR. WILSON: Dr. Rosner?

8 DR. ROSNER: I mean, clearly, Mr. Chairman,
9 there are a lot of very smart people in this room.
10 These studies, I think, were actually good studies
11 and well performed. But just to sort of take it
12 down a level, there's a lot of men in this room,
13 and so there's theoretically a lot of prostate
14 cancer. And we know from autopsy studies that
15 prostate cancer is present in men in their 20s.
16 And so I don't really care for the word
17 "prevention" because I'm not really sure, as Dr.
18 Sesterhenn was talking about and Dr. Walsh, if
19 we're really preventing -- or really what we're
20 doing to the disease.

21 But I think the -- and I feel very strongly
22 about this, and it's getting back to what we're

1 talking about, is that this is going to go out to
2 the clinicians. So most of us here are medical
3 oncologists or urologic oncologists, and we can
4 handle the PSA gyrations and questions. But for
5 the family practitioners, the hospitals, the
6 internal medicine doctors, and the thousands of
7 patients who may go on this drug in addition to the
8 ones that are already on it, I think there's a lot
9 of confusion and a lot of assumptions that are
10 going to be made. And perhaps the patients are not
11 going to be truly managed well. You can do all
12 the education that you want, but I can still see,
13 now patients, they're on Proscar for their BPH and
14 they certainly don't understand what happens to
15 their PSA kinetics.

16 So I think from a public health issue, this
17 is a big issue, and I think it's a little
18 frightening, to be honest.

19 DR. WILSON: Dr. Kelly?

20 DR. KELLY: Yes, as somebody who actually
21 treats high-risk patients, this argument is sort of
22 circular because we're sort of blending what's

1 high-grade cancer and what's high-risk cancer. And
2 I wonder if we have any sense from any of the
3 sponsors, if the patients who are actually
4 diagnosed are actually truly high-risk category or
5 are we just talking about high-grade? I mean
6 because we think of high-risk prostate cancer as
7 more than just Gleason score.

8 DR. ANDRIOLE: Gerry Andriole from the
9 REDUCE trial. So we do have biopsy tumor volume
10 information among the Gleason 8 to 10 cancers, and
11 they were rather small, suggesting that these would
12 be organ confined surgically curable, very likely
13 to be in that category.

14 DR. THOMPSON: And vis-a-vis the Prevention
15 Trial, the data that I showed you earlier, is that
16 if they were high-grade cancers detected in the
17 finasteride arm, they were smaller, less likely to
18 be multifocal, and less likely to be bilateral. So
19 that's the extent.

20 DR. WILSON: Now, that data is not on a
21 select group who had prostatectomy? You're just
22 talking about what they found on the needles?

1 DR. THOMPSON: No, sir. They're not. The
2 other thing, if you give me just a moment, which I
3 was going to respond to your original question,
4 there's unequivocal -- when you asked the question
5 of whether or not we increased the risk of high-
6 grade disease, I'll be the first to tell you we
7 don't know. It is unknowable in the absence of
8 doing prostatectomies in all the subjects exposed
9 to any chemoprevention agent. But all the evidence
10 that we've encountered afterwards is unsupportive
11 of that notion.

12 Now, we heard the FDA's analysis vis-a-vis
13 volume earlier. It's unpublished. We don't know
14 the methodologies. But the evidence that we've
15 looked at from a volume standpoint, which has been
16 peer reviewed, is consistent with the volume bias.
17 As we talked about earlier, there was a PSA
18 detection bias, and there's a DRE bias. Despite
19 these biases that enhance detection of the disease,
20 there was a 26 percent risk reduction. And when you
21 incorporate those for the 7 through 10s, you no
22 longer see that increased risk. With regard to

1 the 8 through 10s, we simply don't know. It is
2 unknowable, except that they are very small
3 numbers.

4 So the risk-benefit analysis, one of the
5 things that you pointed out, is that one man in six
6 in this room, probably higher than that if he's
7 having PSA testing, will be diagnosed with prostate
8 cancer. If that's an okay thing, then perhaps this
9 is not the right agent.

10 But it's a little different from the general
11 chemoprevention of a disease that may be pancreatic
12 cancer or something with low incidence. This is
13 very, very high incidence, and if it's okay for a
14 man to be diagnosed with prostate cancer, we no
15 longer need chemoprevention because we can truly
16 cure all of them or the majority of them. But we
17 certainly know that the profound impact of a
18 diagnosis of prostate cancer, thus chemoprevention.

19 DR. ANDRIOLE: I can say that among patients
20 with Gleason 7 to 10 cancer, there were three known
21 placebo 7 to 10s that had a positive node and one
22 dutasteride 7 to 10 associated with a positive

1 node. The vast majority of the tumors were organ
2 confined.

3 DR. WILSON: Okay. Thank you. I'm going to
4 take two more questions, and then we're going to
5 move to the vote.

6 So Dr. Logan.

7 DR. LOGAN: Not a question, just a couple
8 comments. First, we have this data indicating that
9 the grade less and equal to 6 tumors is decreased
10 with each of these agents with the contradictory
11 evidence of the higher-grade tumors. There had
12 been a number of exploratory analyses; however,
13 they are exploratory analyses. Each one of them
14 has some inherent assumptions, which are often
15 unverifiable usually because of missing data. We
16 just don't know what would have happened to those
17 patients. So it's difficult to interpret those
18 additional analyses. So that's the first point.

19 So the second point is we have from the FDA
20 document some estimates of benefit and risk.
21 Treatment of 200 patients will result in three
22 patients fewer on the treatment arm identified with

1 grade less and equal to 6 disease, and one
2 additional patient identified with grade 8 to 10
3 disease. So that's one summary of the benefit-risk
4 to consider.

5 Then the third thing is, as has been
6 mentioned several times, we are talking about
7 cancer chemoprevention in a general population. I
8 think this does require a substantive benefit to
9 risk ratio as well as a very strong level of
10 certainty about the benefit as well as the risk,
11 and I'm not sure that we have it here. I'm
12 concerned particularly about the monitoring of PSA
13 levels in a general population of people that are
14 on the drug. This is a general population that may
15 or may not be taking it as prescribed, and what's
16 the impact of that on those PSA levels.

17 DR. WILSON: Okay. Thank you.

18 Finally, Dr. Steers?

19 DR. STEERS: Thank you, Mr. Chairman.

20 Again, germane to what we've been told by
21 the FDA, this is different than other clinical
22 efficacy individual decisions I make on a patient.

1 And like Dr. Penson, I've been using these agents
2 for years without a concern for higher-grade
3 cancers. Urologists, oncologists in the country
4 have known this data for a couple of years, and you
5 haven't seen a groundswell of people going on these
6 agents. So it would have been very useful for me -
7 - and it could still be done. I did a back-of-the-
8 envelope calculation on the 1 million men who the
9 sponsors identified, who, by their definition, are
10 at high risk and how many men have been spared
11 treatment of that 1 million over a four-year period
12 if you use for-cause biopsy, which would be more
13 clinical practice. And whether you use the PCP
14 trial or the REDUCE trial, you'll get numbers from
15 300 to 2,100 men reduced cancers you've spared with
16 an uptick to maybe 10 men with Gleason 8.

17 So it becomes for me an epidemiologic
18 decision for chemoprevention in large populations.
19 I can't separate that because of all the drug
20 exposures. This is tremendous with very, in my
21 opinion, loose labeling, although we don't consider
22 labeling, with very generic labeling with complex

1 issues. In an ideal world with all 1 million men
2 getting these exposures, that is an enormous drug
3 exposure, in my opinion, for the small -- in total
4 absolute amounts in, in for-cause biopsies, if you
5 believe the data, the autopsy data.

6 Do we want to make a decision like that? On
7 the individual patient basis, it's a complex thing.
8 But it would be nice if the FDA would have
9 presented for us that data out, exactly what this
10 will mean in the United States for reduction, how
11 many cancers are we talking about preventing and,
12 of those, how many are clinically significant, and,
13 of those, how many are Gleason 8. I think that
14 would be a very appropriate way of presenting this
15 sort of data to help us make such a decision. I
16 think the individual -- the specialists have
17 already seen this data and know. But this is
18 another whole level that we're going to go to with
19 approval of this labeling.

20 DR. WILSON: Well, I think those are very
21 good comments. I think that we just have to --
22 obviously, we don't want to extrapolate from this

1 data any more than we want people to take it and
2 try to do ad-hoc evaluations. I think what we know
3 is there's a modest reduction in low-grade tumors,
4 and there is a concern -- well, there is a risk of
5 an increase in high-grade tumors. Whether or not
6 it's real or not, I think we don't know, but it's
7 there and it's there in both studies. And so
8 that's what we have to deal with, and the fact
9 that, again, probably millions of people will
10 actually end up on this drug.

11 So with that, let's go ahead and turn to the
12 questions. Now, the way the voting works here is
13 if you look on your mic, first make sure that your
14 mic has your name on it. And there is a "yes" and
15 there is a "no," and there is an "abstain" button.
16 And so you're all going to vote, and then the
17 results will come up on the screen. And then I
18 would want you to go around the room, say your name
19 into the record, say how you voted because your
20 name's going to be associated with the vote up
21 there and tell us why.

1 So the first voting question is, number 1,
2 is the finasteride risk-benefit profile favorable
3 for reduction in the risk of prostate cancer in men
4 greater than or equal to 55 years of age with a
5 normal digital rectal examination and a PSA of less
6 than or equal to 3 nanograms per mil?

7 A vote of yes says that the risk benefit
8 favors using this as a preventive agent. No is
9 that we do not believe the risk benefit is
10 favorable to use this as a preventative agent.
11 Please go ahead and vote.

12 [Voting.]

13 DR. WILSON: Okay. I would like to read
14 into the record regarding voting item number 1;
15 Yes, zero; No, 17; Abstain, 1.

16 May I please start over on the right side of
17 the first voting member? Dr. Steers, would you
18 please say your name into the record, say how you -
19 - well, we know how you voted; or, no, we don't
20 know how you voted. Somebody abstained. And tell
21 us why you voted why you did.

1 DR. STEERS: Actually, I hit the no button
2 and it shows abstain, I think, under my name, so
3 it's kind of odd. Okay. All right. I voted no
4 for the preponderance of data showing uncertainty
5 on Gleason 8 disease, the uncertainty on people who
6 go off this drug and its potential for what happens
7 biologically. We don't know with cancer
8 pathogenesis, because many men will be on this and
9 then go off. And because of the risk-benefit for
10 the population at large, with grade of drug
11 exposures, and the change of clinical practice
12 because of the very -- I think the labeling, it's
13 imprecise, based on the data that's presented.

14 DR. HAWK: I voted no predominantly because
15 of the --

16 DR. WILSON: Say your name into the record,
17 please.

18 DR. HAWK: -- Hawk, I'm sorry --
19 predominantly because the average risk of the
20 cohort. I think an approach like this might be
21 very useful in high-risk individuals, but in
22 average risk, I too am concerned about the

1 possibility of the high-grade disease, particularly
2 if the FDA's unable -- or the population of
3 practitioners is unable to restrain themselves or
4 educate themselves appropriately about dealing with
5 PSA levels as has been suggested by the
6 conversation.

7 DR. GARNICK: Dr. Garnick. I voted no, but
8 I want to first acknowledge the extraordinary
9 effort, both by Merck, GSK, and the FDA in really
10 providing an extraordinary amount of information.
11 I can't imagine the amount of work and human
12 resource hours that went into these documents. So
13 from a prostate cancer perspective in terms of
14 shedding light on the natural history of this
15 disease, it's been sort of an extraordinary
16 experience for me to participate.

17 I voted no for several reasons. The first
18 is I really tried to embrace the alternative
19 explanations of the high-grade Gleasons in both the
20 PCPT trial and the REDUCE trial, and despite all of
21 the statistical explanations, if one takes a look
22 at the Table 71 on page 150 of the dutasteride

1 study, prostate volume seemed to have no influence
2 whatsoever on the detection rate of Gleason 8 to 10
3 cancers. I was very concerned that when this gets
4 into general clinical practice, that the indicated
5 population will probably be only a small percentage
6 of the actual treated population in prostate cancer
7 prevention patients.

8 Male patients are completely consumed about
9 developing prostate cancer, and the amount of
10 dietary intervention and nutraceutical
11 intervention, I'm trying to grab onto every
12 potential thing that may have some effect on
13 prostate cancer risk reduction -- would almost
14 require a demand for this product if it were
15 approved, even well beyond the indicated
16 population.

17 I was not convinced that the non-prostate
18 cancer high-grade abnormalities had really been
19 fully explained. As I mentioned in one of my first
20 questions, the all-cause incidence of both cancer
21 death, non-prostate cancer death, and other
22 abnormalities was really quite striking to me, both

1 in the gastrointestinal cancers and the
2 hematological cancers. And I think until that's
3 further understood, I think that would be a
4 potential issue that needs to be not only addressed
5 for this study but also for the use in BPH.

6 Finally, I just wanted to make one comment
7 in terms of the actual selection of the dose on the
8 finasteride. I think you've got 1 milligram data
9 that does a lot of the same sort of physiological
10 activities, and one wonders whether or not even a
11 lower dose of finasteride could have been studied
12 for this particular indication. So those are my
13 reasons.

14 DR. FURBERG: Furberg. I voted no,
15 primarily due to the concern of an increase in
16 high-grade Gleason scores, and particularly in
17 light of the fact we need a lower bar for primary
18 prevention. I'm not convinced about the clinical
19 significance of the change in reduction in low
20 grade. And secondly, what's troubling me also is
21 that we don't have long-term follow-up data,

1 mortality, morbidity. That's missing totally.
2 We're dealing with primarily intermediate outcomes.

3 DR. EISENBERGER: I'm Mario Eisenberger. I
4 voted no for several reasons. I think the main
5 issue is I have a great deal of difficulty in
6 linking the findings on these two studies with the
7 real world in practicing. First of all, I'm
8 concerned about the lack of long-term follow-up,
9 and I'm having difficulty in determining that
10 seven- and four-year studies in a disease which is
11 characterized by the very long natural history,
12 that the findings in seven and four years will
13 allow me to make a determination of benefit over a
14 lifetime period.

15 Second, the one thing that I'm also having a
16 great deal of difficulty is that much of the
17 benefit is based on biopsy or Gleason, some
18 findings on digital rectal recommendation and those
19 that had for-cause biopsies, and some data on PSA.
20 And the possibility that PSA determinations and
21 defining what becomes significant using a 5 alpha-
22 reductase inhibitor, in my mind, are not totally

1 well explained to a level where it can be divulged
2 as guidelines to the general practitioner.

3 Moreover, the difficulty that I have is that
4 there is no link in terms of outcome. I recognize
5 the difficulty of having outcome data in terms of
6 progression, development of metastatic disease,
7 response to subsequent treatment, and I find that
8 to ask that there is a survivability or mortality
9 data linked to these studies is probably too much
10 to ask. I think by the time when you finish the
11 study in which you have survival data, most for
12 sure, the drugs will be obsolete and we'll
13 hopefully have other modalities of treatment, maybe
14 even doing better with treatment so that this is
15 not going to be so helpful.

16 But I would have liked to see surgical
17 pathology data. I would like to see more final --
18 even if it was in a subset of patients, I would
19 have liked to see a surgical Gleason score extent
20 of disease, things that are, in my mind, more
21 tangible to allow me to address the issue of
22 benefit.

1 To a lesser extent, I'm concerned about the
2 incidence of high-risk disease. As much as I
3 recognize that we haven't resolved the explanation
4 for that, I am not so impressed about the
5 possibility that this, in fact, a worsening of the
6 Gleason or high-grade disease is linked to
7 treatment. I cannot see that so well. I recognize
8 it remains unexplained. And that's certainly
9 another reason. And so these were the main reasons
10 why I voted no.

11 DR. D'AGOSTINO: D'Agostino. I voted no.
12 The main reason that was driving me was the public
13 health implications that this is a population
14 that's coming in with not a problem, and heaven
15 knows what kind of use will happen and how it will
16 be controlled and so forth, and what the
17 implications are in terms of adverse events.

18 Second is very important, also, and close to
19 it, was the high-grade issue. The sponsor had
20 talked about detection bias and so forth, but I
21 don't think those arguments actually answered the
22 question. So we're still left with this notion of

1 the high grade. It seems to be very likely to be
2 elevated. And all the above, I'm not going to
3 repeat what was said so well by previous people.

4 DR. LOGAN: Brent Logan. I voted no. I
5 basically had the same issues as Dr. D'Agostino. I
6 think the bar that should be set for approval for a
7 cancer chemoprevention agent with an otherwise
8 healthy population should be very high, and I
9 didn't think that this met it. There was certainly
10 concerns with the high-grade disease, and I'm not
11 sure that the exploratory analyses that were
12 presented were completely convincing. And so
13 that's the main reasons.

14 DR. TEMPERO: Margaret Tempero. I voted no.
15 I was more concerned about the side effect profile
16 in a perfectly healthy population. Also, a bit
17 concerned about the higher-grade malignancy, but
18 not so sure that -- I just felt that more needs to
19 be done to understand that.

20 DR. SEKERES: I'm Mikkael Sekeres. I voted
21 no. There is no doubt that finasteride reduces the
22 amount of early-grade prostate cancer that was

1 detected. At the same time, there's also no doubt
2 that the rates of high-grade prostate cancer were
3 increased, and even the sponsoring companies had to
4 acknowledge they could not exclude the possibility
5 that this drug may have caused that increased risk
6 of high-grade prostate cancer. And that's an
7 unacceptable risk in a population of men who don't
8 have prostate cancer.

9 DR. FREEDMAN: Ralph Freedman. I voted no.
10 I think it's important that the risk-benefit
11 profile assessment is dependent on having a very
12 high degree of certainty and particularly in a
13 population such as this, if this drug were to be
14 approved, the population that would receive this
15 drug. And also knowing the ultimate outcomes of
16 the disease that's being treated and we lack that
17 information. And we lack understanding of the
18 biology of this drug in the long-term setting. And
19 because of the fact that it will be used on
20 patients who have a long-term survival, I think
21 this is very critical.

1 Also, it's important that we consider what
2 other alternatives are available for managing these
3 patients, for monitoring and managing these
4 patients. And I don't think we have any idea that
5 this intervention will add anything to what is
6 currently available, however imperfect that may be.

7 DR. WILSON: Wyndham Wilson. I voted no. I
8 do not see that there was any benefit to this drug
9 in terms of long-term cancer. The benefit that was
10 put forward was that it reduced the number of
11 patients that might go on to surgery. I recognize
12 that PSA testing is imperfect; biopsying is
13 imperfect. And I think that the clinical and the
14 scientific folks are working hard on improving
15 sensitivity and specificity, but I do not think
16 simply taking another drug to try to hide or to try
17 to change problems with an imperfect system is
18 really a true benefit.

19 On the other side, we did, in fact, see an
20 increased incidence of higher-grade disease.
21 Whether or not it is because it was delaying
22 detection because of the reasons I mentioned or

1 because it was even a more ominous biological
2 effect depleting, somehow changing the
3 microenvironment and the ratios of the various
4 androgens, I couldn't say. But, clearly, both
5 studies showed the same thing. And I think in a
6 setting like this, the onus is on the drug to be
7 completely safe and to show benefit, and I don't
8 think it reached that level.

9 DR. KELLY: My name is William Kelly. I
10 voted no. I really teeter-tottered at the end here
11 about my decision because I think there is some
12 very encouraging results from the trial. I wasn't
13 so worried about the high-risk patients because
14 most of those are salvaged, and there's no evidence
15 that there's a decreased benefit for those patients
16 or risk for those patients.

17 But the concern I had is how you employ this
18 in the general population, how are you going to use
19 it. And I'm concerned that we didn't -- if you just
20 generally use it out there and we're not having a
21 targeted strategy, it's going to be defeating the
22 purpose. So that really swayed me at the end.

1 DR. LOEHRER: I'm Pat Loehrer. At the age
2 of 61, my father was diagnosed with prostate
3 cancer, so I'll be a couple of years from now. And
4 so, actually, I did take your suggestion to heart,
5 Rick, and figure out what I would do. And in
6 looking at this, I think there are some unmet needs
7 in prostate cancer, and that is to reduce the
8 incidence of high-risk disease and high-grade
9 disease and decrease mortality. And I think it was
10 a very noble effort that these trials tried to do
11 this. They did exactly the right thing. They did
12 include grade 6, I think, because they needed the
13 numbers.

14 But the truth of the matter is it met a
15 un-need, and that is that it decreased the
16 incidence of low-risk prostate cancer. And as a
17 result, actually, there were some other increases
18 of the high-risk disease. And so I think from a
19 practical matter and a personal matter, I would
20 have a very hard time taking this drug. I wouldn't
21 do it.

1 There was another issue that has not been
2 brought up, but it was discussed by some of the
3 speakers, particularly by Dr. Walsh, that the
4 patients with low-risk disease, many of them are
5 undergoing treatments; 90 percent of them undergo
6 prostatectomy or radiotherapy, and a few of them
7 undergo observation. And although this treatment
8 may actually decrease the number of patients who
9 are undergoing surgery and radiation therapy, the
10 truth of the matter is, that's a man-made decision.

11 We could make that decision today when we
12 see patients with low-risk disease to just do
13 observation. And I think, as Dr. Walsh mentioned,
14 there is a conflict of interest that I think many
15 of the physicians have. So I think from that
16 perspective, I think, again, the charge is really
17 to identify the high-risk patients and figure out a
18 way to impact their life expectancy.

19 DR. MAJUMDER: I'm Mary Majumder, and I
20 voted no. Like others, I think I was swayed by
21 looking at the data in relation to a very high
22 standard, demanding a high degree of confidence,

1 which the degree of disagreement suggests simply
2 wasn't there, and then the broader public health
3 implications.

4 DR. KIEFERT: My name is Jim Kiefert. I
5 voted no. I wanted to vote yes so bad. We would
6 love to have some chemopreventive treatments for
7 all the men who are dealing or going to deal with
8 prostate cancer. But the question that tipped the
9 balance for me was when I heard Dr. Penson say that
10 these drugs are used with thousands and thousands
11 of patients without any of those negative side
12 effects, and yet there wasn't a way to explain that
13 high-grade Gleason score that was in that
14 subpopulation in the studies. Is it a biochemical
15 change? Is something going on within the cancer,
16 and it doesn't do it when you use it with people
17 who have PIN? It was that question that made me
18 realize that I needed more data to comfortably say
19 to my sons, I'd like you to start taking this drug.

20 So it's the question of what is it that's --
21 what's the cause and the effect of these men who
22 are taking these drugs and having that incidence of

1 high-grade PIN? Once that question is answered,
2 I'd feel more comfortable being able to advise my
3 sons whether that's the right thing for them.

4 DR. PENSON: David Penson, I voted no. I
5 don't have a lot to add to what's already been
6 said. Simply put, I actually believe this drug in
7 the proper clinical practice is a good drug. It
8 does reduce prostate cancer. The problem becomes
9 is that in my practice, I know many urologists will
10 continue, and I will continue, to use this off
11 label in high-risk patients. I'm following those
12 patients very closely. I know what I'm doing with
13 the PSA, and I don't mean that in an arrogant way;
14 I mean that as a statement of fact, that there are
15 people who make a living treating prostate cancer
16 all the time.

17 The problem becomes is that I was told by
18 the FDA, and I think this is a very well taken
19 point, to consider the real world situation. And
20 the real world situation is exactly as Marc Garnick
21 pointed out. These patients are seeking out
22 nutraceuticals. They are changing their diet. We

1 will have 25- and 30-year-old men asking us to put
2 them on 5 ARIs, and someone is going to do it. And
3 if you look at the risk-benefit profile on that
4 situation, there's very little benefit, and there
5 may be a risk of increased disease over the long-
6 term. So in my mind, there was no way I could
7 justify it from a public health standpoint.

8 DR. ROSNER: Inger Rosner. I certainly have
9 nothing else to add. I voted no for -- I agree
10 with what everybody has said, and there's been a
11 lot of very interesting profound things said. And
12 prostate cancer and prevention and disease and
13 prevention are all very difficult to treat as a
14 clinician and something that I think we all
15 struggle with.

16 DR. SESTERHENN: I abstained because I'm not
17 a clinician, and I'm a pathologist. I want to see
18 what you tell me is true, and I wonder if you could
19 in the future use imaging techniques or so to
20 really show that you are reducing this disease.

21 DR. WILSON: Okay. I would like to thank
22 you all. So let's move on to the second question,

1 and that is, is the dutasteride risk-benefit
2 profile favorable for reduction in the risk of
3 prostate cancer in men at increased risk of
4 developing the disease, defined as those who have
5 had a prior negative biopsy due to clinical concern
6 and have an elevated serum PSA?

7 A vote of yes says that the risk-benefit
8 favors it, and it should be used to prevent cancer.
9 A vote of no is a vote of no. So please go ahead
10 and vote.

11 [Voting.]

12 DR. WILSON: All right. I would like to
13 read into the record for the second voting
14 question. Yes is 2, No is 14, Abstain is 2. Can I
15 please go ahead and have you start? Say your name
16 into the record and say why you voted. Let me just
17 say we're running out of time and so if you voted
18 no, perhaps you could keep it short.

19 DR. STEERS: I voted no, and I would have
20 voted yes if it would have shown a reduction in
21 clinically significant prostate cancer and no
22 questions raised about high grade.

1 DR. HAWK: My name is Ernie Hawk. I voted
2 yes because in this case we're dealing with a
3 higher-than-average-risk cohort, therefore, I don't
4 know that, as you put it, Dr. Wilson, all patients
5 should be treated with this medication, but I think
6 it should be available for use because I do think
7 adequate clinical benefit was demonstrated by the
8 reduction of low-grade disease. The question of
9 higher-grade disease remains a question, but I
10 think there are many compelling arguments as to why
11 that may be an artifact. And so really, it was the
12 safety of the agent, demonstrated use in millions
13 of individuals, as well as the clinical benefit
14 that I saw in the data.

15 DR. GARNICK: Marc Garnick. I voted no for
16 many of the same reasons that I voted no on
17 Question number 1, and also the practical issues of
18 keeping it to the indicated population; and then
19 really not knowing how the eventual outcomes,
20 clinical benefits with long-term use are going to
21 be used, and how long the drug should be utilized
22 for, and how we're going to manage patients that on

1 this for four years, seven years or 10 years or 12
2 years. It's simply unknown.

3 DR. FURBERG: I thought the findings that we
4 discussed today from the two trials were remarkably
5 consistent, so I'm trying to be consistent. I'm
6 voting no again.

7 DR. EISENBERGER: Mario Eisenberg. Same
8 here. I still have a great of difficulty with a
9 four-year study; how can I extrapolate that to a
10 lifetime use of a drug. I would have liked to have
11 a bit more tangible data on the pathology, which
12 was somewhat disappointing.

13 The other thing I didn't articulate in the
14 previous comment is that I know that it appears
15 that these drugs are safe, but safety data in a
16 lifetime basis, or long-term basis, prospectively
17 collected with the criteria is different than just
18 getting sort of retrospective data or data in just
19 a short period of time. And I would have liked to
20 see that as well since the indication would have
21 been for that kind of use.

1 Again, what bothers me with these compounds
2 is the inability to make a clear-cut or develop a
3 clear-cut set of guidelines that practitioners can
4 use for patients who are actually using these
5 compounds, and what should be done, and what points
6 should be done, particularly when we deal with the
7 unresolved issue of a possibility of an increase in
8 high-risk disease, which again, I can't just be so
9 worried about this. I don't think it's so much
10 drug related. Thanks.

11 DR. D'AGOSTINO: D'Agostino. I voted no.
12 This is obviously a much more focused study. It's
13 dealing with a higher-risk group than the previous
14 study, but the questions or comments or concerns I
15 had before still translate here, in terms of the
16 public health and in terms of the high-risk group.
17 In addition to that, I think with something that's
18 focused on individuals who they say that are at
19 elevated risk, along the study, 8,000 subjects for
20 four years is not a very large study for the types
21 of things that I'd see all the time in
22 cardiovascular research.

1 Certainly, it should I think require a
2 longer-term study. I don't know if you can get
3 hard outcomes as the endpoints, but you certainly
4 get more information about the potential problems
5 of the drug and possibly a good idea of the hard
6 outcomes.

7 DR. LOGAN: Brent Logan. I voted no. I
8 think the issues were pretty consistent. The study
9 results were consistent with the previous one, so I
10 don't have any additional comments.

11 DR. TEMPERO: Margaret Tempero. I voted
12 yes, and I primary was persuaded by the opportunity
13 to minimize unnecessary procedures in this higher-
14 risk patient population. And so that was the risk-
15 benefit piece of it that I felt that this drug met.

16 DR. SEKERES: Mikkael Sekeres. I voted no.
17 I just couldn't justify voting yes for a drug that
18 may cause higher-grade prostate cancers, in
19 patients who don't have prostate cancer, for the
20 benefit of diagnosing prostate cancer that for the
21 majority of people may never amount to anything.

1 DR. FREEDMAN: Ralph Freedman. I voted no
2 for the same reasons basically that I did on the
3 finasteride study. In addition, I am not certain
4 how substantially different these two populations
5 actually are. We've heard some discussion from our
6 experts about that. And also, the follow-up was
7 only four years compared with the seven years from
8 the previous trial, so I didn't feel there was any
9 basis for changing my vote.

10 DR. WILSON: Wyndham Wilson. I voted no for
11 the same reasons, but a couple of caveats here. As
12 Dr. Freedman said, I'm not convinced there is
13 really a higher risk. Yes, they were higher risk
14 because they ended up undergoing a biopsy once, but
15 having had a negative biopsy, that therefore culled
16 out the highest risk folks. And so the risk went
17 back down lower.

18 The follow-up was very short. It was only
19 for four years. If, in fact, a drug is either
20 selecting biochemically higher-grade tumors or
21 delaying diagnosis, this will probably become
22 magnified over time, and we're talking about people

1 who will be at a lifetime risk of prostate cancer.
2 We're talking about people being on this drug for
3 their entire life, and I think we have no idea what
4 this drug might do. And my attitude is you do no
5 harm.

6 DR. KELLY: William Kelly. I voted no,
7 also, for the previous reasons. And it's just one
8 of those things; we have to move past the
9 pathological endpoint into more of a clinical-based
10 endpoint.

11 DR. LOEHRER: My name is Pat Loehrer. I
12 voted no. I have nothing to add.

13 DR. MAJUMDER: This is Mary Majumder. I
14 abstained. I felt that the indication was
15 narrower, so the public health picture was somewhat
16 different. And given that, I chose to defer to the
17 clinicians.

18 DR. KIEFERT: My name is Jim Kiefert. I
19 voted no, and I have nothing more to add.

20 DR. PENSON: My name is David Penson. I
21 also voted no. I agree with Dr. Freedman's
22 comments. This isn't necessarily a high-risk group

1 of patients. It's a group of patients where we
2 have clinical uncertainty on what to do next, and
3 then it becomes the same as the earlier question,
4 and that's why I voted no.

5 DR. ROSNER: Inger Rosner. I voted no, and
6 no further comment.

7 DR. SESTERHENN: I have no further comment,
8 either.

9 **Adjournment**

10 DR. WILSON: Okay. Let me thank you all for
11 coming, and meeting is adjourned.

12 (Whereupon, at 5:09 p.m., the meeting was
13 adjourned.)
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