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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS
ADVISORY COMMITTEE

70TH MEETING

FRIDAY
MAY 15, 1998

The Advisory Committee met in Versailles Rooms 1 and 2 in the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Robert Marcus, M.D., Acting Chair, presiding.

PRESENT:

ROBERT MARCUS, M.D.	Acting Chair
CATHY CRITCHLOW, Ph.D.	Committee Member
JAIME A. DAVIDSON, M.D.	Committee Member
JULES HIRSCH, M.D.	Committee Member
D. ROGER ILLINGWORTH, M.D., Ph.D.	Committee Member
MARK E. MOLITCH, M.D.	Committee Member
ROBERT S. SHERWIN, M.D.	Committee Member
GLENN BRAUNSTEIN, M.D.	Consultant
KENNETH D. BURMAN, M.D.	Consultant
PIPPA SIMPSON, Ph.D.	Consultant
VERNON M. CHINCHILLI, Ph.D.	Consultant

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

2 Time: 8:08 a.m.

3 CHAIRMAN MARCUS: The 70th meeting of the
4 Endocrine and Metabolic Drugs Advisory Committee is
5 called to order.6 I'm Robert Marcus. I'm the Chairman of
7 today's panel, and I'd like to begin by having
8 everybody at the table go around in sequence and
9 introduce themselves, and we'll start with Dr. Sobel
10 from Food and Drug Administration.11 DR. SOBEL: Sol Sobel, FDA, Division of
12 Metabolic and Endocrine Drugs.13 DR. ORLOFF: David Orloff, FDA, Metabolic
14 and Endocrine Drugs.15 DR. CASTILLO: Sonia Castillo, Division of
16 Medical Imaging and Radiopharmaceutical Drug Products.17 DR. BURMAN: Ken Burman, head of Endocrine
18 at the Washington Hospital Center, a visitor today.19 DR. HIRSCH: Jules Hirsch, Rockefeller
20 University.21 DR. DAVIDSON: Jaime Davidson, University
22 of Texas, Dallas.

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1 DR. CRITCHLOW: Cathy Critchlow,
2 University of Washington, Seattle.

3 DR. MARCUS: Robert Marcus, Stanford
4 University.

5 MS. REEDY: Kathleen Reedy, Food and Drug
6 Administration.

7 DR. SHERWIN: Robert Sherwin, Yale School
8 of Medicine.

9 DR. NEW: Maria New, Cornell Medical
10 School.

11 DR. ILLINGWORTH: Roger Illingworth,
12 Oregon Health Science University, Portland, Oregon.

13 DR. SIMPSON: Pippa Simpson, University of
14 Arkansas, medical sciences.

15 DR. MOLITCH: Mark Molitch, Northwestern
16 University, Chicago.

17 DR. CHINCHILLI: Vern Chinchilli, Penn
18 State, Hershey Medical Center.

19 DR. BRAUNSTEIN: Glenn Braunstein, Cedars
20 Sinai Medical Center, UCLA.

21 CHAIRMAN MARCUS: Thank you. We convene
22 today to discuss NDA 20-898, Thyrogen. The sponsor is

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1 Genzyme.

2 Before we initiate the proceedings,
3 Kathleen Reedy has a statement to read.

4 MS. REEDY: Conflict of interest
5 statement: The following announcement addresses the
6 issue of conflict of interest with regard to this
7 meeting and is made a part of the record to preclude
8 even the appearance of such at this meeting.

9 Based on the submitted agenda for the
10 meeting and all financial interests reported by the
11 committee participants, it has been determined that
12 all interests in firms regulated by the Center for
13 Drug Evaluation and Research present no potential for
14 an appearance of a conflict of interest at this
15 meeting.

16 In the event that the discussions involve
17 any other products or firms not already on the agenda
18 for which an FDA participant has a financial interest,
19 the participants are aware of the need to exclude
20 themselves from such involvement, and their exclusion
21 will be noted for the record.

22 With respect to all other participants, we

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1 ask, in the interest of fairness, that they address
2 any current or previous financial involvement with any
3 firm whose products they may wish to comment upon.

4 I would like to clarify that Dr.
5 Braunstein, Dr. Burman and Dr. Oppenheimer and Dr.
6 Simpson are SGE consultants, special government
7 employee consultants, and are temporary voting
8 members.

9 Dr. Chinchilli is a member of another
10 committee, the Pulmonary Allergy, and is a full
11 member, voting member.

12 That's the status of all of those at the
13 table.

14 CHAIRMAN MARCUS: Thank you. It is a
15 feature of the American system of drug regulation that
16 we invite commentary from interested members of the
17 public, and we have several public statements that
18 will either be read into the record or given at the
19 microphone. How many at the microphone? There will
20 be three speakers from the microphone.

21 May I ask you to be sure to identify
22 yourself fully and to please state whatever financial

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1 interests have resulted in your being brought to
2 Bethesda for this meeting today.

3 So the first speaker will be Dr. F.
4 Deaver Thomas from SUNY Health Science Center,
5 Syracuse. No, that's a letter. Okay, Richard
6 Robbins, M.D. from Sloan-Kettering.

7 DR. ROBBINS: Good morning. I would like
8 to thank the committee for the opportunity to address
9 you this morning. I hope the microphone is on
10 completely.

11 What I'd like to do is just to read a
12 letter that I submitted to the committee or excerpts
13 from it, as well as two letters from my patients that
14 I've just received in the last few weeks. I think
15 they might be important in your deliberations.

16 First of all, I'm Professor of Medicine at
17 Cornell University Medical College and Chief of the
18 Endocrinology Service at Memorial Sloan-Kettering
19 Cancer Center.

20 Thyroid cancer has been a longstanding
21 interest at our medical center, and I currently
22 actively manage the care of over 200 patients with

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1 metastatic thyroid cancer.

2 The committee also needs to be aware that
3 I have been involved with the company Genzyme in a
4 compassionate need program where the company does
5 provide this medication to our patients at no charge
6 under this compassionate need protocol and, in
7 addition, I've just entered in with the company into
8 a new clinical trial, looking at whether or not this -
9 - to look at one of the detailed effects of this drug
10 in our patients in comparison to hypothyroidism.

11 One of the most sensitive and specific
12 means for determining the presence of thyroid cancer
13 is to use whole body radioactive iodine scanning and,
14 as many of the committee members know, it's the
15 current practice in the United States to remove the
16 patients from their thyroid hormone for four to six
17 weeks in order to enable their own TSH levels to get
18 high enough to stimulate iodine uptake in metastatic
19 lesions.

20 Hypothyroidism is usually an uncomfortable
21 and debilitating process for these patients. It's
22 often associated with sleepiness, fatigue, reduced

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1 cognitive skills, constipation, weight gain, changes
2 in personality. Patients frequently have to take off
3 several weeks from work or drop out of school for a
4 few weeks in order to go through the treatments.

5 A number of my patients actually have
6 refused to become hypothyroid, feeling that the
7 complications of that problem are much more troubling
8 to them than the possibility that they might have a
9 recurrence of thyroid cancer.

10 The recent availability of human
11 recombinant TSH through this compassionate need
12 program from Genzyme has enabled me to learn firsthand
13 about the use of this reagent in patients with
14 metastatic thyroid cancer.

15 Our center has performed over 20 scans in
16 12 patients. Actually, we're now to 14 patients who
17 have received this, and they've gone through whole
18 body iodine scanning with it. They have been
19 generally very positive about how simple the procedure
20 is when they stay on their thyroxin compared to how
21 they were when they were hypothyroid.

22 Again, my experience has only been with

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1 patients who have metastatic thyroid cancer. I have
2 not compared the thyroid scanning in patients who are
3 hypothyroid and then on Thyrogen. So we haven't done
4 direct comparisons of that question.

5 The possibility that the agent may become
6 available in the future has resulted in a flurry of
7 activity in patients with metastatic thyroid cancer.
8 One place you can see this is on Internet thyroid
9 cancer chat lines. Many patients are awaiting the
10 availability of Thyrogen until they undergo their next
11 scan.

12 The fact that the patients do not have to
13 suffer with hypothyroidism for two or three weeks
14 every time they need a whole body scan is a major
15 quality of life issue, and as a practitioner of
16 thyroid cancer care and as a friend to many scores of
17 patients with thyroid cancer, I strongly support the
18 approval of this human recombinant, thyrotropin, for
19 the diagnosis of thyroid cancer.

20 Now a few weeks ago when I learned I would
21 be able to come down to the committee, I asked a
22 couple of patients who were in the hospital receiving

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1 Thyrogen for their treatment, and they have written
2 two short comments about their experiences. I'd like
3 to read from them briefly.

4 The first is from a gentleman, I.D. "I've
5 been treated with the radioactive iodine seven times
6 since the start of my thyroid cancer in 1990. In the
7 first six instances my treatment was the traditional
8 method. As I stopped taking synteroid prior to my
9 nuclear medicine scans and radioactive iodine
10 treatment, the withdrawal of synteroid over a six week
11 period essentially incapacitates the individual as one
12 loses their physical and psychological equilibrium and
13 becomes totally devoid of all energy.

14 "When combined with scans, treatments and
15 then the gradual resumption of synteroid, the entire
16 process takes 12 weeks and represents a significant
17 deterioration of the quality of life.

18 "My last treatment was with Thyrogen, and
19 I continued my thyroid replacement throughout. The
20 entire treatment, including scans, took only two
21 weeks. Not only did I gain ten pounds, but I never
22 lost my energy or equilibrium.

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1 "Thyrogen is the most favorable thing that
2 has happened to me during my eight-year battle with
3 thyroid cancer."

4 A second letter from patient R.S.: "I
5 commenced Thyrogen treatment on April 18th and am
6 presently..." -- He wrote this on his Power Book while
7 he was an in-patient, sitting around in the hospital.

8 "My previous two experiences with the
9 treatment of thyroid cancer were quite personal
10 disasters for me. Each time I was off my supplement
11 from four to six weeks, I gradually began to suffer
12 serious physical problems. I had severe muscle
13 spasms, headaches, constipation, terrible fatigue,
14 sweats and chills, a great deal of difficult walking
15 and climbing, trouble with digestion and focusing of
16 my eyes.

17 "These problems seriously interfered with
18 my normal life, to the point that by the time I was
19 ready for the radioactive iodine, I was practically a
20 basket case. At the end I had to give up all activity
21 and remain sedately at home, quite depressed, awaiting
22 the procedure.

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1 "I must say that, even though the Thyrogen
2 protocol I've undergone has some side effects, such as
3 a mild headache and some muscle spasms, there have
4 been virtually none of the other problems that were
5 present the prior two times. I have been able to
6 carry on with my life normally unhindered, traveling
7 and working as usually and, most importantly, have had
8 no lack of energy or good spirits.

9 "Being able to participate in the study
10 has been a gift for me, and I can unhesitatingly
11 recommend it as being a major advance in the treatment
12 and most helpful in my case."

13 Now I'm sure the committee is aware that
14 there are approximately 1600 Americans who die each
15 year from thyroid cancer, and I estimate that there
16 are over 20,000 patients in the country who have
17 metastatic thyroid cancer who need annual or semi-
18 annual whole body scans to determine the presence of
19 residual or recurrent disease.

20 A number of our patients at our medical
21 center have had involvement with brain tumors
22 especially, some with tumors that have resulted in

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1 radiation treatments to the brain, and they can
2 actually not make TSH even when they're hypothyroid.
3 So Thyrogen in their case is one of the only ways they
4 can actually get radioactive iodine.

5 We have an even larger number of our
6 metastatic thyroid cancer patients that we take care
7 of who are over 60 years old and suffer very severe
8 medical illnesses when they become hypothyroid to the
9 point where, in many cases, we have to put them back
10 on thyroid hormone.

11 So I would like to say that I think this
12 is a major advance, possibly the major advance in
13 clinical thyroidology in the last 30 years, and to
14 reiterate that the company, Genzyme, although I'm
15 involved with them in studies, has not asked me to
16 come here or has not discussed my remarks in any way
17 with me before coming here.

18 I'd like to remind you and speak on behalf
19 of many of the patients who are too sick or too afraid
20 to come here and speak to the committee, it is a very
21 significant element in their life, and I ask the
22 committee, after you analyze all of the -- carefully

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1 analyze the details of the application that you have
2 before you, keep in mind that many patients are very
3 anxious and waiting to have access to this modality.

4 Thank you.

5 CHAIRMAN MARCUS: Thank you, Dr. Robbins.
6 May I remind the other public speakers that I'm going
7 to try to hold you to a five-minute maximum. We
8 simply need to progress with the work of the
9 committee, and we have 18 letters, not all of which
10 will be read into the record.

11 The next speaker will be Maura
12 Goldsborough.

13 MS. GOLDSBOROUGH: Hopefully, everybody
14 can hear me okay. My name is Maura Goldsborough. I'm
15 a nurse from Johns Hopkins in Baltimore, came here of
16 my own personal free will, and I'm going to read some
17 thoughts about my thyroid cancer.

18 My thyroid cancer was diagnosed three
19 years ago today. As I sat in my doctor's office
20 waiting to hear the results of my biopsy, I knew
21 before he even said one word.

22 Following the recovery period after my

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1 surgery, I would soon learn what it meant not to have
2 a thyroid gland, that really small gland in your neck
3 that can make you feel very bad.

4 My first thyroid scan that I had was
5 terrible, weeks and weeks without medication, that
6 left me weak, tired and a much different person. We
7 all know what it's like to be tired, but you don't
8 know what tired is until you've been hypothyroid.

9 It means driving to work not being able to
10 feel your hands because they are so numb by the time
11 you get to the end of your commute. It means
12 struggling to get up the stairs, not being able to
13 exercise or not having enough energy to eat.

14 I'm not a mother, but I'm not sure how a
15 mother would handle being in such a physical condition
16 with small children.

17 It also means that by 1:30 or two o'clock
18 in the afternoon you're ready to go home, but you
19 still have three hours of work left to complete, which
20 you can't concentrate on.

21 While I was in the lab room waiting for my
22 radioiodine dose, the medical resident with about ten

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1 interns in tow stopped by to examine me. Everyone got
2 a turn with the hammer to see for themselves how
3 really slow your reflexes can get when you're totally
4 hypothyroid.

5 With the use of the drug Thyrogen, I was
6 able to be feeling good and functional up to the time
7 of my scan. I had no side effects.

8 My reasons for participating in this study
9 were both for myself and for others with thyroid
10 cancer. For myself, as a young person with cancer, I
11 know over the course of my lifetime I will need
12 multiple scans to monitor my health. For others with
13 thyroid cancer who may have similar symptoms, as well
14 as emotional symptoms when hypothyroid and off
15 medication, this new drug can help facilitate
16 compliance with follow-up tests and reduce the amount
17 of complications.

18 Thank you.

19 CHAIRMAN MARCUS: Thank you very much.
20 The next speaker is Melvin Smith.

21 MR. SMITH: Ladies and gentlemen, my name
22 is Melvin Smith, and my expenses to come down here

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1 were borne by Genzyme. I have no other connection
2 with the company.

3 In 1991 I had a very serious enlarged
4 neck. It was determined to be a thyroid problem, and
5 they tried to shrink it for a year, and that didn't
6 work, they operated on it because it got larger,
7 removed a better than a pound mass from my neck.

8 It was diagnosed as follicular with
9 possible anaplastic traits. Thus, I was a candidate
10 for metastases. What happened is that we had the
11 iodine ablation followed by radiation, and then they
12 said, well, now we're going to start on this
13 withdrawal. Didn't think anything of it. This is
14 1992, and I never went through such difficulty in my
15 life.

16 I'd like to describe it to you. First
17 they took me off of the synteroid and gave me Cytomel
18 for three weeks. Then they took me off of the
19 Cytomel, and that final three weeks was -- I would say
20 it's just the worst condition I ever underwent.

21 If you don't have a good solid marriage,
22 you're going to get a divorce. You have a lot of

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1 problems. You can't walk. You can't talk. My wife
2 refers to it as my cuckoo time.

3 Then after that, you have the scan, and
4 then you've got two or three weeks of recovery; and I
5 don't care if they give you Cytomel and synteroid,
6 your level is going to rise. You're going to need
7 more when you come back.

8 So that now I'm up to 400 micrograms per
9 day. This is a real slug. My face swells like a
10 pumpkin. My eyes recede. If you're in any kind of a
11 position where you face the public, this is
12 unacceptable.

13 There's weight gain, extremely moody and
14 irritable. Cruel and inhuman punishment would be a
15 mild term for what you go through. You're unable to
16 concentrate during work. You lose your computer
17 skills. Recall is diminished. Your speech starts to
18 slur, and during the last three to five days you can't
19 walk 20 feet.

20 The total incapacitation time, I estimate,
21 is about seven weeks, and I had since refused during
22 1996, '97 and '98 to undergo it while awaiting for --

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1 to see what happens to the Thyrogen.

2 My endocrinologist, Dr. Rodacobabn, has
3 said if it doesn't get approved, he's going to admit
4 me to the hospital and strap me down. All I can say is
5 that I recommend to the board that I know there are
6 others in my condition, and I know that Thyrogen will
7 allow them to at least survive the retesting, and I'd
8 like to urge the committee to really seriously look to
9 approve this material.

10 Thank you.

11 CHAIRMAN MARCUS: Thank you, Mr. Smith.
12 I understand that there is a fourth speaker, but I
13 don't have that person's name.

14 DR. RIDGEWAY: Sorry, Dr. Marcus. I'm Dr.
15 Ridgeway. I'm from the University of Colorado, and my
16 travel expenses have been borne by Genzyme for this
17 trip, and I'm here to read a letter from the Thyroid
18 Foundation of America, which is the largest patient
19 advocacy group for thyroid patients in the United
20 States. It's written by Dr. Lawrence Wood, who is the
21 President of the Foundation.

22 "Dear Ms. Reedy. I am writing with

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1 reference to the notice published in the Federal
2 Register on March 26, 1998, announcing the
3 Endocrinologic and Metabolic Drugs Advisory Committee
4 meeting on May 15, 1998, to discuss the Thyrogen NDA.

5 "This letter is being submitted as
6 documentation of my views and comments. In addition,
7 since I am unable to appear in person, Dr. Ridgeway
8 will read this letter during the public forum at the
9 start of the meeting.

10 "In several continuing education programs
11 for physicians and at national meetings of the
12 American Thyroid Association, I've heard expert
13 thyroid investigators, including Dr. Lawton of Johns
14 Hopkins, Dr. Ridgeway of Colorado, describe the
15 results of studies evaluating the efficacy of using
16 Thyrogen in evaluation and treatment of patients with
17 thyroid cancer.

18 "It is clear to me that it is extremely
19 uncommon to have a patient in whom thyroid cancer can
20 be demonstrated after thyroid hormone withdrawal, but
21 not after Thyrogen treatment. Almost invariably,
22 thyroid scans, increased thyroid globulin levels post

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1 Thyrogen or both are evident in both evaluations.

2 "The Thyroid Foundation of America is a
3 nonprofit organization dedicated to education and
4 support of thyroid patients. On their behalf I
5 recommend that you give their thyroid specialists who
6 are evaluating and treating thyroid cancer the
7 opportunity to decide which of the two approaches,
8 thyroid hormone withdrawal or Thyrogen, is best for
9 the evaluation and treatment of thyroid cancer suited
10 for their particular situation.

11 "Managed care raises other issues.
12 Recently, we were contacted by a young man in
13 California whose radioiodine evaluation and treatment
14 were delayed for nearly two months because of problems
15 in coordinating his therapy in his particular health
16 care system.

17 "There simply were not appointments
18 available immediately following his thyroid surgery in
19 evaluating him and treat him in an expeditious manner.
20 Consequently, he had nearly one month of profound
21 hypothyroidism, during which his job performance
22 declined. Inappointment could also have deleterious

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1 effects on the thyroid cancer itself.

2 "At a thyroid forum for patients which we
3 presented in San Francisco earlier this spring, a
4 patient with cancer described the terrible fatigue and
5 depression which he had experienced during thyroid
6 hormone withdrawal prior to radioiodine evaluation and
7 treatment.

8 "He had heard of Thyrogen and vowed that
9 he would not again undergo thyroid hormone withdrawal
10 for evaluation of cancer unless a physician indicated
11 it was absolutely necessary.

12 "Patients do have the ability to
13 understand and appreciate the value of Thyrogen, yet
14 are willing to let their physicians make the choice
15 for what is best for them. I urge you to let thyroid
16 specialists in charge of thyroid cancer evaluation and
17 treatment decide whether thyroid hormone withdrawal or
18 Thyrogen is the best way to evaluate and manage
19 patients with thyroid cancer.

20 "I look forward with great interest to the
21 outcome of the advisory panel and future availability
22 of Thyrogen. Sincerely yours, Laurence Wood."

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1 Thank you.

2 CHAIRMAN MARCUS: Thank you, Dr. Ridgeway.

3 There are a series of 18 letters -- I
4 guess 17, in addition to the one which was just read,
5 and in the interest of time we are not going to read
6 them all out loud. They will be available for anybody
7 to peruse. Is that correct?

8 MS. REEDY: This is true. There are a
9 packet of actually all 18 letters plus Dr. Robbins'
10 and Mr. Smith's remarks at the table where the agenda
11 is. All of the committee members and everyone at the
12 table has a copy of all of the letters here, and every
13 agenda in the audience has a list of the writers of --
14 the authors of all the letters.

15 CHAIRMAN MARCUS: Good. I think we should
16 proceed now to the presentation by Genzyme. The
17 morning will proceed with presentation of the
18 company's material, and we're going to try to withhold
19 all questions throughout that presentation unless
20 there is some specific point of clarification that
21 needs to be made; but I would appreciate your
22 withholding any questions relating to the substance or

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1 the intellectual content of the issues that we're
2 facing until after the presentation. We'll try to
3 have our break at 10:15.

4 Before turning over the meeting to
5 Genzyme, let me just remind you that every member of
6 this panel has seen all this material. We have all
7 read it. So any redundancy -- It would be appreciated
8 if it could be avoided.

9 MS. LAWTON: Good morning, ladies and
10 gentlemen, members of the panel. My name is Allison
11 Lawton. I'm Vice President of Regulatory Affairs for
12 Genzyme Corporation, and I would like to outline for
13 you this morning the format of Genzyme's presentation.

14 First of all, I'll provide an introduction
15 to Thyrogen, and then Dr. Mazzaferri, who is Chairman
16 of Internal Medicine at Ohio State University Health
17 Center and is a recognized expert in the management of
18 thyroid cancer patients, will present to you the
19 current management of these patients.

20 Dr. David Meeker, who is Vice President of
21 Medical Affairs for Genzyme Corporation, will then
22 present the clinical trial results in support of the

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1 safety and efficacy for Thyrogen.

2 Dr. Mazzaferri will then return to the
3 podium to discuss the potential uses of Thyrogen in
4 different clinical settings. Finally, Dr. Rich
5 Moscicki, who is the Chief Medical Officer for
6 Genzyme, will summarize some of the key points for
7 consideration today.

8 Before I give you an overview of Thyrogen,
9 I'd just like to introduce to you a number of
10 participating experts that we have here with us today
11 and who are available to answer questions from the
12 panel. All of these people have been involved in at
13 least one clinical study with Thyrogen, and are all
14 experts in their own right.

15 I would just like to point out certain
16 people on this list. Dr. Harry Maxon was one of the
17 three independent reviewers involved in the two
18 pivotal studies in reviewing the whole body scans.

19 Dr. Carole Spencer operates the central
20 laboratory where all the testing of assay samples was
21 conducted for thyroglobulin and TSH.

22 Dr. Bruce Weintraub has been instrumental

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1 in cloning the beta subunit for thyroid stimulating
2 hormone.

3 Moving on now to my overview of Thyrogen,
4 Thyrogen is recombinant human thyroid stimulating
5 hormone. Thyroid stimulating hormones stimulate the
6 uptake of iodine and the synthesis of triiodothyronine
7 and thyroxine, which we will refer to as T3 and T4
8 from here in.

9 It also causes the release of
10 thyroglobulin. Both of these pharmacological actions
11 are utilized in the diagnostic testing of thyroid
12 cancer by looking at the uptake of radioiodine and
13 measuring serum thyroglobulin levels.

14 The patient population for which Thyrogen
15 has been studied and for which it's proposed is in
16 patients with well differentiated thyroid cancer who
17 have undergone thyroidectomy, and this is an orphan
18 population, and we estimate there's about 20,000 whole
19 body scans conducted per year in the United States in
20 these patients.

21 The alternatives to Thyrogen for elevating
22 TSH levels is to withdraw or decrease patients' T3/T4

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1 hormone therapy for approximately two to six weeks.
2 Other products that have been available in the past
3 are bovine TSH and human pituitary TSH.

4 These products are no longer available due
5 to the potential risks of infection with prions such
6 as Cruetzfeldt-Jakob disease and, in addition, due to
7 issues with the bovine TSH with antibody formation in
8 patients.

9 So the clinical rationale for Thyrogen is
10 that it was developed as an exogenous source of
11 thyroid stimulating hormone which allows patients to
12 undergo diagnostic testing while avoiding signs and
13 symptoms of hypothyroidism.

14 Thyrogen is manufactured by recombinant
15 DNA technology using mammalian cell culture of a
16 transfected Chinese hamster ovary cell line and a
17 five-step purification process. The finished product
18 is a lyophilized powder which is reconstituted with
19 water for injection and is administered by
20 intramuscular injection.

21 The proposed dose, which Dr. David Meeker
22 will discuss further in his presentation, is .9mg

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1 given as a 1ml volume every 24 hours for two doses.

2 To summarize quickly the animal studies,
3 with Thyrogen administered in single doses at up to 50
4 times the proposed human dose and multiple doses at up
5 to ten times the proposed human dose, no toxic effects
6 were seen.

7 Thyrogen does not have mutagenic
8 potential, as demonstrated by the AMES assay, and the
9 pharmacology of Thyrogen has been demonstrated in
10 animals by showing the uptake of radioiodine,
11 stimulation of T3/T4, and thyroglobulin production.

12 This slide outlines four clinical studies
13 that have been conducted with Thyrogen during the
14 clinical development program. The first study was a
15 dose ranging study which identified the dose to be
16 used in the first Phase III clinical study that was
17 conducted.

18 At the end of the first Phase III study,
19 a pharmacokinetic bioequivalence study was conducted
20 to look at the distribution and clearance of Thyrogen
21 and to compare two different formulations of Thyrogen
22 which consisted of two different concentrations.

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1 A second Phase III study was initiated in
2 1995. In total, in this orphan population 420
3 patients have been treated with Thyrogen.

4 I would just like to take a moment to talk
5 about the proposed indication for Thyrogen. During
6 the initial review process with the NDA, the FDA had
7 proposed that Thyrogen should be recommended for a
8 limited patient population. That limited patient
9 population was part of the latest document sent to the
10 panel members from the FDA and is actually the point
11 under question number 2 for discussion today.

12 Genzyme believes that this is a very
13 important patient population for Thyrogen. However,
14 we believe that the clinical data supports a much
15 broader use for Thyrogen and, as I'm sure you've all
16 read our briefing document, our proposed indication is
17 in there, but I'd just like to read that out to you
18 now.

19 Thyrogen is indicated as an alternative to
20 thyroid hormone withdrawal for radioiodine imaging in
21 combination with thyroglobulin testing conducted for
22 detection of thyroid remnants in well differentiated

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1 thyroid cancer in post-thyroidectomy patients.

2 It is a management option for patients
3 maintained on thyroid hormone in order to avoid the
4 morbidity associated with hypothyroidism. Finally, it
5 is also indicated for the enhancement of the
6 sensitivity of a serum thyroglobulin test when
7 patients are maintained on their hormone suppression
8 therapy.

9 Now I'd like to introduce Dr. Mazzaferri.

10 DR. MAZZAFERRI: Thank you, Allison.

11 Dr. Marcus, members of the panel, ladies
12 and gentlemen, good morning. I'm delighted to be here
13 this morning to talk to you from the viewpoint of a
14 clinician who manages patients with this disease.

15 What I'd like to do this morning is to
16 briefly summarize what we think the natural history of
17 this disease is, and mention something about the
18 therapy of the disease.

19 It's clear that this is a disease of low
20 incidence, and I'll show you some data on this, low
21 mortality. It's curable in many patients, probably
22 upwards to 80-90 percent of patients, and it's

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1 characteristic of the disease to have prolonged
2 survival with active disease. Because of the low
3 mortality, there's a relatively high prevalence of the
4 disease.

5 This slide is taken from the American
6 Cancer Society, and it just simply estimates new cases
7 of thyroid cancer in comparison with other cancers
8 that we anticipate will occur in 1998.

9 Here's thyroid cancer on the list. It's
10 sixteenth. It accounts for 17,200 cases, and it's a
11 disease that is about twice or three times as frequent
12 in women as men. These low numbers explain why there
13 have been no prospective randomized clinical studies
14 to look at the treatment of thyroid cancer.

15 This is taken from the SEER database.
16 This is a national database that looks at mortality
17 rates of thyroid cancer, and this is age at the time
18 of diagnosis, and this is rates per 100,000, and this
19 is the incidence of thyroid cancer of all types in
20 females.

21 You can see, it peaks at about the 30-40
22 year range, whereas in men the disease is slower in

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1 its rise and peaks somewhat after age 60. Mortality
2 rates typically with this disease are not seen before
3 about age 40 at the time of diagnosis, and then rise
4 progressively thereafter.

5 What I want to use is our database. I
6 mentioned before, there really are no prospective
7 randomized studies of the treatment of this disease,
8 and so we've all had to rely on retrospective data.

9 This is a database that we put together
10 almost 30 years ago. It contains 1355 patients, and
11 we've been progressively following these patients ever
12 since. There's a couple of points on this slide.

13 This is age at the time of diagnosis by
14 decade, and this is the number of patients in our
15 cohort. This is the group with follicular carcinoma,
16 and this is the group with papillary carcinoma.

17 The main point I want to make from this
18 slide is the broad spectrum of ages that one sees with
19 these diseases, and to point out that this is a
20 disease of middle aged persons primarily. The median
21 age of our papillary carcinoma patients is age 32, and
22 the follicular carcinoma patients 36 in this series.

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1 I believe this is a very important slide.
2 This is from our data, and this is years after initial
3 therapy, and this is cumulative percent here. This
4 green line is the mortality rate from thyroid cancer
5 that we've observed over the years, and it's eight
6 percent out here at 30 years.

7 The important feature of this slide, I
8 think, even more so than the death rates, is this high
9 recurrence rate that one sees. About 20 percent of
10 all the recurrences occurred in the first decade of
11 follow-up, but the other third -- there are about 30
12 percent recurrence rates at 30 years in this group.
13 The other third occurred after the first decade of
14 follow-up.

15 This says this is a very indolent disease.
16 It's a disease with a slow growth pattern that one has
17 to follow for many years on a regular basis, as you're
18 dealing with patients with this problem.

19 The other point that I would make is that,
20 when you begin talking about endpoints of this cancer,
21 doctors talk about mortality rates. Patients talk
22 about recurrence rates. So from a patient standpoint,

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1 when there's a recurrence of this disease, it's an
2 absolutely devastating problem.

3 This is a piece of data -- It's the only
4 piece of data that I'm aware of that is quite like
5 this. At the time that we put this database together,
6 we recorded when the patient first had a palpable
7 tumor in the neck and when the patient was
8 subsequently operated on.

9 This was back in an era 20-30 years ago
10 when it was common practice to treat patients with
11 thyroid hormone suppression. So we had the
12 opportunity retrospectively to see what a long delay
13 in therapy would mean.

14 Now these are people with large palpable
15 tumors, and you can see -- this is on a log scale here
16 -- that up until about eight months there is no change
17 in cancer death rates, but after about a year one
18 starts seeing substantially increased mortality rates
19 from thyroid cancer with this long delay in therapy.

20 Let me just say a few words about therapy.
21 Current therapy, by and large, around the country is
22 total or near total thyroidectomy for patients with

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1 papillary or follicular carcinoma. It's in the last
2 ten or 15 years we feel so strongly about this that a
3 number of centers have employed completion
4 thyroidectomy. That is, patients who have less than
5 total thyroidectomy who have the other side of their
6 thyroid taken out. The subsequent therapy is lymph
7 node surgery in those patients who require it.

8 This just shows you that there is some
9 impact -- this is cancer recurrence, again years after
10 surgery, and the percent recurrence. These are
11 patients who have undergone near total or total
12 thyroidectomy, and the recurrence rates are
13 significantly lower than they are in patients who have
14 had less than total thyroidectomy.

15 The other main component of therapy is
16 radioactive iodine, and we use this basically for two
17 indications. We use it for the ablation of thyroid
18 remnant and for the treatment of residual disease.

19 In addition, we use L-thyroxine
20 suppression therapy. Ordinarily, we keep the TSH
21 relatively low in these patients, particularly those
22 with active disease. External radiation is a third

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1 rather distant choice in therapy.

2 This slide shows our data again, and it
3 shows cancer recurrence in four groups: Those who had
4 no post-operative medical therapy whatsoever, those
5 who received thyroid hormone alone, those who received
6 I¹³¹ therapy for known residual disease, and those who
7 received I¹³¹ ablation when there was no apparent
8 residual disease, although our belief is that these
9 patients harbor occult disease.

10 It's important to point out that this is
11 a retrospective study, and the study groups are not
12 exactly symmetrical. It turns out that this group
13 that was treated with thyroid hormone actually had a
14 lower stage disease, as you might guess, than the
15 patients treated with radioiodine.

16 Nonetheless, the patients treated with
17 radioiodine had significantly lower recurrence rates
18 as a result of this treatment.

19 Let me talk just a second about some of
20 our current diagnostic methodologies. The limitations
21 of whole body scan -- the main limitation that you've
22 heard this morning is the arduous preparation that

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1 lasts four to six weeks in preparing the patients, and
2 another two or three weeks to get the patient back to
3 normal life following -- and you heard this much more
4 eloquently this morning than I can express it.

5 The hypothyroidism is devastating. My
6 experience is exactly what you heard this morning.
7 Patients are very unhappy. They're very sick when
8 they come in for their scans. It's very poor patient
9 acceptance.

10 The other problem with diagnostic scanning
11 is something called the stunning effect where, when we
12 use a small dose of radioiodine to study the thyroid
13 gland and then we subsequently go to treat the patient
14 with a larger dose of radioiodine, the initial dose
15 seems to have altered in some patients, sometimes
16 significantly, the uptake of iodine. So that the
17 treatment dose is less effective.

18 Thyroglobulin: This is currently one of
19 the best tests we have, but it's not without
20 limitations. It's highly dependent on the methodology
21 of the laboratory performing it. Antithyroglobulin
22 antibodies continue to be a major problem for us.

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1 Upwards of ten to 15 percent have this problem, and it
2 significantly interferes with our ability to study our
3 patients.

4 We all recognize that TSH stimulated
5 thyroglobulin is much more sensitive in the diagnosis
6 of residual disease or recurrent disease than is
7 thyroglobulin measured when the patient is taking
8 thyroid hormone. There is also no consensus regarding
9 cutoffs of thyroglobulin.

10 Together, however, current practice is to
11 use combination whole body scan and thyroglobulin in
12 an attempt to find out who has residual disease,
13 recurrent disease. We think this is the best approach
14 currently for this problem. It's the most sensitive
15 and specific, but there are a couple of problems with
16 it.

17 It requires that the patient has total
18 thyroidectomy to make these tests function properly,
19 and the patient currently has to become hypothyroid
20 with a TSH at least over 25 or 30.

21 That's a relatively inflexible regimen,
22 because it only gives us two places. We can either

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1 study the patient on thyroid hormone, which means we
2 miss a few patients with recurrent or residual
3 disease, or off thyroid hormone, when the patients
4 have to go through this arduous preparation.

5 What I want to do on the next three slides
6 is to show you how we currently manage disease and the
7 way I think about this. The disease really is -- the
8 management is in three phases.

9 The first phase is what happens
10 immediately after surgery. The second phase is during
11 a time that the physician is trying to determine how
12 effective the therapy was, and the third phase is
13 during a time when you believe the patient is free of
14 disease and you're following a patient long term.

15 This is the first treatment phase when the
16 patient has undergone total or near total
17 thyroidectomy, and this is thyroid hormone suppression
18 therapy withdrawal.

19 Generally, the high risk patients -- and
20 this is where most of the patients who have
21 significant disease flow -- have a whole body scan and
22 thyroglobulin measured, and they have I¹³¹ ablation.

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1 Then they're placed back on thyroid hormone for
2 subsequent follow-up.

3 In lower risk patients, and in my practice
4 this is a relatively small number of patients, the
5 lower risk patients, one can forego all these tests or
6 the ablation and simply look more carefully at the
7 whole body scan and thyroglobulin and, if both are
8 negative, one option is to simply place the patient on
9 thyroid hormone.

10 If the whole body scan is negative and
11 thyroglobulin positive or vice versa or if they are
12 both positive, then the clinician makes more
13 assessment, may run further tests, may just opt to
14 ablate the patient.

15 This is now that middle phase during
16 follow-up. Now we're looking at the patient we've
17 initially treated and trying to see how effective our
18 treatment was. Same thing happens. We withdraw
19 thyroid hormone.

20 If both the whole body scan and the
21 thyroglobulin are negative, and in our clinic this
22 means the thyroglobulin less than .5 -- if they're

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1 both negative, then the patient goes back on thyroid
2 hormone suppression therapy for follow-up.

3 The other route that the patient can take
4 is similar to the last slide that I showed you. If
5 any of these are positive or both are positive, then
6 further study with CT scans, MRIs and whatever is
7 necessary to find out where you are with the patient.

8 On the next slide, this is the late phase
9 in follow-up. This is the patient who you're
10 reasonably confident is free of disease, and you're
11 beginning that long term surveillance with the
12 patient.

13 This is when the patient is on thyroid
14 hormone suppression therapy, and currently what we do
15 is we use thyroglobulin, and we measure TSH to make
16 sure the TSH is suppressed, and we simply follow the
17 patient, recognizing that we're missing some
18 recurrences because this is not the optimal way to
19 look at thyroglobulin.

20 If the thyroglobulin rises under these
21 circumstances, then this is usually -- detectable
22 thyroglobulin in our clinic is what I mean by rising -

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1 - then this is a matter for immediate withdrawal and
2 further assessment.

3 If it remains suppressed, we're moderately
4 confident that the patient is free of disease, but
5 that's highly dependent on the pretest probability of
6 disease.

7 The last slide I want to show you, and I
8 just want to reiterate this issue of hypothyroidism.
9 The patient population that I just showed you is a
10 typically young, middle aged patient population.
11 They're in the middle of their lives. They're busy.
12 They're doing all sorts of things.

13 They may be seriously ill with thyroid
14 cancer, and we add to this burden by making them
15 hypothyroid. It's often aggravated by whatever -- if
16 the patient has comorbid illnesses, renal failure,
17 pulmonary disease, what have you.

18 It's clear. You've heard this morning
19 that thyroid hormone is terribly debilitating to the
20 patient. They have problems driving. They have
21 problems working in all sorts of jobs, professionals,
22 white collar workers. Industrial jobs become suddenly

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1 dangerous. Students can't perform their tasks at
2 school. Mothers really can't take care of their
3 children when they're sick, and it makes any kind of
4 technical or manual labor job difficult.

5 At this point I would like to introduce
6 Dr. David Meeker, who will talk about Thyrogen
7 clinical data. David.

8 DR. MEEKER: Thank you, Dr. Mazzaferri.
9 Dr. Marcus, members of the panel, you've all received
10 the FDA and Genzyme briefing documents, and they are
11 different. They analyze the same data, but they
12 clearly reach different conclusions.

13 In the next 35 minutes, what I'd like to
14 do is try to reconcile some of those differences and
15 present the argument for the clinical utility of
16 Thyrogen.

17 Let's start with what the issues are.
18 First, Thyrogen whole body scan results were not
19 numerically equivalent to the withdrawal whole body
20 scan results.

21 Secondly, the Thyrogen thyroglobulin
22 values were not identical to withdrawal thyroglobulin

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1 values; and when detectable, Thyrogen thyroglobulin
2 values tended to be lower than the corresponding
3 withdrawal thyroglobulin values.

4 I think an important question is: Does
5 Thyrogen have to be identical to have clinical
6 utility? If the answer to that question is no, how
7 good does it have to be?

8 The FDA position is that, since the
9 results are not identical, approval of Thyrogen may be
10 justified in a limited population, specifically
11 patients unable to elevate their endogenous TSH or in
12 whom withdrawal is medically contraindicated.

13 We would certainly agree with this
14 position, and add perhaps the patient who absolutely
15 refuses to undergo withdrawal, and argue that testing
16 is better than no testing at all. However, we would
17 also suggest that the results support the use of
18 Thyrogen in a broader patient population where the
19 benefits of avoiding hypothyroidism outweigh the risk
20 of utilizing a potentially less sensitive test.

21 Let me briefly overview the presentation.
22 I'm going to start out by briefly reviewing the Phase

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1 I/II trial which formed the basis for dose selection.
2 We'll look at the issue of hyperthyroid symptoms. I
3 think you've heard eloquently described this morning
4 that issue, but it's something that we often
5 understate, and Thyrogen was developed to address an
6 unmet medical need, specifically that patients undergo
7 -- need to undergo hypothyroidism or experience it to
8 undergo testing.

9 Next we'll look at the efficacy of
10 Thyrogen with regard to primary endpoints of whole
11 body scans in both the first Phase III trial, with
12 particular attention to the issue of discordant scan
13 in those patients with known metastatic cancer.

14 There was some confounding scan issues
15 which are improved upon and incorporated into the
16 design of the second Phase III trial, and we'll look
17 at those results.

18 Finally, we'll finish examining the issue
19 of thyroglobulin testing used both in combination and
20 alone, and lastly we'll look at the safety. Thyrogen
21 has been administered to 419 patients, and the data
22 shows that it's eminently safe.

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1 As Allison Lawton outlined for you, the
2 clinical trial program consisted of four trials,
3 including two Phase III trials, totaling the 419
4 patients. I would also like to emphasize that 134
5 patients have received Thyrogen under a compassionate
6 use program through March of 1998.

7 In addition, there was 12 normal
8 individuals who were treated under an investigator
9 IND.

10 We're proud of the fact that this program
11 has been developed in consultation with a group of
12 international thyroidologists. This is a list of the
13 investigators from our second Phase III trial, and I'm
14 sure you'll recognize some of the names. Many of
15 those people are here today with us and, as has been
16 indicated, available to answer your questions.

17 So who do we treat? The patient profile
18 of the patients in our clinical development program
19 mirrors that of the general population with thyroid
20 cancer. The male/female ratio was one to two. The
21 mean age was approximately in the mid-forties, and the
22 predominant histological cell type was papillary.

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1 In our first Phase I/II study we enrolled
2 19 patients who were post-thyroidectomy but pre-
3 ablation. This was a dose ranging study where we
4 looked at doses ranging from 0.9 milligrams to 3.6
5 milligrams, and the lower doses included also multiple
6 dosing regimens.

7 I¹³¹ uptake was seen in the thyroid bed in
8 all 19 patients, and the 0.9 milligram dose was
9 selected for further evaluation, because it was both
10 safe and effective. I'd like to point out the reason.
11 The lower starting dose was selected based on
12 information from the bovine TSH literature where the
13 0.9 milligram dose is approximately equal to the 10
14 unit dose which is the -- or was the recommended daily
15 dose for the bovine preparation.

16 Recognizing that uptake into thyroid
17 cancer may require more prolonged elevation of TSH, we
18 took the 0.9 milligrams but administered once every 24
19 hours times two into our first Phase III trial.

20 So let's look at the pharmacokinetics of
21 a single IM administration of 0.9 milligrams. As you
22 can see, the TSH levels peak at over 100 and remain

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1 above this targeted level of 25 million units per
2 liter for approximately two days.

3 This was done in the context of a
4 bioequivalence study where we compared the 3.6
5 milligrams per ml. formulation which was used in our
6 first Phase III trial with a different concentration,
7 0.9 milligrams per ml. formulation, which was studied
8 in our second Phase III trial and is, in fact, the
9 preparation that we propose for commercialization.

10 If you use that pharmacokinetic data to
11 model what the pharmacokinetics of a two-dose regimen
12 would be, you can see in purple that the TSH level
13 peaks well in excess of 100 and remains elevated for
14 approximately four days.

15 Now in consultation with the FDA and to
16 further explore the possibility that a more sustained
17 elevation in TSH might result in improved activity, we
18 incorporated a three-dose regimen where Thyrogen was
19 administered once every 72 hours for three doses.

20 It was felt that this three-dose regimen
21 really represented the outer limits of practicality in
22 terms of patient tolerance in that it required

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1 administration -- an IM administration in the trial,
2 for example, on Tuesday, Friday, Monday and then
3 subsequent scanning thereafter.

4 The yellow boxes that you see -- Although
5 the lines represent modeling, the yellow boxes were
6 actual TSH levels drawn during the trial, and suggest
7 that the model predicted very well what the expected
8 TSH levels might be at that time.

9 So let's move now to the efficacy
10 endpoints. As I indicated, the primary endpoint for
11 both trials was whole body scanning and a hypothyroid
12 assessment. The secondary endpoints, in addition to
13 the quality of life assessment in the first trial,
14 included the -- formally included thyroglobulin
15 testing in the second trial.

16 I'll briefly describe the study design.
17 The two-dose regimen for both the first and second
18 Phase III trial was similar. All patients entered the
19 trial on their thyroid hormone suppression therapy.
20 They received Thyrogen on day one and two, followed 24
21 hours later by their I¹³¹ dose.

22 In the first trial, patients could be

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1 administered a dose between 2 and 4 millicuries. They
2 were subsequently scanned during the hypothyroid phase
3 with an identical dose of I¹³¹, but we did not fix that
4 dose.

5 In the second Phase III trial, to better
6 standardize the procedure all patients were scanned
7 with 4 millicuries in both the Thyrogen and
8 hypothyroid phase.

9 The second point I'd like to make is that
10 the Thyrogen phase always preceded the hypothyroid
11 phase, simply because it was felt to be unethical to
12 potentially withdraw the patient a second time, in the
13 event that they required therapy.

14 The three-dose regimen differed from the
15 two-dose only in the timing of administration of
16 Thyrogen on days one, four and seven. gain 24 hours
17 after the last Thyrogen dose, they received their I¹³¹.
18 They were scanned 48 hours after that. They were then
19 withdrawn.

20 Fourteen days after their final Thyrogen
21 administration, they were withdrawn from their thyroid
22 hormone, and the TSH was allowed to rise to

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1 approximately 25 milliunits, at which time they had
2 their hypothyroid phase scanning performed.

3 So let s look at the results of the
4 hypothyroid and quality of life assessments. I think
5 we take them for granted. It's expected, if a patient
6 remains on their thyroid hormone, they will avoid
7 hypothyroidism, but I think this trial has been
8 instructive in telling us the extent to which patients
9 may develop symptoms of hypothyroidism and the impact
10 it may have on their quality of life.

11 The hypothyroid signs and symptoms were
12 assessed using a Billewicz scale, which is a validated
13 physician rated scale looking at 14 signs and symptoms
14 of hypothyroidism. The bar graph reflects the
15 percentage of patients newly developing this sign or
16 symptom during the course of that treatment phase.

17 As you can see in red, during the
18 hypothyroid phase there was a statistically
19 significant increase in the number of patients
20 developing all signs or symptoms. During the Thyrogen
21 phase there was essentially no change from baseline.

22 The development of these hypothyroid

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1 symptoms, in fact, translates into a worsening quality
2 of life, as you might expect. This was assessed in
3 the second trial using the SF-36, which is a validated
4 general health survey, broken into two parts, looking
5 at both physical functioning and mental health.

6 The physical functioning part included a
7 physical functioning score, raw physical or
8 essentially activities of daily living, bodily pain
9 and general health. As you can see, there was a
10 statistically significant worsening in their quality
11 of life in those measures.

12 If you look at the mental health score,
13 the most prominent change was in their emotional
14 status, again quite a dramatic change from baseline,
15 while during the Thyrogen phase the patient's quality
16 of life was preserved.

17 So let's move now to the results of the
18 whole body scans. I'd like to start by addressing an
19 issue which was raised in the FDA briefing document.
20 specifically, that was the question of bias in the
21 interpretation of these scans. So to help address
22 that and better understand that issue, I'm going to

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1 very specifically explain the procedure for reviewing
2 the scans.

3 All scans were reviewed by three
4 independent reviewers, Dr. Harry Maxon, Dr. Ralph
5 Cavaliere and Dr. David Becker. Each one of these
6 individuals is an expert in nuclear medicine
7 endocrinology, and each has in excess of 25 years of
8 experience reviewing nuclear medicine scans.

9 Dr. Harry Maxon is here in the audience
10 today and is, again, available to answer questions.

11 The procedure was as follows: The scans,
12 once they were completed at the site, were sent to
13 Genzyme. Genzyme reviewed those scans for
14 completeness. There was no preselection of scans that
15 were sent to the independent reviewers.

16 The scans were blinded, sent to the
17 reviewer in pairs. Each reviewer individually read a
18 single scan from that pair, scored and recorded it,
19 put it away, read the subsequent scan, scored and
20 recorded that and put it away.

21 Now in the first Phase III trial,
22 concordance, which was our endpoint, or

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1 disconcordance, was determined subsequently by side to
2 side comparison. So the scans were placed side by
3 side, and concordance was determined if the patients
4 had the same number and distribution of foci.
5 Conversely, discordant scans had a different number
6 and different distribution of foci.

7 In the event -- So for concordance to be
8 scored, two out of the three reviewers must agree. In
9 the event that two out of three did not agree, then
10 these scans went to panel review where all three
11 reviewers together reviewed the scans, and an attempt
12 to reach a consensus was made.

13 In the event that there was no agreement,
14 those scans were read as indeterminate.

15 Now the results of the first Phase III
16 trial are as follows -- these are in your briefing
17 document, but I think it's worth quickly reviewing
18 them: Thyrogen was as sensitive or more sensitive
19 than withdrawn in 86.2 percent, while withdrawn was
20 more sensitive -- as sensitive or more sensitive than
21 Thyrogen in 97.8 percent.

22 If you look at the number of discordant

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1 scans, 19 favored the withdrawal phase, while three
2 favored the Thyrogen phase. This difference was
3 statistically significant.

4 Now the 19 discordant scans favoring
5 withdrawal only included four patients with metastatic
6 disease.

7 So in summary, at the end of the first
8 Phase III trial we felt that Thyrogen had proven that
9 it could effectively stimulate I¹³¹ uptake into both
10 thyroid remnant and metastatic cancer, but had clearly
11 proven less sensitive than the withdrawal phase scan
12 in this study.

13 We were asked in conjunction with
14 discussions with the FDA to perform a second Phase III
15 trial, and we had learned a number of things in the
16 first Phase III trial that we could then incorporate
17 as improvements into the second trial, and I'll
18 highlight those for you now.

19 Perhaps the most important issue is this
20 standardization of scanning technique. In the first
21 Phase III trial patients were scanned based on an
22 institutionally specific protocol. In the second

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1 trial we mandated that all scans have a minimum
2 scanning time or number of counts, anatomical markers
3 be used, and that a standard imaging format be
4 followed.

5 Secondly, given the well known observation
6 that I¹³¹ clearance is increased in the new euthyroid
7 state, as compared to the hypothyroid state, we
8 mandated, as I indicated, that all patients be
9 scanned with the 4 millicurie dose of I¹³¹.

10 Now this is data from 33 patients from the
11 first Phase III trial which looks at whole body
12 retention of I¹³¹ at 48 hours. As you can see, in the
13 Thyrogen phase it was about half of that during the
14 hypothyroid phase.

15 So simplistically, the available amount of
16 iodine during the euthyroid phase is about half -- The
17 effective scanning dose is about half of what was seen
18 during the hypothyroid phase.

19 It was important to us that we use the
20 same scanning dose for both phases, despite this
21 difference, so that there would not a perceived bias
22 in favor of the Thyrogen phase, but in fact it may

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1 have actually biased the results against the Thyrogen
2 phase.

3 The third point was that we adopted a more
4 clinically relevant whole body scan rating system, and
5 I'll describe that system for you now. A Class 1 scan
6 was simply uptake in the thyroid bed.

7 In the first Phase III trial, again a
8 Class 1 scan could be broken into a 1A and 1B,
9 depending on the number of lesions in the thyroid bed;
10 and as our reviewers pointed out, it was sometimes
11 difficult to differentiate if there was two or three
12 lesions perhaps in the thyroid bed or multiple lesions
13 elsewhere, and at times the number of lesions may not
14 have been clinically relevant.

15 A Class 2 is 2A, solitary lesion in the
16 neck, since that solitary lesion might be resected
17 surgically, while 2B were multiple lesions in the
18 neck, since that might require systemic therapy.

19 A discordant reading would be a patient --
20 one scan being read as 2A, the other scan being read
21 as 2B. Class 3 is as follows, and Class 4 is as
22 follows.

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1 The final point that was incorporated into
2 the second Phase III trial was the thyroglobulin
3 values that I indicated, since between 1992 and 1995
4 when the second trial was performed, this was clearly
5 the emerging standard of practice.

6 Let me review again the differences now in
7 the review process for the second Phase III trial.
8 The initial process was the same. Scans were reviewed
9 for completeness at Genzyme, no preselection, send to
10 the reviewers where each reviewer looked first at one
11 scan in the pair, read, scored and recorded the
12 classification for that scan, put it away, read the
13 second scan in the pair in the same fashion.

14 In the event that that reading was
15 discordant, and the discordancy in this case was a
16 different extent in distribution of foci, there was no
17 further evaluation by that reviewer of those scans.

18 In the event that his reading was
19 concordancy, then in fact -- again, in discussion with
20 the FDA -- we were asked to have the reviewers put the
21 scans back up side by side to ensure that those scans
22 were, in fact, truly concordant. In other words,

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1 there was a second opportunity for the independent
2 reviewer, if you will, to make a change in their
3 reading.

4 Again, consensus required that two of the
5 three reviewers agreed. If there was no consensus, it
6 went to pane review for mutual review.

7 Now let's look at the results of the
8 second Phase III trial. They were improved. We had
9 a two-dose and three-dose regimen. Thyrogen was as
10 sensitive or more sensitive in 92 percent and 92.5
11 percent; whereas, withdrawal was as sensitive or more
12 sensitive in 97 and 95.3 percent, respectively. If
13 you look at the confidence intervals, you can see that
14 they overlap.

15 Importantly, if you looked at the two-dose
16 and three-dose regimen, there is no difference between
17 the two groups -- between the two dosing regimens.

18 Now since the issue has been raised, with
19 which we would agree, an excessively large number of
20 negative scans might drive that previous observation,
21 let's look at the cohort or the group of patients with
22 positive scans.

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1 In this case, the Thyrogen was as
2 sensitive or more sensitive in 81.3 and 86.7, as
3 compared to 93 and 91.7. If you look at those
4 patients with discordant scans, nine favored
5 withdrawal while three favored Thyrogen in the two-
6 dose. Eight favored withdrawal while five favored
7 Thyrogen in the three-dose regimen. In neither case
8 was this difference statistically significant.

9 Now since I think this issue of
10 discordancy is an extremely important issue for the
11 panel today to understand the differences between
12 Thyrogen and withdrawal, let's look at the listing of
13 nine patients who were discordant in the two-dose
14 regiment.

15 Six of the patients were discordant by
16 virtue of having a withdrawal whole body scan Class 1,
17 while the Thyrogen whole body scan was Class Zero.
18 Three of these patients were not treated. Three were
19 treated.

20 I'd just like to highlight as an
21 introduction perhaps the incremental value of
22 thyroglobulin levels where you can see, with the

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1 exception of one case, they were elevated or
2 detectable, above the level of sensitivity of our
3 assay.

4 The one case where it was not elevated,
5 the withdrawal Tg value was also not elevated, and
6 that patient was not treated.

7 The additional three patients in this
8 cohort were patients with metastatic disease, and
9 we're going to look at those patients in a little more
10 detail in a couple of slides.

11 So if you look at the group of patients
12 with confirmed metastatic disease -- and confirmed
13 metastatic disease in this case we defined as those
14 patients with a post-therapy scan greater than or
15 equal to two, the post-therapy scan being the most
16 sensitive way of looking for metastatic disease -- in
17 both arms four discordancies favor withdrawal, while
18 one favored Thyrogen.

19 So let's look at these eight patients
20 specifically. The two-dose arm patients are on top;
21 three-dose are on the bottom. I'd just like to
22 highlight a couple of points.

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1 There was one patient who, although
2 discordant, was a 4A and 4B, and clearly both the
3 Thyrogen and withdrawal phases had identified the
4 presence of metastatic disease; and three of the
5 patients, again in the metastatic group, had a
6 discordancy based on a zero and 1 class scans. In
7 other words, both withdrawal and the Thyrogen scans
8 had failed to confirm the presence of metastatic
9 disease. These were 3B, 3B and 2B.

10 I'd like to finish this slide by again
11 highlighting the incremental value of thyroglobulin
12 values where you can see that in all cases the
13 Thyrogen Tg's were elevated.

14 So in summary, with regard to whole body
15 scanning, the first Phase III trial, Thyrogen
16 effectively stimulated I¹³¹ uptake, but the results of
17 the Thyrogen scans were less sensitive than that for
18 withdrawal.

19 In the second Phase III trial the
20 following improvements, most importantly
21 standardization of imaging technique, the Thyrogen
22 scans were comparable to the withdrawal scans, and the

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1 two and three-dose regimens were not different.

2 I'd like to move on now to the issue of
3 thyroglobulin testing, looking first at it in
4 combination with whole body scanning. I'd like to
5 open with just a general comment, that we have come to
6 appreciate that, certainly, interpretation of
7 thyroglobulin values is an extremely controversial
8 area and at times emotionally charged.

9 There does seem to be a clear consensus
10 that the combination of a whole body scan and
11 thyroglobulin value is more sensitive than whole body
12 scanning alone. However, there is no clear consensus
13 on interpretation of individual values.

14 I'd like to emphasize that the following
15 analysis that we're going to perform simply compares
16 thyroglobulin values after Thyrogen withdrawal against
17 three cutoffs, prospectively defined cutoffs that
18 we'll use for this analysis of 2, 5 and 10 nanograms
19 per ml. But I'd like to emphasize that we are not
20 suggesting that a patient with a thyroglobulin value
21 greater than 2 should be treated.

22 Management decisions based on

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1 thyroglobulin values are clearly at the discretion of
2 the treating physician. We will suggest, however,
3 that an elevated Tg or detectable thyroglobulin value
4 reflects the presence of tissue of thyroid origin,
5 whether it be thyroid remnant or cancer.

6 I would also like to emphasize that one of
7 the confounding issues in the interpretation of
8 thyroglobulin values has been the availability and use
9 of multiple assays with differing levels of
10 sensitivity. In our trial all assays were run in a
11 central research laboratory run by Dr. Carole Spencer
12 at the University of Southern California. Dr. Spencer
13 is here today.

14 She used a sensitive radioimmunoassay with
15 a lower limit of detection, 0.5 nanograms per ml.,
16 which had been rigorously standardized against an
17 international standard.

18 It was also important to know that in this
19 analysis any patient with positive antibodies,
20 antibodies with thyroglobulin, were excluded from this
21 analysis, since those patients -- the use of the assay
22 is less reliable, arguably not useful, in patients who

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1 have thyroglobulin antibodies.

2 So the original analysis that we had
3 proposed was to use these prospectively defined
4 Thyrogen thyroglobulin cutoffs, two, five and ten
5 nanograms per ml. They were selected -- The lower
6 limit was selected, since it was comfortably above the
7 lower limit of detectability for our assay, which was
8 0.5 milligrams.

9 The ten nanogram was selected, because
10 that is the value that has been looked at in the
11 literature or suggested to be one where patients might
12 -- I'm sorry, physicians might choose to treat based
13 on a level greater than ten, and give was selected,
14 because it fell in the middle.

15 Now the reference standard we originally
16 proposed was one designed to identify the presence of
17 metastatic cancer, and that was defined as those
18 patients having a post-therapy scan greater than or
19 equal to two or patients having a negative scan and a
20 withdrawal Tg greater than ten and they had to be
21 treated.

22 Now the problem with that reference

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1 standard is that there were patients who, our
2 investigators felt, had clinically significant disease
3 who were being called false positive; and in
4 discussion with our investigators, they felt that a
5 much more relevant reference standard was a broader
6 reference standard designed to define the presence of
7 thyroid remnant or cancer.

8 So in the following analysis we'll look at
9 this broader reference standard in a head to head
10 comparison of Thyrogen in withdrawal phase
11 thyroglobulin values, two versus two, five versus
12 five, ten versus ten.

13 There's a lot of other analyses performed
14 that are presented in your briefing document. We're
15 not going to get into those in our presentation, but
16 I do think the head to head comparison will be a
17 useful exercise. We have presented predominantly the
18 two data, and we will also present today the five and
19 ten data.

20 Now the FDA briefing document presents the
21 similar data, and I'd just like to orient you to one
22 minor difference, which is that they have focused in

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1 their analysis on the false negative rate; whereas,
2 the data that I will present is focused on the true
3 positive rate.

4 Just to highlight again, using this
5 reference standard, which was patients with a Class 1
6 withdrawal or post-therapy scan and/or a withdrawal Tg
7 greater than or equal to the cutoff, using the cutoffs
8 of 2, 5, and 10, the false negative rates for the two-
9 dose and three-dose are listed here.

10 As you can see, for the two-dose regimen
11 there was 12 false negative patients. For the five
12 cutoff, there was also 12 false negative patients, and
13 for the ten cutoff there was 15 false negative
14 patients. We'll look at the end in a few slides
15 specifically at these patients, the false negative
16 patients, because again I think that's instructive for
17 the ensuing discussion.

18 As I present the data, there's four
19 categories that you'll see on the slide. There's a
20 subgroup of patients with metastatic cancer, and those
21 are the patients with a post-therapy scan greater than
22 or equal to 2.

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1 There is the group of patients with Class
2 1 scan, uptake limited to thyroid bed. There's a
3 group of patients who have a negative scan and a
4 thyroglobulin greater than 10, and for the cutoffs of
5 2 and 5 there are the group of patients who have a
6 negative scan, the thyroglobulin value is greater than
7 2 or 5 but less than 10.

8 So let's start with the highest cutoff
9 first, 10 nanograms per ml, ten nanograms of Thyrogen,
10 ten for the withdrawal. A Thyrogen/thyroglobulin
11 value greater than or equal to 10, and/or a Thyrogen
12 whole body scan greater than or equal to one,
13 identified 92 of the 108 patients or 85 percent in
14 this category, and 90 percent of those patients who
15 actually received therapy.

16 If you look at the group with metastatic
17 uptake, it was 28 of 32 that were identified. Now we
18 would argue that a lower detection -- or lower
19 threshold value was, in fact, more appropriate, and
20 let's look now at the 5 and the 2 cutoffs.

21 For 5, the combination again of Thyrogen
22 thyroglobulin greater than or equal to five and/or a

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1 Thyrogen with whole body scan of greater than or equal
2 to 1 identified 89 percent and 96 percent of those
3 patients receiving therapy, and all 32 patients with
4 metastatic disease.

5 Dropping down to the 2 nanogram per ml.
6 threshold, that combination identified 90 percent of
7 all patients, and 72 of 74 or 97 percent were actually
8 treated, and again, all 32 patients with confirmed
9 metastatic disease.

10 Now let's look at the 12 false negative
11 patients. The top two patients were treated, and I'll
12 look at those patients in detail in the next slide.
13 I'd like to focus your attention on the bottom ten
14 false negative patients.

15 None of these patients were treated, and
16 their thyroglobulin values are listed, Thyrogen here,
17 withdrawal here.

18 Now let's look at the two patients where
19 the disease was felt to be significant enough to
20 actually require therapy. The first patient had a
21 Thyrogen whole body scan of zero, a withdrawal whole
22 body scan of zero.

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1 The Thyrogen Tg value was .5. The
2 withdrawal Tg -- The patient was treated based on a
3 site specific thyroglobulin value of 11.8, but the
4 assay that was performed in our central laboratory was
5 actually 5. That patient was treated with 194
6 millicuries of I¹³¹, and the post-therapy scan was
7 class zero, no uptake.

8 The second patient was treated based on a
9 withdrawal phase scan of one, but the Thyrogen Tg
10 value and the withdrawal Tg values were both
11 nondetectable. That patient was treated, but there
12 was no follow-up whole body scan.

13 So in summary, with regard to combination
14 testing the detection rate using a Thyrogen whole body
15 scan greater than or equal to one and/or cutoffs of 2,
16 5, or 10, ranged from 85-90 percent. In fact, if you
17 used the lower levels of 2 and 5, that detection rate,
18 as I indicated, was 89-90 percent of patients.

19 We've looked at the false negative
20 patients who were missed, again for the 2 cutoff.
21 Importantly, it detected all patients, 32 of 32, with
22 confirmed metastatic disease.

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1 Now how might we manage the fact that
2 we're not identical? What we would propose is that
3 with appropriate labeling, in fact, the physician can
4 be guided in the accurate and, as I indicated,
5 appropriate use of Thyrogen.

6 Things that we would consider including in
7 the labeling are: (1) a detailed description of the
8 imaging procedures, since clearly the refinements that
9 we had made in the second Phase III trial resulted in
10 a significant improvement in the scan performance, not
11 only in the Thyrogen side but for the withdrawal whole
12 body scans as well, and we could look at that data
13 later, if you wish.

14 The Thyrogen whole body scans were less
15 sensitive than withdrawal whole body scans, and that
16 acknowledgment could be included, an acknowledgement
17 that withdrawal Tg values, when detectable, tended to
18 be higher than Thyrogen Tg values; and finally, it's
19 extremely important, we feel, to emphasize that a
20 combination of whole body scanning and thyroglobulin
21 testing should be utilized to optimize diagnostic
22 sensitivity.

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1 Now I'd like to finish the efficacy
2 portion looking at the issue of thyroglobulin testing
3 alone. As you know, many physicians are increasingly
4 utilizing thyroglobulin testing alone, despite the
5 fact that it's a less sensitive test, but they're
6 doing so in order to avoid the morbidity that's
7 associated with hypothyroidism.

8 For this analysis we used the same
9 reference standard, specifically patients with a
10 withdrawal whole body scan greater than or equal to
11 one and/or a withdrawal thyroglobulin value greater
12 than or equal to two. We asked the question, in how
13 many patients was the baseline thyroglobulin on
14 thyroid hormone greater than two, and then in how many
15 was the Thyrogen stimulated thyroglobulin greater than
16 two?

17 So the baseline thyroglobulin on thyroid
18 hormone detected 42 percent of the 120 patients who
19 fell in that category. The Thyrogen stimulated
20 increased that detection rate up to 73 percent, and if
21 you look at those patients with metastatic cancer, in
22 fact, the thyroglobulin on thyroid hormone missed

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1 seven patients with confirmed metastatic disease who
2 would have been picked up using a Thyrogen stimulated
3 thyroglobulin.

4 So in summary, Thyrogen improves the
5 sensitivity of thyroglobulin testing as compared to
6 thyroglobulin testing on thyroid hormone alone, with
7 the increase for the 2 cutoff of 42 to 73 percent; but
8 in fact, if you look at cutoffs of 5 and 10, there's
9 a similar, albeit not quite as high, incremental value
10 of using Thyrogen testing. Again, we could look at
11 that data later, if you wish.

12 So let's finish with safety. As I
13 indicated, 419 patients treated. With regard to
14 serious adverse events, there was a total of six, all
15 in the Phase III trials. Two occurred during the
16 Thyrogen phase, both judged as unrelated, and four
17 during the withdrawal phase.

18 There was one death, who was included int
19 that group. That patient died of a pulmonary embolus
20 approximately eight days after receiving Thyrogen.
21 The patient was extremely sick and had been in the
22 hospital for several weeks prior to treatment with

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1 Thyrogen.

2 Thyrogen is recombinant protein, and the
3 issue of antibodies is important. There was no
4 patient who developed antibodies, zero out of 419, and
5 this included 27 patients who had multiple exposures
6 by virtue of having participated in more than one
7 clinical trial.

8 If yo look at the most common adverse
9 events, defined as those occurring in greater than
10 five percent of the population, the most common were
11 nausea, occurring in 11.5 percent, and the breakout
12 between the two-dose and three-dose was 13 and 4.5
13 percent, a difference that was statistically
14 significant, and we believe that the slightly more
15 common occurrence of nausea in the two-dose arm may
16 have related to the greater rise of TSH and/or the
17 peak level.

18 It's important to emphasize that the
19 nausea was transient in all cases and mild to
20 moderate. Headache was the second most common,
21 occurring in approximately seven percent of patients.

22 Drilling down further, looking at the

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1 number of patients with adverse events occurring in
2 greater than one percent of the population as listed
3 by body system, the only one I'll highlight here is
4 this issue of pain.

5 We did have two patients during our Phase
6 III trials who developed pain at the site of known
7 metastatic disease, and this is something we've also
8 seen in a total of six of the 134 patients who have
9 been treated in our compassionate use program.

10 We believe this may reflect transient
11 swelling of the tumor in response to TSH stimulation
12 which accounts for the pain. Again, in those patients
13 that pain was transient.

14 So in conclusion, I submit to you that
15 Thyrogen is safe, that we have shown that it
16 effectively eliminates the hypothyroidism and
17 preserves quality of life during diagnostic testing,
18 that the combination of a Thyrogen whole body scan and
19 Tg test identified the presence of thyroid remnant or
20 cancer, specifically with a detection rate of 89-90
21 percent using cutoffs of 2 or 5 nanograms per ml.
22 They detected all 32 of 32 patients with metastatic

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1 disease and 71 or 74 using the 5, or 72 of 74 using
2 the 2, patients who actually received treatment with
3 radioiodine.

4 Finally, the Thyrogen thyroglobulin value
5 proved significantly more sensitive than thyroglobulin
6 testing on thyroid hormone alone.

7 Thank you. I'll now ask Dr. Mazzaferri to
8 come back to the podium.

9 CHAIRMAN MARCUS: Thank you very much, Dr.
10 Meeker. Let me just ask if there's any members of the
11 committee who need a point of clarification. This
12 would be a good time to ask it. Hearing none --

13 DR. MAZZAFERRI: Thank you, David.

14 Listening to this discussion this morning,
15 a former vice chairman of my department of medicine
16 used to say something all the time to students, and he
17 said, when the din quiets down and you walk in the
18 room and close the door, in the final analysis it's
19 between the doctor and the patients.

20 Let me tell you how I think physicians
21 should and will use this drug. On the first slide I
22 want to make a couple of general statements that I

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1 think are important, and I'm sure we've already made
2 the point that follow-up is prolonged.

3 This is an indolent tumor, and the follow-
4 up may be two or three decades of living with a
5 patient with this disease. It's difficult -- you've
6 already heard this this morning -- and currently we
7 have relatively few options.

8 We just have an on switch and an off
9 switch to study these patients, and Thyrogen offers us
10 a degree of flexibility we simply haven't had. Now
11 I'll show you how this flexibility is going to be
12 important.

13 These are some things that I think
14 everyone would agree with in the thyroid community,
15 and that is that detectable thyroglobulin after
16 ablation means that there's some thyroid tissue left.
17 We frequently don't know if it's normal thyroid tissue
18 or malignant thyroid tissue, and this occurs even
19 following so called total thyroid ablation, a
20 procedure that we use regularly.

21 Conversely, undetectable thyroglobulin
22 under TSH stimulation, most would agree, means no

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1 thyroid tissue. So this is the black and white. The
2 problem is there's a gray area in here, and this gray
3 area is the patient in whom we can detect some
4 thyroglobulin, we can't find tissue. We can't find
5 tumor. We may not even be able to find much of a
6 thyroid remnant.

7 The way we deal with that is with
8 sequential testing. We look for trends. We try to
9 see what's happening with the patient over a period of
10 time.

11 The other thing that's important to
12 emphasize is that thyroglobulin levels don't always
13 reflect the true tissue burden of disease. It's true
14 that, with large tumor metastatic disease, you tend to
15 have the highest thyroglobulins, but you can't equate
16 the amount of thyroglobulin in the blood stream
17 directly to the amount of tumor.

18 Well, let's go back and look at the
19 benefits of thyroid hormone withdrawal. It's clear
20 that there's a higher likelihood of detecting residual
21 -- identifying residual tissue with whole body scan
22 alone with withdrawal.

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1 It's also clear that thyroid hormone
2 stimulated whole body scans and thyroglobulin detects
3 nearly all the patients with important disease.
4 There's one very important caveat in here, though.

5 In the last decade we've recognized that
6 there are patients who have high serum thyroglobulins
7 who have negative withdrawal scans, who in fact have
8 pulmonary metastases that we can't even see with
9 diagnostic scans, but it's only after we treat the
10 patient with large therapeutic doses of radioiodine
11 that we then can visualize the pulmonary metastases.

12 So this is -- and that group in our series
13 represents about five percent of our patients, and
14 it's about 20 percent of patients whose thyroglobulin
15 levels get up fairly high, in the 10-15-20 nanogram
16 range.

17 It's also clear that we have higher serum
18 thyroglobulin levels with withdrawal than we do with
19 Thyrogen, and one advantage is that we can promptly
20 follow -- after studying the patient, we can promptly
21 follow with a therapeutic dose of radioiodine.

22 What about the risks of withdrawal? Well,

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1 it's clear that we're unable to test certain patients.
2 The hypopituitarism patient, patients with certain
3 complicating illnesses, renal failure, what have you.

4 One of the more worrisome things to all of
5 us who treat these patients is with this prolonged --
6 six or seven or eight-week is what it boils down to --
7 stimulation withdrawal that we see tumor growth, and
8 when the tumor is in sensitive places like the CNS or
9 spinal cord or in the airway, this can be a major
10 problem.

11 We haven't mentioned this this morning,
12 but during the period that we use T3s cytomel in
13 preparing the patient for withdrawal, there are a
14 substantial number of symptoms, and patients no
15 infrequently develop symptoms of thyrotoxicosis.

16 I had a patient not so long ago develop
17 atrial fibrillation during this period, and the
18 quality of life, even though we're trying to help
19 patients, is no better. This prolonged TSH elevation,
20 I've already said, promotes tumor growth, and just to
21 reiterate, that continues for two or three weeks after
22 we put the patient back on thyroid hormone.

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1 You've heard plenty about this, and I must
2 admit that I prepared this slide before I read the
3 letters this morning, and I had no notion what was
4 going to be said by the patients that were here this
5 morning; but this is a real phenomenon. Patients
6 forego testing due to the discomfort, particularly
7 when you have to do this sequentially.

8 I can tell you, I have no patients who
9 will tolerate this more than once a year. Sometimes
10 you would like to test a patient more carefully more
11 than once a year.

12 Well, what about the risks of Thyrogen
13 testing? Well, there clearly is the possibility of
14 potential delay in the diagnosis if we use this only
15 with whole body scanning. The other problem is that,
16 if we find disease that we have to treat, currently we
17 would have to withdraw the patient's thyroid hormone
18 to properly treat them.

19 You've already heard, there may be some
20 relatively minor but, nonetheless, real side effects
21 from the drug. There are some benefits, though, that
22 we believe.

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1 You just heard Dr. Meeker tell you that it
2 detects virtually all the tumor that's clinically
3 important that requires treatment, at least in this
4 study that we've done, and that it can be used in
5 patients with special problems that we've just
6 mentioned. It avoids prolonged TSH.

7 You saw the curves. It's a relatively
8 short period of TSH stimulation for tumor growth, and
9 it avoids symptomatic hypothyroidism. This translates
10 into some interesting things.

11 Patients studied sequentially at more
12 frequent intervals might be able to undergo -- might
13 forego whole body scanning, depending on what the risk
14 of the patient is and what have you. Patients are
15 much less likely -- I, like most of the Thyrogen
16 investigators, have a number of patients who are
17 waiting for approval of this drug. They simply don't
18 want to undergo withdrawal.

19 They're much less likely to pass on
20 further testing, and we can use it at more frequent
21 intervals, if necessary.

22 Let me show you how I fit this into the

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1 algorithm now. This is now Phase I. The patient has
2 been operated on, and it's now turned over to the
3 internist to manage, and we put the patient on thyroid
4 hormone suppression therapy, often cytomel, for the
5 first few weeks, if it's a patient who we believe is
6 at high risk.

7 If I make the decision up front, based on
8 the tumor and the extent of disease at the initial
9 operation, that it's almost a certainty that I'll want
10 to treat that patient with radioiodine, then I would
11 withdraw that patient and go through the algorithm
12 just as you saw it, do a whole body scan, measure
13 thyroglobulin, do I¹³¹ ablation, and put the patient
14 back on thyroid hormone.

15 There may be patients, although I don't
16 think there will be many, in this part of the
17 algorithm who are lower risk, who could be tested with
18 Thyrogen. If both the Thyrogen and the whole body
19 scan were negative -- and by negative I mean
20 undetectable thyroglobulins and less than 1/2 percent
21 uptake on scan -- you might be able to forego ablation
22 and get right into the follow-up treatment.

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1 If one or the other of these tests were
2 positive or they were both positive, then you have to
3 go back into the clinical assessment withdrawal and
4 study the patient with total body scanning, perhaps
5 use other tests like ultrasound, MRI and CT scan.

6 In the second phase of the disease, the
7 patient who has been treated who you are curious --
8 more than curious, but that you need to know where you
9 are with the effects of your treatment, Thyrogen might
10 play a bigger role.

11 If the Thyrogen stimulated thyroglobulin
12 was undetectable and the whole body scan showed uptake
13 only in the thyroid bed, there's a high degree of
14 probability that that's a patient that does not have
15 any significant disease, and could be placed right on
16 thyroid hormone or maintain their thyroid hormone
17 withdrawal.

18 Now if there is any suspicion -- and there
19 are times that you just intuitively see patients who
20 you know are probably going to have a problem, and it
21 doesn't matter what the numbers look like. Then you
22 have to go through and do withdrawal scanning, perhaps

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1 ablate the patient again, and other testing.

2 Again, if any of these are positive, back
3 to this route with withdrawal scanning and more
4 arduous testing.

5 Now this group represents about 80 percent
6 of the patients -- when the dust settled, this is
7 about 80 percent of the patients who seem to be free
8 of disease and are cruising in a long term follow-up
9 mode.

10 Concurrently, as I told you before, what
11 we do with these patients is we simply follow
12 thyroglobulin while the patient is on thyroid hormone.
13 Thyrogen will allow us the opportunity to check the
14 patient periodically.

15 If the thyroglobulin is negative,
16 undetectable, they could stand suppression. If it
17 becomes positive, a nanogram or so of thyroglobulin,
18 it's time to do withdrawal scan and check the patient,
19 as we currently do now, if the thyroglobulin just
20 rises spontaneously.

21 Let me show you three cases. These are
22 three patients that I saw Tuesday of this week, and it

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1 gives you a feel for how you can manage patients with
2 this disease.

3 The first is a 23-year-old woman who is an
4 OSU undergraduate student. She had a relatively small
5 tumor. It had no invasion of the thyroid capsule. It
6 was not metastatic. She underwent near-total
7 thyroidectomy three years ago. Post-operatively, her
8 body scan showed just a small amount of uptake in her
9 thyroid bed. Thyroglobulin rose to 11 when her TSH
10 was 144, and we treated her with 30 millicuries of
11 radioiodine.

12 One year later, her post-therapy ablation
13 scan showed still a little bit of uptake in the
14 thyroid bed and still some measurable thyroglobulin,
15 although certainly not at a worrisome level, when her
16 TSH was 88.

17 Since then her thyroglobulin levels have
18 been undetectable, and I'd like to study her again,
19 but she doesn't want to be studied again. She misses
20 classes. Summer vacations are too valuable, and she's
21 been nickel and diming me now for 24 months, which is
22 the typical scenario.

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1 Next case: this is a 35-year-old man with
2 polycystic kidney disease. This is a man that both
3 Dr. Maxon and I both cared for in the last year, and
4 it's a man who will die from his polycystic kidney
5 disease if we can't get him a transplant in the next
6 few years.

7 Well, in addition to that problem, he's
8 got a thyroid cancer with pulmonary metastases, and
9 these are metastases that only can be seen on a close
10 treatment scan. We can't see them with X-ray. We
11 can't see them with CT scan. We can't see them with
12 a diagnostic scan. They're only apparent on a post-
13 treatment scan.

14 He's had declining renal function in the
15 last couple of years, to the point that the
16 nephrologists now tell us we can't make him
17 hypothyroid, because they're worried that he will have
18 irreversible renal problems.

19 So in October, with the help of Dr. Maxon,
20 we calculated some doses, and we treated him using
21 Thyrogen stimulation alone without making him
22 hypothyroid, and his thyroglobulin rose 144. His

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1 post-therapy scan showed diffuse uptake of I¹³¹. So he
2 still has tumor in his lungs, but this 144 was a bit
3 lower than it had been before.

4 When I saw him Tuesday, his thyroglobulin
5 level was 1.5. Now we would both like to know how
6 he's doing. I think he's still probably got some
7 tumor, and we're talking to the transplant people, but
8 I can't withdraw this man six months after I just did
9 this. This is a patient who some clinical decisions
10 are hanging on, knowing where we are.

11 The third patient is -- This tell you
12 about the vagaries of this disease. This is a 54-
13 year-old sports writer from Dayton, Ohio, who had an
14 isolated brain metastasis, a 1 centimeter brain
15 metastasis from a papillary thyroid carcinoma from
16 which he had a seizure back in 1995.

17 This was surgically excised. We
18 vigorously treated him, 200 millicuries of I¹³¹, and he
19 showed no disease, much to our tremendous surprise,
20 and had a relatively low thyroglobulin. In fact, I've
21 never seen this before.

22 His diagnostic scan in 1996 was negative,

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1 and his thyroglobulin was low. We did another
2 diagnostic scan in 1997. Again, it was clean. Well,
3 it's 1998, and we both would like to know, but the
4 question is how many years in a row do we keep doing
5 withdrawal scanning on this man, when there's no
6 evidence of disease on the last two scans.

7 I would submit that this is a man who
8 eventually we could be following with thyroglobulin
9 scanning.

10 What I'm really trying to say is, I think
11 that Thyrogen is a new and important tool. It gives
12 us -- It gives me much greater flexibility in the
13 management of my patients in this indolent disease
14 that I have to take care of over decades.

15 Dr. Moscicki will now give you the
16 summary. Thank you.

17 CHAIRMAN MARCUS: Are there any questions
18 that need to be asked before we proceed?

19 DR. MOSCICKI: Dr. Marcus, members of the
20 panel, I hope you'll indulge my voice and me for a few
21 moments as I summarize for you some important points
22 that we feel we would like you to consider during your

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1 contemplation of the issues and questions put forward
2 to you today and that are in front of you regarding
3 the adequacy of the study design, the acceptability of
4 the diagnostic sensitivity, the predictability of the
5 thyroglobulin assay values, and the appropriate uses
6 of Thyrogen.

7 Next slide, please.

8 I would like to point out to you that in
9 the Thyrogen development program it includes the
10 largest single prospective, randomized, controlled,
11 multi-national study in the history of thyroid cancer,
12 and that this population that was studied reflects the
13 limits of an orphan disease, including the number of
14 those patients who have metastatic thyroid cancer.

15 To point this out, I would suggest to you
16 to consider that it took 14 centers, all of which are
17 quite busy centers, in four different countries at
18 least a year to enroll the number of patients that
19 were able to be presented to you today.

20 The design of the program was put together
21 with the very close and constant input of thyroid
22 experts from around the world, and the second Phase

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1 III was prospectively discussed in detail with the FDA
2 before its conduct.

3 At the end of the day, we believe that the
4 design of these studies demonstrated a clinical
5 utility for Thyrogen. It clearly stimulated
6 radioiodine uptake, and the second Phase III program
7 provided good evidence, we believe, for a comparative
8 performance of the assay in relationship to
9 withdrawal.

10 In fact, given the relative variability
11 that can occur with the rise of TSH levels related to
12 withdrawal, I might speculate for a moment. What
13 would a study look like if there were a serial
14 comparison between withdrawal in the same patient and
15 withdrawal again in that same patient? Would it, in
16 fact, provide identity in terms of the results? I
17 perhaps expect not.

18 As you contemplate the diagnostic
19 sensitivity in regards to Thyrogen versus withdrawal,
20 we would say that, in fact, it's clear that Thyrogen
21 stimulated whole body scans are probably less
22 sensitive than the withdrawal scans. They are

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1 comparative, but not identical, and that's probably
2 evident in the first trial and even in the second
3 trial where there was no statistical difference
4 between the values obtained with Thyrogen and that
5 with withdrawal, there was a trend that would support
6 that. But I would point to you, as Dr. Mazzaferri has
7 said, that the current standard of care is the
8 combination of whole body scan and thyroglobulin
9 testing.

10 I believe Dr. Meeker has carefully pointed
11 out to you that the differences observed are, in fact,
12 minimized by this combined use of Thyrogen whole body
13 scan and thyroglobulin. In fact, the Thyrogen
14 proposed label is a combination of whole body scan and
15 thyroglobulin testing.

16 Now we as physicians are, in fact, I
17 think, very used to the concept that when we choose
18 diagnostic modalities, we think of a tradeoff. We
19 think of a tradeoff between the benefits that are
20 provided by a certain test, such as convenience,
21 issues related to cost or issues related to
22 radioactivity that might be exposed to the patient,

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1 versus the issue of its sensitivity.

2 For example, we may often choose a chest
3 X-ray over a chest CT scan in a patient, despite the
4 fact that the chest CT scan is a more sensitive
5 procedure.

6 Thyroidologists have already made such a
7 choice. They are already using a less sensitive
8 method in a subset of their patients on a regular
9 basis; that is, the use of a thyroglobulin assay while
10 on thyroid hormone alone, in order to avoid
11 hypothyroidism.

12 So we believe that these issues of
13 sensitivity can be well addressed with an adequate
14 labeling and physician advisement regarding an
15 appropriate use of the product.

16 Next, please. Now as you contemplate and
17 discuss the predictability of thyroglobulin assay
18 values, we would agree that there is no direct one to
19 one correlation between the Thyrogen stimulated
20 thyroglobulin value nor, for that matter,
21 thyroglobulin values obtained on thyroid hormone alone
22 when compared directly with withdrawal thyroglobulin.

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1 No matter how you analyze it, no matter
2 how you slice the manner in which cutoff is used, it
3 always turns out that the Thyrogen stimulated
4 thyroglobulin value in these studies is more sensitive
5 than the thyroglobulin value obtained on thyroid
6 hormone alone.

7 We believe that it is the prediction of
8 disease that is important to consider, the identity of
9 patients who are at risk for the presence of that
10 disease being at least as important as any such direct
11 correlation between Thyrogen stimulated thyroglobulin
12 values and withdrawal values.

13 Next, please. So the stimulation of
14 radioiodine uptake, we believe, would support at the
15 very minimum a treatment of patients in which Thyrogen
16 is used as an alternative to withdrawal for follow-up
17 management of patients who are unwilling or unable to
18 undergo thyroid hormone withdrawal where the benefits
19 outweigh the risk of lower sensitivity.

20 We include in this group those patients
21 who currently refuse, having experienced before
22 hypothyroidism, to undergo that once more, because

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1 they, too, have little other recourse when it comes to
2 an option of using radioiodine imaging in the
3 management of their thyroid cancer.

4 I believe Dr. Mazzaferri has pointed out
5 to you his practice. He would use it to stimulate
6 thyroglobulin as an alternative to thyroglobulin
7 testing on thyroid hormone alone for the follow-up
8 management of low risk patients where the sensitivity
9 is significantly enhanced.

10 Finally, you will be asked this afternoon
11 to look at it for general use. Is it general use that
12 we need to be speaking about or, in fact, we would
13 propose what we're really talking about is its proper
14 use in a broader group of patients within the context
15 of appropriate precautions and back-up strategies.

16 Again, Dr. Mazzaferri, I believe,
17 presented to you rather eloquently, I thought, how one
18 could present and use Thyrogen within this broader
19 population under a separate and different number of
20 circumstances using the useful methods that most of us
21 physicians do to add additional other management
22 modalities based on prognostic factors that the

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1 physician perceives in the care of his patient.

2 Next. So I believe this afternoon what
3 this really all boils down to is perhaps two
4 fundamental issues. Is equivalency absolutely
5 necessary to consider Thyrogen outside a very limited
6 patient population? Is thyroglobulin after Thyrogen
7 useful only if it provides a direct one to one
8 correlation with withdrawal values?

9 The data and our discussions with experts
10 in Europe, in the United States suggests to us that
11 the answer to these is, in fact, no, that the
12 comparability in its performance of Thyrogen makes it
13 useful in a broader group of patients and that the
14 identity of patients who are at risk for the disease
15 makes it also useful for thyroglobulin testing.

16 Next, please. So we would suggest to you
17 that, taking into consideration the indolent nature of
18 the disease, the available current management, the
19 proposed labeling for advising and managing the known
20 limitations of Thyrogen and, perhaps most importantly,
21 from what you've heard this morning and for the reason
22 that Thyrogen was developed, the debilitating effects

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1 of hypothyroidism, that Thyrogen is a very reasonable
2 alternative in the management of a broad group of
3 thyroid cancer patients.

4 Next, please. In this, we believe we're
5 not alone. I hope that you, the panel, have had the
6 opportunity to review the letters that have been sent
7 to you by the American Thyroid Association, the
8 Endocrine Society, the American Association of
9 Clinical Endocrinologists, the Thyroid Foundation of
10 America, and the Thyroid Society.

11 Next. So in the end, we believe that the
12 labeling that has been provided to you is a very good
13 way to propose the use of Thyrogen for patients with
14 thyroid cancer.

15 Now we ask your help in this matter, and
16 we invite questions of us and of all the experts
17 gathered with us today. Thank you.

18 CHAIRMAN MARCUS: Thank you. I wish to
19 congratulate Genzyme on a very concise and interesting
20 presentation. May we turn the lights on, please, and
21 see if there are any questions from the panel. This
22 is the time for general questions. Certainly, Dr.

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1 Burman.

2 DR. BURMAN: Thank you again. That was a
3 very nice, succinct presentation. I just want a few
4 points of clarification to make sure I understand some
5 of the issues.

6 One issue is with regard to TSH
7 antibodies. The TSH antibodies were not detected in
8 any patient as you presented, but how long were they
9 followed, and what techniques were used?

10 My understanding is they didn't use -- you
11 didn't use repetitive studies over several years to
12 show that antibodies didn't develop later on, which,
13 of course, would be a confounding factor in the
14 follow-up of patients with thyroid cancer.

15 DR. MOSCICKI: I believe I can answer that
16 for you. The patients were tested only once, and that
17 was at one month afterwards when we thought that there
18 would be an appropriate time period for antibodies to
19 have been tested. However, 27 of the patients were
20 tested after repeat administration, because they had
21 been used in previous clinical studies.

22 So because of the nature of this, we have

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1 not been able to study it in patients over many
2 repeated exposures, and that certainly will be done in
3 the future.

4 Does that answer your question?

5 DR. BURMAN: Yes. Thank you.

6 CHAIRMAN MARCUS: Did you have some
7 others? Might as well go on.

8 DR. BURMAN: If you don't mind.

9 CHAIRMAN MARCUS: Sure.

10 DR. BURMAN: A couple. My understanding
11 also is that the studies --

12 DR. MOSCICKI: I'm sorry. You asked about
13 the method. It was an ELISA method.

14 DR. BURMAN: Thank you.

15 CHAIRMAN MARCUS: Bruce, want to identify
16 yourself, and use the microphone.

17 DR. WEINTRAUB: Bruce Weintraub,
18 University of Maryland.

19 Just to point out that the methodology
20 used for the manufacture of this product is similar to
21 the manufacture of many other recombinant
22 glycoproteins made in Chinese hamster ovary cells.

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1 For example, erythropoietin and other drugs where
2 there's been a large experience with this same type of
3 glycosylation.

4 So although the studies haven't been
5 performed here, we have a long experience with many
6 other drugs where that has not proven to be a problem.
7 So the studies need to be done, but we do have this
8 little background from the biotech industry.

9 DR. BURMAN: Thank you. My understanding
10 also is that the really nicely designed studies that
11 you performed of the two larger scale studies always
12 had the I¹³¹ scanned first, done on recombinant TSH,
13 and then they were taken off and scanned while they
14 were hypothyroid, and that it was a several week time
15 period between those two studies.

16 How do you know with any degree of
17 certainty that there isn't an effect of stunning from
18 the first scan, affecting the second scan such that
19 you might be underestimating the amount of lesions
20 that might be present on the second scan?

21 DR. MAXON: I am Harry Maxon. I'm a
22 nuclear medicine physician at University of

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1 Cincinnati. As the sole nuke, Ken, I guess I get to
2 answer that one.

3 In the first Phase III study, the
4 administered activity was 2 to 4 millicuries. In both
5 studies the Thyrogen was done first. Now the
6 kinetics, and I don't believe they showed you very
7 much of today, that were largely done by the group at
8 NIH showed that in the euthyroid patient renal
9 clearance of radioiodine is not altered, as it is in
10 the hypothyroid patient.

11 Therefore, the bioavailability of
12 radioiodine is much less in the Thyrogen treated
13 patient. When we looked at this -- and if I -- I
14 thought they might bring some of the data that was
15 done at NIH with them. In any event, when we looked
16 at this with Jim Reynolds, in essence, if you gave 4
17 millicuries with Thyrogen, for example, it would be
18 roughly equivalent in bioavailability to 2 millicuries
19 with I¹³¹.

20 Now stunning can occur. It has been
21 documented after 2 millicuries of I¹³¹ in the
22 hypothyroid patient. We have quantified that. So has

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1 David Becker at New York Hospital. So has a group in
2 India.

3 Fundamentally, at 2 millicuries you have
4 about a 20 percent decrease in subsequent uptake of a
5 therapeutic administration. That is due to a
6 subclinical radiation thyroiditis in the remnant.
7 That is not enough to inhibit the subsequent
8 diagnostic value of a withdrawal scan where you have
9 roughly twice the bioavailability, especially when you
10 are giving the same administered activity, which is
11 what was rigidly set in the second protocol.

12 So I don't -- The other thing, of course,
13 is that when you get stunning, one of the very good
14 correlates of that is thyroglobulin, because with the
15 induction of the radiation thyroiditis you get
16 dramatically increased thyroglobulin values. Okay?
17 And that occurs very shortly.

18 To my knowledge, their thyroglobulin data
19 did not show a rapid increase in the second study
20 following the administration of Thyrogen, which one
21 would have expected if you had seen that radiation
22 thyroiditis stunning sequel.

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1 Does that answer your question? Yes, sir?

2 DR. MOLITCH: My understanding was
3 stunning was not something that was 100 percent in its
4 occurrence. So that with your 2 millicurie dose, you
5 say you had a 20 percent reduction in subsequent I¹³¹
6 uptake. In what percentage of patients would that 20
7 percent occur?

8 DR. MAXON: That occurs, in our experience
9 -- okay? -- in about half the patients. I think
10 Uvanram in India found it up to three-quarters of the
11 patients.

12 CHAIRMAN MARCUS: Roger.

13 DR. ILLINGWORTH: Roger Illingworth.
14 Although you haven't detected any thyroid -- any
15 antibodies, will you propose that these be tested
16 patients who are getting this scan on a yearly basis?

17 DR. MAXON: Excuse me. You're talking
18 about TSH antibodies?

19 DR. ILLINGWORTH: Yes.

20 DR. MAXON: I think I'm going to let one
21 of the non-nuclear medicine colleagues answer that.

22 DR. MEEKER: Yes. We would continue to

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1 monitor antibody formation long term, and we have an
2 existing recombinant protein that's on the market.

3 DR. ILLINGWORTH: And there are good
4 assays available for this?

5 DR. MEEKER: Yes.

6 DR. DAVIDSON: Jaime Davidson. You know,
7 in one of your adverse events, the 77-year-old lady
8 that was hospitalized with hypertension, you know,
9 could somebody go a little more in detail on that
10 case? You know, the final diagnosis was a background
11 thyroiditis, you know. How much thyroid tissue in
12 that lady had, you know, to cause symptoms?

13 DR. KINGNA: Please continue, and I'll
14 just pull out the slide so that I can show you the
15 case of the patient. I believe it was the clinical
16 trial patient 516.

17 CHAIRMAN MARCUS: Would you identify
18 yourself, please?

19 DR. KINGNA: Yes. I know I have a
20 difficult name. Dr. Kingna. I didn't mention that in
21 the beginning. I apologize.

22 CHAIRMAN MARCUS: Thank you. Dr. Kingna

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1 is Genzyme's Director of Pharmaco Vigilance. I think
2 our transcriber may want to see how that's spelled.

3 DR. MOSCICKI: Perhaps while they're
4 searching for the appropriate slide, it might be okay
5 to go on with another question, if you have one.

6 CHAIRMAN MARCUS: I'd like to ask a
7 question about just who is it that's taking care of
8 these approximately 20,000 people per year? My
9 understanding, and my prediction, will be that this is
10 largely a practice of medicine that is restricted
11 maybe 90 percent to endocrinologists with a special
12 interest in the thyroid. Is that correct or are there
13 a fair number of primary care internists who are also
14 taking care of patients like this?

15 The reason I'm asking this is that,
16 obviously, the proper use of a test like this requires
17 a fair amount of sensitivity to many subtleties, and
18 I just wanted to satisfy myself that, in fact, the
19 population of physicians who are taking care of these
20 patients are attuned to those.

21 DR. RIDGEWAY: Dr. Marcus, you're correct.
22 In this country, and I think the same holds for

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1 Europe, thyroid cancer and its management is mainly a
2 disease managed by endocrinologists. Primary care
3 physicians and internists would not do this kind of
4 therapy, and in my experience oncologists don't do
5 this therapy either, because of the special nature of
6 the preparation, the radioactive iodine, all of which
7 are part of training programs in endocrinology.

8 In fact, there would be a medical legal
9 issue if somebody without training in this kind of a
10 disease and going through the boards of endocrinology
11 were to try to treat these patients. So I think the
12 vast majority of patients with thyroid cancer are
13 treated by endocrinologists, and usually people that
14 have a special interest in thyroid disease.

15 CHAIRMAN MARCUS: Thank you. Glenn, did
16 you have a question? Okay, Dr. Kingna.

17 DR. MEEKER: This patient's history is up
18 on the board. As you can see, she's a 76-year-old
19 lady who had a prior history of Grave's disease, in
20 addition to her thyroid cancer, treated in mid-June
21 and hospitalized for approximately five days.

22 About June 20th after being discharged,

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1 apparently -- again, there was an issue of heat at
2 that time of year as well -- she had a syncol episode
3 and was admitted to the hospital with a complaint of
4 tenderness in her thyroid bed or in the area of her
5 thyroid bed at the site of a prior biopsy which had
6 been done in 1992.

7 Thyroid function tests were performed, and
8 it was felt that she did not, in fact, have
9 thyroiditis, and the syncol episode was felt to be due
10 to dehydration. That's the available information I
11 have now. I don't know if that answers the question
12 you asked.

13 CHAIRMAN MARCUS: Dr. Davidson.

14 DR. DAVIDSON: If that was the final
15 diagnosis, I'm satisfied.

16 CHAIRMAN MARCUS: Good. Are there other
17 pressing questions? Dr. Braunstein?

18 DR. BRAUNSTEIN: Braunstein. I have two
19 questions. First of all, were the patients made
20 iodide depleted before they got their scan with the
21 Thyrogen?

22 DR. MEEKER: Yes. There was a ten-day

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1 iodine restricted diet.

2 DR. BRAUNSTEIN: And they were maintained
3 on that then through the withdrawal phase also?

4 DR. MEEKER: In preparation, right, both
5 phases.

6 DR. BRAUNSTEIN: The second question is to
7 Dr. Mazzaferri. What would you do in the patient who
8 has positive antithyroglobulin antibodies? Would you
9 just withdraw them or would you still use Thyrogen?

10 DR. MAZZAFERRI: Yes, that's a very tough
11 question, and I might ask Dr. Spencer to back me up on
12 this, because she knows more about these assays. But
13 I think, if it's a high risk patient, I would do what
14 I do today, and that's withdraw the patient and scan
15 them.

16 There are some other techniques that
17 Carole is much more versant than I am.

18 DR. SPENCER: The antithyroglobulin
19 antibodies occur in about 15 to 20 percent of the
20 patients. I think it was 15 percent in this study,
21 and it's a problem whichever thyroglobulin method you
22 use, although some are better than others.

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1 We just published the value of actually
2 following the antibody titers serially in conjunction
3 with thyroglobulin testing, and we find that
4 antibodies tend to go down when disease is
5 successfully treated and remain detectable or rise
6 when patients have recurrence.

7 That's one reason that we would suggest
8 patients that have antibodies detected at the time of
9 their initial surgery receive an ablation dose, even
10 if they are low risk, in order to remove the
11 antibodies with the hope that the antibodies will
12 resolve to undetectable when there's no more thyroid
13 tissue present.

14 There is a promising new technique that's
15 being worked out, which is measurement for
16 thyroglobulin messenger RNA, which is very new,
17 beginning to become quantitated, and we have an
18 abstract in to the thyroid meetings this year
19 suggesting that in antibody positive patients it's
20 going to give us another test to help us detect the
21 presence of disease when the thyroglobulin
22 measurements may be unreliable, but this is still very

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1 much in its infancy.

2 CHAIRMAN MARCUS: Thank you. Did you have
3 -- That was your second question. Jules?

4 DR. HIRSCH: A question of Dr. Mazzaferri.
5 Maybe I didn't understand one thing, but I thought one
6 of the three cases that you showed in one instance --
7 is it true that someone received ablative therapy on
8 the basis of Thyrogen stimulation rather than
9 withdrawal?

10 DR. MAZZAFERRI: Yes. That was a patient
11 who --

12 DR. HIRSCH: Does that happen? I mean
13 often. Is that --

14 DR. MAZZAFERRI: No. You mean use it for
15 treatment?

16 DR. HIRSCH: Correct.

17 DR. MAZZAFERRI: No. It was for
18 compassionate use, and it was a man who, because of
19 his polycystic kidney disease, was unable to withdraw
20 from thyroid hormone, because his creatinine -- We had
21 done it a few years before, and his creatinine rose
22 remarkably, and --

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1 DR. HIRSCH: I see. I guess the point I
2 would wonder about is it's really so attractive to use
3 Thyrogen rather than thyroid withdrawal for anything,
4 and I wonder if anyone would get in their mind to
5 start using this for therapy, and that perhaps the
6 advice to physicians or package insert or whatever, if
7 this is used, should indicate that this is not to be
8 used in lieu of withdrawal when therapy is anticipated
9 except in the most extraordinary circumstances.

10 Is that a wise thing to do?

11 DR. MOSCICKI: We would think that would
12 be an appropriate thing to include in the precautions,
13 as we would, I would say, regarding the issue of
14 thyroglobulin antibodies.

15 DR. HIRSCH: Right.

16 CHAIRMAN MARCUS: I would like to propose
17 that we take our 15 minute break now, and we'll come
18 back at, let's say, 10:25.

19 (Whereupon, the foregoing matter went off
20 the record at 10:06 a.m. and went back on the record
21 at 10:25 a.m.)

22 CHAIRMAN MARCUS: We have reached the

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1 point in the program where the agenda states that the
2 agency will present its analysis of the data, but I
3 would like to begin with a brief statement, and to ask
4 Dr. Sobel, representing FDA, to comment on it.

5 As a clinical endocrinologist for more
6 than 20 years, I've -- maybe it's 25 years; at least
7 as long as Bruce Weintraub -- over the years I've had
8 occasion to use the following peptide hormones: ACTH,
9 pentagastrin, secretin, 1 to 34 parathyroid hormone,
10 LRH, TRH, and even HCG. These are all agents which
11 are standard hormones, which are biologically active
12 and safe to administer.

13 Yet if I think back on the literature
14 supporting a protocol to see whether HCTH stimulation
15 could really define a suppressed adrenal axis, there
16 were many different papers that would be in the
17 literature whether you should use three days or five
18 days or different schedules of doses.

19 The use of TRH to diagnose thyroid
20 suppression or even hypothyroidism -- there were
21 papers, all sorts, defining different criteria,
22 different endpoints. It was never standardized, and

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1 approval -- Clearly, all these agents were approved by
2 FDA or we never would have had an opportunity to use
3 them.

4 There was never any standard such as we're
5 being asked to look at today of certain false
6 negatives, false positives, that sort of analysis. I
7 think that this is a precedent setting event that
8 we're participating in today.

9 So I would like to ask Dr. Sobel, who is
10 the one person perhaps who really understands the
11 history of the approval of biological agents
12 throughout the history of the agency, what has
13 happened that we're now elevating it or changing a
14 standard to a different standard, and whether it isn't
15 still appropriate just to approve the use of a
16 purified, biologically active and safe agent for a
17 variety of purposes.

18 DR. SOBEL: I quite agree that Thyrogen is
19 a biologically active agent and is biologically active
20 in the same way as endogenously secreted TSH. What is
21 the aim of today's meeting?

22 Actually, this situation is a bit

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1 different, because we have before us clearly two
2 approaches to diagnosis, and I would say that this
3 problem of which approach to use is the reason for the
4 meeting.

5 The company and we both agree that there
6 is somewhat diminished sensitivity of the Thyrogen
7 test as compared to the withdrawal test -- scan, I
8 should say. We had a great deal of discussion with
9 the company over the last several years, as was
10 evident from some of the remarks of the company in
11 regard to the design of Phase III study, the
12 increasing doses of Thyrogen which aimed perhaps to
13 raise the sensitivity so as the period of exposure to
14 the TSH would be more closely -- would more closely
15 simulate the endogenous release on withdrawal.

16 So what is different today is we have two
17 approaches to diagnosis with really a third factor
18 which was introduced, the thyroglobulin test, both on
19 suppression and on stimulation. It's very complex,
20 and we felt that doctors out there would need more
21 guidance in the selection and use of this drug, its
22 limitations and its strengths.

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1 Admittedly, as was pointed out, most of
2 the people who will use these drugs will be experts in
3 the field, but I think they, too, could benefit from
4 some of the deliberations of today and recommendations
5 that will arise.

6 CHAIRMAN MARCUS: Thank you. David, did
7 you want to add anything? Anybody on the committee
8 want to pursue this line? Dr. New?

9 DR. NEW: Dr. Sobel, I wonder how we can
10 enter into the discourse that a doctor is going to
11 have with a patient in advising from the outside and
12 not in the specific clinical situation how the
13 diagnostic test should be carried out and interpreted.
14 I find that hard.

15 This morning Dr. Mazzaferri presented at
16 least six protocols, depending in his judgment on how
17 he sees the patient. I imagine that, if we have
18 another excellent thyroidologist, as Dr. Mazzaferri
19 is, they might give a different protocol.

20 I feel that that's sort of a
21 patient/doctor relationship and an ethical problem a
22 patient has to agree with, providing they have

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1 informed consent.

2 DR. SOBEL: You are absolutely right. The
3 FDA likes to keep out of the doctor's office. The
4 doctor/patient interaction is not an area that we
5 enter, and the practice of medicine is not which we
6 wish to control.

7 We approve drugs, and we try to make their
8 use, at least at the time of approval, most clearly
9 labeled so as to help the physician, but we do rely on
10 the good judgment of the physician to use the drug.

11 So our recommendations are advisory to
12 physicians.

13 CHAIRMAN MARCUS: Okay. Dr. Orloff, do
14 you want to begin the -- Oh, I'm sorry. Dr. Temeck.

15 DR. TEMECK: Thank you, Dr. Marcus, and
16 good morning, ladies and gentlemen. I would like to
17 give a perspective here on Thyrogen and present some
18 of the database that we looked at.

19 Next slide, please. I'd like to discuss
20 Thyrogen as a diagnostic modality to replace
21 withdrawal for detection of remnants and/or cancer in
22 patients with well differentiated thyroid cancer.

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1 Can exogenously administered TSH -- that
2 is, recombinant Thyrogen -- mimic endogenous TSH
3 withdrawal regarding stimulation of iodine-131 uptake
4 on scan and stimulating thyroglobulin production?

5 Next slide, please. In this presentation
6 I will discuss the design and conduct of the two Phase
7 III clinical trials, TSH-92 and TSH-95. I will
8 discuss the scan data from these two clinical trials,
9 and I will also discuss the thyroglobulin data from
10 the second Phase III trial.

11 Next slide. The first Phase III trial was
12 a multi-center, open label trial. 152 adult patients
13 were enrolled, and they all had well differentiated
14 thyroid cancer. Approximately 20 percent were
15 recently diagnosed. So they were status post
16 thyroidectomy but pre-I¹³¹ ablation, and the remaining
17 80 percent were follow-up patients. So they were
18 status post thyroidectomy and I¹³¹ ablation therapy.

19 Next slide, please. To summarize in brief
20 what the protocol schematic was, essentially there
21 were two phases. There was the Thyrogen phase, which
22 was always followed by the withdrawal phase.

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1 On the Thyrogen phase, patients remained
2 on their suppressive doses of thyroid hormone. They
3 all received two injections of Thyrogen, 0.9
4 milligrams IM per day for two consecutive days, and 24
5 hours after the last injection a 2 to 4 millicurie I¹³¹
6 scanning dose was administered.

7 Forty-eight hours after the scanning dose,
8 a Thyrogen scan was performed. Patients then were
9 withdrawn from their thyroid hormone suppressive
10 therapy for at least two weeks to allow endogenous TSH
11 levels to rise to at least 25 micro-units per ml.

12 When this occurred, the patients received
13 a second scanning dose of I¹³¹, followed again in 48
14 hours by the withdrawal scan. So each patient had two
15 scans. They had the Thyrogen scan, and they had the
16 withdrawal scan.

17 Following the withdrawal scan, some of the
18 patients were treated with I¹³¹, and some of those
19 patients then received subsequently a post-therapy
20 scan. Because the post-therapy scan is more sensitive
21 than a diagnostic scan, it was used to confirm disease
22 when it was done -- just confirm disease seen on

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1 either the Thyrogen scan or the withdrawal scan.

2 Next slide, please. The scans were read
3 as concordant, as Dr. Meeker pointed out, if they had
4 the same number and distribution of the lesions.
5 Essentially, this is in brief what the disease staging
6 system was used, but it wasn't good enough for the
7 scans to have the same disease stage. They were rated
8 as concordant if they had the same number and
9 distribution of the lesions.

10 A stage zero scan was a negative scan.
11 Stage one, uptake within the thyroid bed; stage two,
12 uptake in the neck consistent with local metastases;
13 and stages three and four were compatible with distant
14 metastatic foci.

15 Next slide, please. Now the way the scans
16 were read in this study is that they were read by
17 three independent reviewers, and Dr. Maxon is here,
18 and the independent reviewers knew which scanned pair
19 belonged to which patient. What they didn't know is
20 which was the Thyrogen scan and which one was the
21 withdrawal scan.

22 Essentially, three readings were done in

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1 this study. The Thyrogen scan was rated. Withdrawal
2 scan was rated, and then the scans were read side by
3 side. What I'm going to be presenting here are the
4 concordances/discordances based on the side by side
5 comparison.

6 Actually, if you look at the independent
7 readings, there were 11 additional scanned pairs which
8 were read as discordant, which became concordant on a
9 side by side read. So what I'm going to show you here
10 in these next few slides are when the scanned pairs
11 were read side by side.

12 The overall concordance rate was 84
13 percent. If you notice, approximately half the scans
14 were positive scans, and these are the clinically
15 relevant scans, because if you see more disease on one
16 scan than the other, then that can potentially be of
17 clinical concern.

18 If you look only at the concordant scans,
19 those with one or greater, the concordant rate was 68
20 percent. Of the 21 discordant scan pairs, 18 showed
21 withdrawal to be the superior scan, and this was
22 statistically significant at the .001 level.

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1 Next slide, please. Now we're going to
2 focus in on the positive scans, first the scans that
3 were stage one. There were 50 scans, either Thyrogen
4 or withdrawal, which were rated as showing disease
5 uptake localized to the thyroid bed.

6 Seventeen of these were discordant.
7 Eleven were stage difference, and six were lesion
8 difference. Of those that were read as discordant for
9 stage difference, in nine of these 11 the Thyrogen
10 scan was negative, but the withdrawal scan showed
11 uptake in the thyroid bed.

12 So of 50 stage one scans, the Thyrogen
13 scan missed remnants and/or cancer localized to the
14 thyroid bed, detected by the withdrawal scan in nine
15 of 50 or 18 percent.

16 Next slide, please. If we focus now on
17 the scans that showed metastatic disease, there were
18 only 15 such scans in this study. Four of these were
19 discordant. That is, the withdrawal scan showed the
20 metastatic disease, but the Thyrogen did not, and this
21 was a miss rate of 27 percent of the patients.

22 Next slide, please. The second Phase III

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1 study was an international developed multi-center, 14
2 sites, was an open label study. Two Thyrogen dosing
3 regiments were studied. The purpose of the second
4 dose, to give a more prolonged period of TSH
5 stimulation, and I'll go over these dosing regimens.

6 117 patients received two doses of
7 Thyrogen, and this was identical to the dosing regimen
8 which was used in the first Phase III study. That is,
9 0.9mg of Thyrogen was administered every 24 hours for
10 two total doses.

11 In this schematic patients received a
12 0.9mg dose of Thyrogen every 72 hours for a total of
13 three doses. As in the first study, most of the
14 patients were follow-up patients.

15 Next slide, please. Because we had only
16 15 scans that were positive for metastatic disease in
17 the first Phase III study, a distinct effort was made
18 in this study to recruit patients who had a history of
19 metastatic disease. We wanted to see how well
20 Thyrogen performed in comparison to withdrawal to
21 detect not only localized disease but metastatic
22 disease.

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1 Approximately half the patients enrolled
2 in this study had a history of metastatic disease, and
3 approximately a quarter of them had metastatic disease
4 on the most recent scan prior to enrollment.

5 In this study every attempt was made that
6 in patients who were treated that a post-therapy scan
7 was done, which is more sensitive than a diagnostic
8 scan. As Dr. Mazzaferri pointed out, a diagnostic
9 scan can be negative for metastatic disease that is
10 only picked up by a post-therapy scan, because you're
11 administering a higher dose of I¹³¹. It's a much more
12 sensitive scan, has a much lower false negative rate
13 than does the diagnostic scan.

14 The post-therapy scan has about a five
15 percent false negative rate historically, based on
16 literature, although withdrawal diagnostic scans can
17 have a false negative rate of ten percent, 15-20
18 percent. So this is very important.

19 Lymph node histology reports were also
20 used to confirm the presence of cancer. For example,
21 if a patient had a very high withdrawal Tg value and
22 a negative withdrawal scan, and the patient was

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1 treated with a therapeutic dose of I¹³¹, and no disease
2 was seen on the post-treatment scan, the high
3 withdrawal Tg could have triggered and did trigger, in
4 fact, in some of the patients to pursue that high
5 withdrawal Tg to see if there was a metastatic focus
6 in the patient, and this prompted performance of a
7 lymph node biopsy.

8 Next slide, please. I will not belabor
9 the protocol schematic for the arm one, which is the
10 two-dose regiment, because this was very similar to
11 that used in the first Phase III study. I will point
12 out that the scanning dose used here was a higher
13 scanning dose.

14 This was on the premise that I¹³¹ is
15 cleared twice as rapidly in the euthyroid state than
16 it is in the hypothyroid state, and it was thought
17 that this might help the performance of the Thyrogen
18 scan to perform better in comparison to withdrawal.

19 I have a slide, but I can show you for
20 anyone who is interested, but actually when I looked
21 at the three scans that favored Thyrogen over
22 withdrawal in the first Phase III study, in two of

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1 those the scanning dose administered was either a 2 or
2 2.5 millicurie scanning dose, and yet that low
3 scanning dose was sufficient to allow the Thyrogen to
4 be greater than withdrawal.

5 So I'm just not sure that, you know, the
6 whole story is because that there was a lower scanning
7 dose administered in the first Phase III study, that
8 that was responsible for the poor performance of the
9 Thyrogen scan in relation to withdrawal.

10 As I said, I have slides which has that
11 data in there.

12 The other difference was that serial Tg
13 measurements were taken post-Thyrogen administration
14 in this study to determine the optimal time to measure
15 Tg on Thyrogen, and it turns out it's actually the 72-
16 hour time point.

17 Next slide, please. This is the schematic
18 for the arm two, and as I said, patients received a
19 0.9mg dose of Thyrogen every 72 hours for a total of
20 three doses, one at day one, four, seven. Then 24
21 hours after the last Thyrogen injection, they got the
22 scanning dose. Forty-eight hours later, Thyrogen scan

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1 was performed.

2 Then they were withdrawn from their
3 thyroid hormone to allow the endogenous TSH levels to
4 rise to 25. Then they got the second scanning dose,
5 followed by the withdrawal scan, and in some patients
6 who were treated, then this is where the post-therapy
7 scan would have been done or a lymph node biopsy.

8 Next slide, please. The efficacy
9 endpoints for the TSH-95 study, amongst others. The
10 ones we're going to look at is the within-patient
11 equivalence for disease class on the 48 hour Thyrogen
12 withdrawal diagnostic scans.

13 The other efficacy parameter we're going
14 to look at is the diagnostic utility of Thyrogen Tg
15 alone and combined with a Thyrogen scan to detect
16 metastatic disease as defined prospectively and post
17 hoc for the detection of remnants and/or cancer.

18 Next slide, please. This is the uptake
19 classification system which was used. As Dr. Meeker
20 pointed out, this uptake classification was developed
21 with the purpose of defining a more clinically
22 relevant difference which would detect a more

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1 clinically relevant difference between the scans,
2 rather than just using the exact number and
3 distribution of the lesions.

4 So in this study, for a Thyrogen
5 withdrawal scan to be rated as concordant, they both
6 had to show, let's say, for example, a solitary focus
7 of uptake in the neck. If one showed multiple foci of
8 uptake in the neck, then that was rated as a scan
9 which was superior to the other.

10 Next slide, please. This is the results
11 of the scan data in the second Phase III trial. The
12 overall concordance was approximately 88-89 percent.
13 Again, about half the scans in each dosing arm -- Only
14 approximately half the scans in each dosing arm were
15 positive.

16 Of the 12 discordances, nine favored
17 withdrawal as showing a higher disease class than the
18 Thyrogen scan in the two-dose regiment, and eight of
19 13 in the three-dose regiment. This discordance rate
20 was not statistically significant, but the trend
21 certainly favored the withdrawal as being the superior
22 scan.

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1 Next slide, please. We are now again
2 going to look at the scans that were positive for
3 stage one disease; that is, disease which was
4 localized to the thyroid bed.

5 Now 77 percent to 80 percent of these
6 scans were rated as concordant. Of those that were
7 rated as discordant, six of the nine in the two-dose
8 regiment and six of the nine in the three-dose regimen
9 showed that withdrawal scan revealed disease localized
10 to the thyroid bed, but the Thyrogen scan was
11 negative.

12 So in patients with class 1 disease, the
13 Thyrogen scan missed remnants, cancer detected by the
14 withdrawal scan in about 15 percent of the patients.

15 One of these three scans -- actually, that
16 favored the Thyrogen scan in the sense that the
17 Thyrogen detected disease localized to the thyroid bed
18 when the withdrawal scan was negative, was treated;
19 and the post-treatment scan was negative. Therefore,
20 this Thyrogen scan was a false positive -- one of
21 these three.

22 Next slide, please. This is the data for

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1 the scans that showed metastatic disease. There were
2 actually a total of 25 scans which were positive for
3 metastatic disease, either Thyrogen or withdrawal.

4 In the two-dose regimen, the withdrawal
5 scan showed metastatic disease, while the Thyrogen
6 scan was negative for metastatic disease. On the
7 three-dosing regiment, there was an even split.
8 However, I would like to point out that in one of
9 these two patients where the withdrawal scan was
10 negative and the Thyrogen scan showed metastatic
11 disease, both the Thyrogen and the withdrawal
12 thyroglobulin levels were less than 1 nanogram per ml.
13 So in all probability one of these two Thyrogen scans
14 was a false positive for metastatic disease.

15 Next slide, please. Let's look at the
16 comparison now side by side of the
17 concordance/discordance rates in both of these Phase
18 III trials. Patients with positive scans -- that is,
19 class 1 or higher -- there was approximately a 70-75
20 percent concordance rate. The discordance rate was
21 approximately 25-30 percent.

22 Next slide, please. In those patients who

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1 had disease localized to the thyroid bed, Thyrogen
2 missed remnants or cancer in the thyroid bed in
3 approximately 15 percent of these patients. In those
4 patients who had metastatic disease, the Thyrogen scan
5 missed it in four of 15 patients or 27 percent in the
6 first Phase III study. In the second Phase III study
7 the Thyrogen scan missed five of 25 patients that were
8 picked up by withdrawal scanning, for 20 percent.

9 I'm sorry, I didn't go over in the first
10 Phase III study. There was actually one of two scans
11 here which favored Thyrogen over withdrawal, but the
12 post -- That patient was treated, and the post-
13 treatment scan was negative. So, actually, again one
14 of these two Thyrogen scans was actually a false
15 positive.

16 There were two of eight scans which
17 favored withdrawal over -- which favored Thyrogen over
18 withdrawal. However, in one of these the post-
19 treatment scan was negative. So that was a false
20 positive Thyrogen scan, and in the other the
21 withdrawal scan, and the withdrawal and Thyrogen
22 thyroglobulin levels were less than 1 nanogram per ml.

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1 So that was probably a false positive Thyrogen scan
2 for metastatic disease.

3 So in all, of the ten scans which favored
4 Thyrogen over withdrawal, three of these were false
5 positives.

6 Next slide, please. The conclusions are
7 that withdrawal scanning is more sensitive than the
8 Thyrogen to detect thyroid remnants and/or cancer, and
9 that the Thyrogen scan may not only underdiagnose
10 remnants or cancer -- that is, be a false negative --
11 but it also may be a false positive.

12 Next slide, please. Now we're going to
13 switch from the scans to the thyroglobulin analyses.

14 The diagnostic utility of the
15 thyroglobulin was looked at in patients who were
16 successfully ablated and Tg antibody negative. A
17 successfully ablated patient was defined as one who
18 had undergone a total or near-total thyroidectomy and
19 had less than one percent uptake in the thyroid bed.
20 These patients, as I said, were also Tg antibody
21 negative.

22 Prospectively, it was computed for the

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1 purposes of defining the missed disease for
2 metastases, and the same thyroglobulin cutoffs were to
3 be used to compare Thyrogen to withdrawal.

4 Next slide, please. The reference
5 standard actually to be used to compare Thyrogen to
6 withdrawal prospectively was a metastatic post-
7 treatment scan. However, as I pointed out previously,
8 in addition, you could have a very high withdrawal Tg,
9 the patient was treated, post-treatment scan was
10 negative, but the high Tg prompted the clinician to
11 look for a metastatic focus, for example, by a lymph
12 node biopsy, and this was also regarded as
13 confirmatory of cancer in this study.

14 This added just two additional patients in
15 arm one and one additional patient in arm two, arm one
16 being the two-dosing regiment, arm two being the
17 three-dosing regimen.

18 So we had a total here of 32 scans, post-
19 treatment scans, which were positive for metastatic
20 disease in this study, an additional three patients in
21 whom the post-treatment scan was negative but the
22 lymph node biopsy was positive for cancer.

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1 Let's look at what the false negative
2 rates are on Thyrogen Tg using these various cutoffs,
3 two dosing versus the three dosing regimen.

4 Four of the 11 patients or 36 percent, the
5 Thyrogen Tg was greater than five but it was less than
6 ten. So those were four false negatives. On the
7 three-dosing regimen, four of the 24 or 17 percent of
8 the patients, the Thyrogen Tg was below the respective
9 cutoff, and here it was actually less than three in
10 this one patient.

11 Next slide, please. Let's look at what
12 the Thyrogen Tg levels were in these patients in
13 comparison to the withdrawal Tg levels. The
14 withdrawal Tg levels, as you can see, are all greater
15 than ten. They ranged from 11.8 to over 100.

16 The corresponding levels on Thyrogen were
17 as low as 2 nanograms per ml. and went up to 9.5
18 nanograms per ml. Again, I want to emphasize, this is
19 a patient who had a negative post-therapy scan.

20 In fact, there was just one patient in
21 these entire eight where either the Thyrogen or the
22 withdrawal diagnostic scan was positive for metastatic

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1 disease.

2 So again, it emphasizes that, you know, it
3 was the post-treatment scan that was detecting
4 metastatic disease in these patients, but what
5 prompted the treatment was the high withdrawal Tg
6 level. That's what prompted the post-therapy scan to
7 be done.

8 Here, despite the negative post-therapy
9 scan, this patient has such a high withdrawal Tg
10 level, the clinician looked further for a metastatic
11 focus, and he found it when he did a lymph node
12 biopsy.

13 Next slide, please. This is a plot, a
14 scatterplot, of the Thyrogen Tg levels versus the
15 withdrawal Tg levels in these eight patients. This is
16 the patient up here with withdrawal Tg, was over 100.
17 The Thyrogen Tg level was seven.

18 As you can see, there is no correlation
19 between the Thyrogen and the withdrawal Tg levels in
20 these patients.

21 Next slide, please. If we take out the
22 patient who had such a high withdrawal Tg level so

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1 that we can then expand the y axis here, which is the
2 withdrawal Tg, you can see better the wide variability
3 in the Thyrogen Tg levels as compared to withdrawal.

4 Next slide, please. To sum this up,
5 Thyrogen Tg failed to detect confirmed metastatic
6 disease by post-treatment scan or a positive lymph
7 node biopsy in eight of these 32 patients or 23
8 percent.

9 Using the Thyrogen scan in combination
10 with the Tg resulted in only one less false negative,
11 because the Thyrogen scan was positive for metastatic
12 disease in only one of these eight patients.

13 Let's see how withdrawal performed. The
14 withdrawal Tg failed to detect confirmed metastatic
15 disease in one of these 35 patients or three percent.
16 The withdrawal Tg level in this patient was 9
17 nanograms per ml. It was just below the 10 nanogram
18 per ml. cutoff. However, the withdrawal scan was
19 positive for metastatic disease in this patient, and
20 this led to 100 percent detection of confirmed
21 metastatic disease in this cohort of patients.

22 Next slide, please. Post hoc the Thyrogen

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1 diagnostic utility analysis was changed from detection
2 of metastatic disease to detection of remnants and/or
3 cancer. Since this is a post hoc analysis, it
4 requires prospective validation.

5 The new reference standard used was a
6 withdrawal positive or a post-treatment scan which was
7 positive, class 1 or higher, or withdrawal Tg greater
8 than or equal to various cutoffs. 100 percent
9 sensitivity and specificity was assigned to this
10 reference standard.

11 Next slide, please. This is an example of
12 one of the problems and how this diagnostic utility
13 analysis was designed. This is data from a patient
14 from this study.

15 Here, this patient's withdrawal Tg level
16 was 16.5 nanograms per ml. The patient's withdrawal
17 scan showed disease uptake localized to the thyroid
18 bed. So disease was defined as present by the
19 reference standard, the reference standard being the
20 withdrawal, either Tg or scan data or the post-
21 treatment scan data.

22 Let's look at the corresponding Thyrogen

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1 Tg level in this patient. This patient had a Thyrogen
2 Tg level of 2 nanograms per ml. The Thyrogen scan:
3 Again, it detected disease localized to the thyroid
4 bed. Therefore, you would say on a combination of
5 using the Thyrogen Tg and the scan, Thyrogen detected
6 disease in this patient.

7 So this patient is not a false negative
8 if you use a combination of Thyrogen Tg and scan.
9 However, look at the marked difference between the
10 Thyrogen Tg and the withdrawal Tg levels in this
11 patient.

12 The point is, it is precisely in patients
13 with low levels of disease on scan, either negative or
14 class 1 scans, that the Thyrogen Tg level is critical
15 for clinical management decisions.

16 Next slide, please. A withdrawal Tg
17 greater than ten is of clinical concern, despite a
18 negative scan. It may either prompt further
19 investigation for metastatic focus, as you've seen
20 previously, maybe by a lymph node biopsy, a CT scan,
21 an ultrasound of the neck, etcetera.

22 Some physicians would actually treat a

1 withdrawal Tg greater than ten, despite the negative
2 scan, and this was most recently addressed in an
3 article in the January issue of The New England
4 Journal of Medicine of this year.

5 Let's take a look at patients in this
6 study in whom the Thyrogen Tg -- this is when the peak
7 is attained. Okay? So we're going to use peak
8 Thyrogen Tg level, and we're going to look at it as
9 compared face to face with withdrawal Tg greater than
10 ten.

11 In approximately 25 percent of patients in
12 this study, the Thyrogen Tg was less than ten, but the
13 withdrawal Tg was greater than ten.

14 Next slide, please. This actually gives
15 you the exact Thyrogen Tg levels in these patients --
16 in these 19 patients versus the corresponding levels
17 on withdrawal.

18 As you can see here, the withdrawal Tg
19 levels ranged from 11.2 to over 100. The
20 corresponding Thyrogen Tg levels ranged from as low as
21 0.5 up to 9.6. The point I want to mention is with
22 regard to this patient here.

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1 In the NDA submission, the clinician who
2 was following this patient made a comment, and he
3 stated that, if he had known that the withdrawal Tg
4 was so elevated, he would have treated this patient.
5 He did not treat this patient, but he said he would
6 have if he had known the withdrawal Tg was 11.

7 It is very -- You know, in a total of five
8 of these 19 patients -- okay? -- the withdrawal Tg was
9 over ten, and the Thyrogen Tg was less than ten. Yet,
10 because there's no clear guidelines for management,
11 this high withdrawal Tg was not pursued. If it had
12 been pursued, it's possible that the false negative
13 rate that we had seen previously with Thyrogen might
14 even be higher.

15 Next slide, please. This is another
16 scatterplot of the Thyrogen Tg levels versus the
17 withdrawal Tg levels in these 19 patients. Again, you
18 can see the wide variability of the Thyrogen Tg to
19 withdrawal. It's actually going to be emphasized more
20 clearly if you remove this patient here, and that's on
21 the next scatterplot.

22

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1 Next, please. Again, demonstrating here
2 the variability of Thyrogen Tg versus the withdrawal
3 Tg levels.

4 Next slide, please. If you give your
5 patient Thyrogen and you get a negative or a class 1
6 scan, and you get a Thyrogen Tg level less than ten,
7 what would be the corresponding Tg level on
8 withdrawal? The reason we're asking this question is
9 because it is in patients with negative or class 1
10 scans that the Tg level helps guide the physician in
11 clinical management of the patient.

12 Next slide, please. This is the data on
13 the two-dose regimen. The first thing is to notice
14 the underlying variability between the Thyrogen Tg and
15 the withdrawal Tg. This dot -- sorry -- should belong
16 up above the 10 nanogram per ml. cutoff, because this
17 is where Tg levels above this point are particularly
18 of clinical concern. So this dot should move up
19 there.

20 The Thyrogen Tg level in this patient was
21 6.9. The corresponding level on withdrawal was 11.8.
22 I wanted to point out that in these 18 -- there were

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1 18 percent of patients again, withdrawal Tg over 10,
2 Thyrogen Tg less than ten. However, some of the
3 patients the Thyrogen Tg was less than ten, and so was
4 the corresponding withdrawal Tg level.

5 I would like to point out some of these.
6 This is a patient with a Thyrogen Tg level of 0.5, but
7 the withdrawal Tg was 5 nanograms per ml. There's
8 another patient here at 0.8 and 3.5, another patient
9 at 2.8 and a 7.6, and it goes on.

10 At other times, the Thyrogen Tg was
11 equivalent to the withdrawal Tg, and there were a very
12 few patients where a Thyrogen Tg actually was higher
13 than withdrawal. Such was the case in this patient
14 where the Thyrogen Tg was 3.6, but the corresponding
15 level on withdrawal was 1.7.

16 Next slide, please. Again not to belabor
17 the point, but we had in this three-dosing regimen 17
18 percent of the patients, again, Thyrogen Tg less than
19 ten, withdrawal Tg was greater.

20 Next slide, please. One of my slides, I
21 guess, has been removed. Could you go back, please,
22 Steve? I had an expansion -- and I apologize for this

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1 -- of this. I think it's on your handout -- of this
2 area in here, just to show the disconnect between the
3 Thyrogen and withdrawal Tg levels, but it was similar
4 to what we saw in the second dosing regimen.

5 I wanted to mention that also again there
6 were some patients -- the majority of them, the Tgs
7 were less than withdrawal. In some cases, they were
8 equivalent, and in a few patients the Thyrogen Tg
9 level was actually greater than withdrawal.

10 In fact, there was one patient here where
11 it was above ten. The Thyrogen Tg level was 16.5
12 nanograms per ml., and the corresponding level on
13 withdrawal was 2.3. This was a recently diagnosed
14 patient, and the treating physician said that he would
15 not treat the patient, because the withdrawal Tg of 2,
16 to him, represented just a small amount of remnant
17 tissue remaining.

18 Yet if you use the Thyrogen Tg level of
19 16.5 -- I mean, that would represent a significant
20 amount of disease which was present in the thyroid
21 bed.

22 Next slide. This is the problem that we

1 are having in the agency to try to reconcile, is that
2 the variance between the -- the marked variability
3 between the Thyrogen Tg and the withdrawal Tg levels,
4 and how can you interpret these values, and how this
5 will impact on clinical management of patients.

6 Next slide, please. What are the
7 pitfalls? Nonpredictability of Tg level on Thyrogen
8 compared to withdrawal. We saw that in the
9 scatterplots and also in the specific data that I
10 showed you on the tables.

11 There's nonproportionality of Thyrogen Tg
12 to the tumor burden. If we presume or assume, based
13 on historical experience, that withdrawal Tg is
14 proportional to the tumor burden present, and Thyrogen
15 Tg can be either less than, equal to or greater than
16 the corresponding level on withdrawal, then we must
17 conclude the Thyrogen Tg is not proportional to the
18 tumor burden present.

19 Then there is the problem with cancer
20 underdiagnosis, both in the fact that the scans, the
21 false negative rates on the scans, which actually
22 might even be higher -- we just don't know. We feel

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1 uncomfortable with how the scans were read.

2 As I pointed out in the first Phase III
3 study, there were 11 additional scans which were
4 discordant which all of a sudden became concordant on
5 a side by side comparison. So we're concerned about
6 that. Then, of course, there is the problem with how
7 to interpret the Thyrogen Tg level.

8 I put in overscanning in the sense that,
9 because of the problems that were seen here with
10 Thyrogen Tg, if this were to be used as a replacement
11 for withdrawal that a patient -- in fact, the sponsor
12 is recommending that a Thyrogen Tg and a Thyrogen scan
13 be done every time the Thyrogen is used as a
14 replacement for withdrawal. There is a question then
15 of possible stunning from overscanning.

16 Then this issue becomes raised, a possible
17 overtreatment, because treatment may be triggered at
18 much lower levels of Thyrogen Tg than they would have
19 been if you had used withdrawal.

20 I didn't put antibodies, possible TSH
21 antibody formation on this slide, because to date we
22 have had no patient who has become positive for TSH

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1 antibodies, but again, you know, it's a very short
2 term experience we've had with Thyrogen to date. So
3 it's very difficult to state what that would be with
4 long term use.

5 Next slide, please. Of course, the
6 benefit of Thyrogen is the avoidance of withdrawal and
7 all that that means to a patient in terms of signs and
8 symptoms of hypothyroidism, as we've heard here today.

9 Last slide, please. Why we might we
10 postulate the Thyrogen is less sensitive and does not
11 -- could be equal to, greater than or less than the
12 corresponding withdrawal Tg level?

13 Iodine 131 uptake and elevation in serum
14 thyroglobulin are related physiologically to the rise
15 in TSH and the duration of the time the TSH is
16 elevated. On Thyrogen the peak TSH were all over 100.
17 So we more than adequately met the first criteria.

18 On the other hand, the mean peak TSH on
19 withdrawal was 65. The difference here lies in the
20 duration of time that the TSH is elevated. It's days
21 with Thyrogen. It's weeks on withdrawal.

22 In conclusion, if you really want to know

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1 the clinical status of your patient, it comes down to
2 withdrawing the patient, because that is the best tool
3 that we have presently. It's not 100 percent, but
4 it's the best that we have.

5 Thank you.

6 CHAIRMAN MARCUS: Are there questions for
7 Dr. Temeck?

8 DR. SHERWIN: Do we know anything about
9 the effect of thyroid status on the turnover of Tg,
10 and that would be the main question, I guess.

11 DR. TEMECK: No, unless the company has
12 some answers to that.

13 DR. SPENCER: I think the best study is
14 the one by Dr. Uller many years ago using bovine TSH,
15 which is an acute stimulus, and was done in normal
16 individuals who were euthyroid where clearance was not
17 a factor, and the die-away following bovine TSH was
18 something like four days.

19 DR. SHERWIN: The question I have is in
20 the hypothyroid state, would the turnover be slower Tg
21 and, consequently, the levels would -- the standards
22 for the level would, obviously, be very different,

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1 depending on what the effect of the thyroid status was
2 on the turnover of Tg.

3 DR. SPENCER: I think that is a fair
4 assumption. It hasn't been studied, but the clearance
5 of drugs and many enzymes, many other factors are
6 certainly prolonged.

7 DR. SHERWIN: While I have you there, I
8 don't know enough about the variability in
9 thyroglobulin measurements in different laboratories.
10 Can you give me a sense of the typical standard
11 deviations, the kind of ranges you would expect to
12 see.

13 Obviously, different tests are done at
14 different times, and I just don't have a good enough
15 sense of -- It's not like a glucose, I assume.

16 DR. SPENCER: I have prepared some slides,
17 but for quickness I have to say that thyroglobulin
18 measurements, although they've been available for 25
19 years, have been much improved in recent years by the
20 development of the more sensitive immunometric assays
21 and the development of a new international reference
22 preparation.

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1 This has been the problem with methods,
2 this method to method difference. A two in one method
3 might be a five or even a ten in either methods, but
4 methods are now becoming more standardized.

5 We re-standardized our radioimmunoassay,
6 which we developed in the early 1980s, against the new
7 international reference preparation. We also measured
8 all the thyroglobulins from this study by a
9 commercially available method, the Nichols method,
10 which is the only method that states that it's so
11 standardized, and find very good concordance.

12 So I think the methods are becoming
13 standardized. The sensitivity -- There is across
14 methods between .5 and, say, 1.5, and on my experience
15 a 2 is certainly a level that should be reliably
16 detected in most of the better quality assays
17 available today.

18 In fact, I have a slide quoting Dr.
19 Schlembochais. Any thyroglobulin that's reliably
20 detected is indicative of thyroid tissue, and Dr.
21 Schlembochais only uses this value of ten on
22 withdrawal as an indicate of the treatment, whether or

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1 not the scan is positive.

2 So I think most physicians -- this is a
3 complex area, as you've heard -- don't treat a number.
4 They factor in all the other elements of the patient,
5 but there is relatively good, improving method-to-
6 method agreement, and I could, if the panel wanted,
7 show some data on the site Tg versus those measured
8 centrally to support that.

9 DR. TEMECK: Dr. Sherwin --

10 CHAIRMAN MARCUS: Thank you. Dr. New?

11 DR. TEMECK: Oh, I'm sorry. Dr. Sherwin,
12 could I just address, please, the question that you
13 asked.

14 All of the Tg levels that I showed you
15 were all measured in Dr. Carole Spencer's laboratory.
16 They were all measured in her centralized laboratory,
17 and they were all run in a single run. So that there
18 was no inter-assay variability whatsoever, and a very
19 sensitive Tg assay was used that were lower limits of
20 detection of 0.5 nanograms per ml, because we wanted
21 to try to avoid any variability, as you rightfully
22 pointed out, so that maybe a 2, you know, could have

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1 been, you know, a 3 if you had measured at some other
2 time.

3 That really was taken into account, and we
4 tried to prevent that type of situation.

5 CHAIRMAN MARCUS: Thank you. Dr. New?

6 DR. NEW: How stable is the measurement of
7 Tg? For instance, does it vary with the menstrual
8 cycle and the production of estrogens, and would it
9 matter whether you determined it at any point in the
10 cycle in a woman, and what is the daily variability?

11 DR. SPENCER: The intra-individual
12 variability is certainly less than ten percent in a
13 euthyroid individual. I think in an individual with
14 thyroid cancer where there might be some noncompliance
15 with thyroxine, the variability relates to that
16 compliance and is very much determined by TSH status;
17 whereas, in a euthyroid individual the thyroglobulin
18 with a four-day half-life reflects the integrated 24-
19 hour diurnal pattern in TSH, and it is fairly constant
20 across the menstrual cycle and across many months, as
21 Dr. Philip Rasmussen has studied.

22 CHAIRMAN MARCUS: Other questions? Dr.

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1 Braunstein?

2 DR. BRAUNSTEIN: If you use as a cutoff
3 point for thyroglobulin 2 nanograms per ml, or if you
4 use a cutoff point of 5 nanograms per ml, and use that
5 in association with the scan, how many patients in
6 this study with metastatic disease would have been
7 missed?

8 DR. TEMECK: Well, I pointed that out to
9 you, that it was seven out of the 32 patients -- No,
10 using a cutoff of ten --two --

11 DR. BRAUNSTEIN: No, it was ten. I'm
12 using a cutoff of 2, because you told that in this
13 assay the sensitivity being 0.5 nanograms per ml, that
14 a level of 2 was significantly different.

15 DR. TEMECK: At a level of 2 it would be
16 one of those 32 patients.

17 DR. BRAUNSTEIN: I think that was three on
18 the slide, if I'm not mistaken. That patient had a
19 level of 3 nanograms per ml.

20 CHAIRMAN MARCUS: Maybe we should go back.

21 DR. TEMECK: Let's just go back to the
22 slides, Steve, please, and we can take a look at that.

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1 I'm sorry. A few more slides back,
2 please. Here we are. You're going to see exact data
3 here. Slide 21, okay. Here we are.

4 So if you use 2, greater than or equal to
5 2, okay, then -- I'm sorry -- then none of those
6 patients would be missed on a combination of Thyrogen
7 Tg and scan, because it's only in patients where it
8 would be less than 2 that would be a false negative.

9 CHAIRMAN MARCUS: You addressed the issue
10 of -- or introduced the issue of a false positive, but
11 you didn't state -- using the same criterion for false
12 positives, that is a negative post-treatment scan.
13 How many withdrawal scans were false positive?

14 DR. TEMECK: There were none.

15 CHAIRMAN MARCUS: Zero?

16 DR. TEMECK: There were some withdrawal
17 scans that were false negatives, if you did a post-
18 treatment scan, and that is true for Thyrogen as well;
19 because the post-treatment scan is more sensitive. So
20 you would expect that, you know, you're going to have
21 false negatives, but there were none that were false
22 positives on withdrawal.

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1 DR. SHERWIN: How many false positives
2 were there?

3 DR. TEMECK: Three of the ten where the
4 Thyrogen scan was favored over the withdrawal scan
5 were false positives.

6 CHAIRMAN MARCUS: Dr. Burman.

7 DR. BURMAN: Yes. Thank you. Just, if I
8 may for a second make a sort of personal opinion and
9 comment, and partly answer what Carole was talking
10 about before.

11 As a clinician taking care of a lot of
12 thyroid cancer patients, there are a lot of subjective
13 qualitative assessments, and thyroglobulin assay in
14 this milieu is one of them.

15 So if it's done in Dr. Spencer's lab,
16 which I personally consider one of the best in the
17 country, if not the world, you get a very reliable
18 answer. In other commercial labs that you may have to
19 send samples to, they may or may not be as reliable,
20 and that's just living with the thyroglobulin
21 measurements.

22 It certainly isn't even in the same

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1 stratosphere as a glucose measurement clinically. But
2 with regard -- All thyroidologists know that you
3 should measure the sample in the same lab, and you
4 shouldn't switch labs over time. That's one comment,
5 just on the general, also applying to the general
6 nature of thyroid cancer.

7 The second is what's most important to me,
8 and I don't know if other members of the panel agree
9 or disagree, is not whether there is concordance in
10 the actual quantitative level of a thyroglobulin off
11 medication and one that's stimulated on TSH, but
12 rather I don't expect them to be the same for the
13 reasons you mentioned. But the critical issue is how
14 many -- to me, is how many scans -- how many patients
15 with real disease will be missed if you measure a
16 thyroglobulin that's stimulated with TSH in
17 conjunction with the scan.

18 If I'm understanding the data right, it
19 seems that that's a small percentage, three/four
20 percent, something like that. Is that -- Am I correct
21 in that?

22 CHAIRMAN MARCUS: I think so. Dr. Temeck.

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1 DR. TEMECK: Well, our concern here is
2 with the data that we saw when you used a post-
3 treatment scan to compare Thyrogen to withdrawal.
4 Okay? Because that's where you have the most
5 sensitive measure of whether a patient has metastatic
6 disease, scan detectable or not, because it's much
7 more sensitive than a diagnostic scan.

8 So if the post-treatment scan is positive
9 for metastatic disease, then you know that the patient
10 does have metastatic disease. Using that external
11 reference standard, doing a comparison of Thyrogen to
12 withdrawal, we noticed, as I showed you here, that the
13 Thyrogen Tg levels were as low as 2, but all the
14 withdrawal levels were over 10.

15 So there was a marked discrepancy between
16 the level of elevation you get for thyroglobulin on
17 Thyrogen versus what you're getting on withdrawal. if
18 you use that in combination with the scan, only one of
19 those eight patients was a Thyrogen scanned positive
20 for metastatic disease, and that's where, depending
21 upon the cutoff you're going to use -- if you use a
22 cutoff of 2, then none of the patients were missed.

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1 If you used a cutoff of 10, then you get a miss rate
2 of seven out of those 32.

3 So it depends upon, you know, also Tg
4 cutoff you're going to use that's going to trigger
5 treatment or, for that matter, further investigation
6 of disease.

7 CHAIRMAN MARCUS: Dr. Sherwin, did you
8 have a question? Was it you? Oh, Dr. Molitch.

9 DR. MOLITCH: Coming back, actually, to
10 the question that Dr. Burman raised: If you have a
11 patient whose Tg scan and thyroglobulin are negative,
12 but in fact that patient's withdrawal scan might have
13 been positive, say a step 1 patient or level 1 patient
14 who has just thyroid bed disease or in-the-neck
15 disease, so that you therefore missed that, and then
16 test them again the next year and find it positive at
17 that point in time and then treat the patient at that
18 point in time one year later, what is the biological
19 penalty to that patient overall from a treatment
20 perspective, as far as their long term outcome?

21 Maybe I can address that either to Dr.
22 Burman or Dr. Mazzaferri.

1 DR. BURMAN: I'd love to hear what Dr.
2 Mazzaferri says. I can give you my opinion as well,
3 but I would certainly appreciate his.

4 In the huge majority of patients, I would
5 think the biologic impact would be minimal in that
6 patient. You will find, as you're well aware, case
7 reports in the literature where microscopic disease
8 may be associated with significant recurrence later on
9 or even mortality in very rare circumstances, but in
10 the huge majority of the time, the biologic penalty
11 would not be high, although I'd love -- if it's all
12 right with Dr. Marcus, I'd love to hear --

13 CHAIRMAN MARCUS: Absolutely. Dr.
14 Mazzaferri.

15 DR. MAZZAFERRI: Well, I think it's fair
16 to extrapolate from the data that I showed you in
17 patients with palpable disease, clinically quite
18 obvious, who were in effect mismanaged for a year,
19 there was no penalty.

20 We're talking about microscopic disease or
21 very small residual tumor. My clinical impression is
22 that that's not a big penalty to the patient, and it

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1 may avoid overtreating patients who you think have
2 disease who, in fact, don't.

3 CHAIRMAN MARCUS: Dr. Davidson.

4 DR. DAVIDSON: Davidson. It is obvious
5 that, you know, you cannot compare the thyroglobulin
6 levels in the two groups, you know, and I think Dr.
7 Braunstein made a very good point, you know. The
8 cutoff may be lower in this particular group.

9 I just have one question, you know, and I
10 think you probably showed some of that data, but just
11 for my own recollection. Is any -- From the evolution
12 of the disease, you know, and the previous treatments,
13 is there anything different in the sensitivity of
14 these two tests, you know, patients that have been
15 treated, according to you, in the discordant group?

16 Do you understand my question?

17 DR. TEMECK: In other words, are you
18 asking, Dr. Davidson, was there a difference if you
19 were recently diagnosed versus whether you are a
20 follow-up patient?

21 DR. DAVIDSON: Correct.

22 DR. TEMECK: And this is with regard to

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1 the scans and the thyroglobulin?

2 DR. DAVIDSON: Right.

3 DR. TEMECK: Just with regard to the scan
4 data?

5 DR. DAVIDSON: The scan data, because the
6 other one, we know, is not going to be --

7 DR. MEEKER: Can I address that question?

8 CHAIRMAN MARCUS: Sure.

9 DR. MEEKER: We did look at that group,
10 Dr. Mazzaferri's Phase I, if you will, follow-up. In
11 the two-dose regimen we have detected 17 of 17 -- the
12 concordance was 17 of 17, and in the three-dose
13 regimen it was 18 and 19, and actually two favored the
14 Thyrogen, one favored the withdrawal.

15 So the concordance was very good in that
16 pre-ablation population.

17 DR. DAVIDSON: Thank you.

18 CHAIRMAN MARCUS: Dr. Meeker, you actually
19 were standing to raise a question.

20 DR. MEEKER: No, I was going to try to
21 help clarify the issue about the metastatic cancer
22 patients.

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1 CHAIRMAN MARCUS: Dr. Sherwin.

2 DR. SHERWIN: Just a question for
3 educational purposes, since I don't see these patients
4 often.

5 What is the downside of overtreatment in
6 terms of giving radioactive iodine inappropriately?
7 I mean, I can think of things, but if somebody could
8 just review them with me that issue.

9 DR. BURMAN: Sure. Assuming that the
10 patient isn't pregnant and it is given properly,
11 etcetera -- and I would also make a few comments and
12 appreciate any comments from any of the other
13 thyroidologists in the audience.

14 In general, taste distortion, because the
15 iodine is concentrated in the salivary glands. It
16 seems to me that it's never been studied very well in
17 prospective studies, and it's sort of idiosyncratic,
18 but in general probably the larger the dose of iodine,
19 the more likely there will be salivary gland
20 dysfunction, maybe dryness of the mouth which can be
21 a significant problem in rare circumstances, and some
22 taste distortion associated with that, as things we

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1 talk to patients all the time about and occur
2 clinically significantly very occasionally.

3 On the other hand, the longer term
4 significant side effects are more problematic. There
5 are many retrospective studies over years looking back
6 to see what happens when patients got I¹³¹ in the doses
7 we're talking about of 100, 200, maybe as much as 3-
8 400 millicuries of I¹³¹.

9 In general, what thyroidologists like to
10 say is that the doses greater than 1,000 millicuries
11 of I¹³¹, the likelihood of leukemia goes up slightly.
12 I'd love to see what Dr. Maxon says about that in a
13 minute, but that, when we look at it and try to review
14 the literature, is still a very small percentage of
15 patients, and it's not an absolute gradation; but it's
16 something potentially to be concerned about with
17 higher doses.

18 Then lastly, the large retrospective
19 studies, in my mind, come to very confusing results.
20 So that there are a few studies suggesting the risk of
21 bladder cancer is a little higher, the risk of gastric
22 cancer is a little higher, the more I¹³¹ a patient

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1 gets, but by and large, clinically, most of us think
2 that those have minimal effect, and those effects
3 really haven't been confirmed in large enough
4 studies.

5 So in summary, I'd say that the
6 complications of serious disease are not thought to be
7 high when we're talking about doses up to 1,000
8 millicuries.

9 DR. BRAUNSTEIN: There's a couple of
10 others also. Pulmonary fibrosis in individuals who
11 have especially diffused metastatic disease of the
12 lung, and you might anticipate that, because the lungs
13 get higher doses.

14 There is also a transient decrease in
15 spermatogenesis in males and decrease in ovarian
16 function that can be shown in females, and they
17 recover from that. There tends to be an increase
18 abortion rate, spontaneous abortion rate, in the first
19 year after therapy, which has been noted
20 epidemiologically. But by and large, unless you're
21 getting up to very, very high doses, it's very safe
22 medication.

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1 CHAIRMAN MARCUS: Thank you. Unless there
2 is some fundamental disagreement with --

3 DR. ORLOFF: I have one question.

4 CHAIRMAN MARCUS: -- I wanted to skip that
5 and go on. One more question, and then --

6 DR. ORLOFF: One question for the experts.
7 Is there not also some bone marrow toxicity at very
8 high cumulative doses as well?

9 DR. BRAUNSTEIN: If there bone metastases.

10 CHAIRMAN MARCUS: Thank you. I think we
11 should proceed.

12 DR. MAXON: Can I say just one thing,
13 please. One of the things that has consistently been
14 overlooked in this discussion is the fact that those
15 of us who treat patients are going to take into
16 account the a priori risk category, and nobody who is
17 a responsible clinician is going to take a patient and
18 give them multiple hundreds of millicuries of
19 radioiodine-131 in someone who is a priori low risk
20 and who does not have compelling reason to do that
21 treatment. And please bear that in mind.

22 When you're starting to talk about the

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1 risks of your 1,000 millicuries -- well, I could go on
2 for hours on that, but the fact of the matter is that
3 patients who get to that level had compelling evidence
4 of disease that can kill them, if not treated.

5 CHAIRMAN MARCUS: Understood. Thank you
6 very much. We're going to go on now to Dr. Castillo's
7 presentation. Thank you, Dr. Temeck.

8 DR. CASTILLO: Good morning. That's me,
9 and I'm in the Division of Biometrics 3. I serve the
10 Division of Medical Imaging and Radiopharmaceutical
11 Drug Products. Next slide, please.

12 Today I'm going to talk about the whole
13 body scan evaluation, specifically how the scan
14 evaluation was done, and problems with that scan
15 evaluation. I will also talk about the analyses of
16 thyroglobulin data, in particular, receiver operating
17 characteristic curve analyses, and then I'll end with
18 a conclusion.

19 Next slide, please. Briefly, this is how
20 the scans were evaluated. A patient's scan package
21 was sent to each of three blinded readers. Just to
22 note that each of these three blinded readers were

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1 used in both Phase III trials.

2 Each package had a Thyrogen scan set and
3 a withdrawal scan set. Blinded readers then did not
4 know which scan set was which, and they evaluated the
5 Thyrogen and then the withdrawal scan.

6 After that was done, they looked at what
7 results they wrote down and, if they were discordant,
8 they stopped, didn't evaluate anymore. If they were
9 concordant, then they did side by side comparisons.
10 I'd also like to note that sometimes these scans went
11 to mediation panel.

12 Next slide, please. The problems with
13 this scan evaluation, the main problem is that
14 withdrawal and Thyrogen scans were not independently
15 assessed. What I mean by that is scans are not read
16 in a randomized order across all patients.

17 Next slide, please. Instead, a within-
18 patient paired read was utilized. When you do
19 something like this, the problem is that judgment from
20 one scan may potentially affect the other.

21 In addition, not only was there within-
22 patient paired read, each scan assessment in the side

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1 by side evaluation is confounded by the presence of
2 the other scan when that happens.

3 Next slide. Also, not all scans for a
4 patient were sent to the blinded readers. When this
5 happens, there is the potential for bias, if only the
6 best scans were selected. We know that not all scans
7 were sent, because if a patient's scans were sent to
8 mediation panel, this mediation panel used additional
9 study scans to make a decision.

10 When you do that, the scan assessments
11 that were used for analyses were confounded with the
12 other scans that were not previously seen.

13 Next slide, please. When you put all
14 these things together, there is the potential for bias
15 in both the withdrawal and Thyrogen scan evaluations.
16 Also, minimal information has been presented to
17 support the use of a Thyrogen scan alone, and
18 questions remain about the comparability of the
19 Thyrogen and withdrawal scanning.

20 What I mean by that is the
21 concordance/discordance data suggests that you can
22 identify the amount of risk -- that is, chances for

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1 missing disease that the patient would incur. But if
2 there are serious problems with the quality of the
3 concordance/discordance data, it becomes difficult to
4 provide the patient with a true estimate of risk.

5 Now I will talk about the thyroglobulin
6 data analyses, which were done to show comparability
7 between Thyrogen and withdrawal values.

8 Next slide, please. I will begin by going
9 over a couple of basic concepts about receiver
10 operator characteristic curve analyses, and most of
11 these aspects also carry over to diagnostic utility
12 analyses.

13 The operative diagnostic test is usually
14 summarized by its sensitivity and specificity,
15 utilizing an external standard of truth. For a new
16 test, an ROC curve is a plot of the sensitivity versus
17 one minus specificity, and some test criterion is
18 varied. For example, in these studies the test
19 criterion was Thyrogen thyroglobulin level.

20 Next slide, please. This is an example of
21 what an ROC plot would be. You have a sensitivity
22 versus a one minus specificity point, and each of

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1 these points correspond, for example, to specific
2 Thyrogen cutoff levels.

3 Suppose this one corresponded to Thyrogen
4 cutoff level of 4 nanograms per milliliter. Then in
5 order to calculate these sensitivity specificities, if
6 the patients had their Thyrogen thyroglobulin level
7 less than four nanograms, they would it be considered
8 not positive for disease; and if it was above 4
9 nanograms, it would be considered positive for
10 disease.

11 Next slide, please. Ideally, these
12 analyses are based on comparing ROC curves for the new
13 test and the comparative test. In this case, the new
14 test would be the Thyrogen test, and the comparative
15 test would be withdrawal, because one of the proposed
16 indications was to have Thyrogen be a replacement for
17 withdrawal.

18 The sensitivities and specificities for
19 each test are determined with respect to the same
20 external reference standard and then compared. So you
21 have three components when you're doing these
22 analyses. You have an external reference standard.

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1 Then you have your test, new diagnostic test, which
2 would be the Thyrogen, and the comparative which is
3 withdrawal.

4 You calculate sensitivities and
5 specificities for Thyrogen based on this external
6 reference standard, do the same thing for withdrawal,
7 and then you can compare sensitivities and
8 specificities or a curve.

9 It is at this point where the ROC curve
10 analyses falls apart. Next slide, please.

11 I'd like you to recall that these ROC
12 curve analyses are done to assess the diagnostic
13 comparability of the withdrawal and Thyrogen
14 thyroglobulin levels. Next slide.

15 As I said, no external standard of truth
16 was used. In this case, in these studies it would
17 have been a post-therapy scan, but that was not
18 available for all patients. So an unorthodox approach
19 was taken.

20 Instead of using an external reference
21 standard as a post-therapy scan, the reference
22 standard became the withdrawal scan or post-therapy

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1 scan or the thyroglobulin level.

2 It was unorthodox, because you have
3 defined now withdrawal as part of the reference
4 standard, but then it is also the comparator. It just
5 does not follow the rules of ROC curves.

6 When you have this type of setup, no
7 direct comparison of withdrawal and Thyrogen
8 thyroglobulin levels can be made, again as I said,
9 when withdrawal is defined to be the standard of
10 truth.

11 Next slide, please. Another problem was
12 that the thyroglobulin levels contributed partial
13 information to the analyses. What I mean by that is
14 that not all patients were classified as positive for
15 disease based only on their thyroglobulin levels for
16 both withdrawal and for the Thyrogen test.

17 Some patients were classified as having
18 disease based on the scan outcome. Again, when you
19 have this type of setup, no direct comparison of
20 withdrawal and Thyrogen thyroglobulin levels can be
21 made, and this is because the comparison done in this
22 test -- in the study was not solely based on

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1 thyroglobulin data. You had it confounded it with
2 scan data.

3 Last, more than one standard of truth was
4 used. Those different standards of truth were based
5 on the different withdrawal thyroglobulin level
6 cutoffs. Typically, you should use only one reference
7 standard or standard of truth.

8 So when you have multiple standards of
9 truth, the question becomes which reference standard
10 is clinically useful. Next slide, please.

11 Putting all these points together, at best
12 the ROC curve analyses were exploratory and hypotheses
13 generating. What I mean by that is that these results
14 apply only to patients in this study and cannot be
15 applied to any other group of patients without
16 perspective testing the utility in actual use.

17 Next slide. So given all these points
18 that I've said previously, many concerns remain about
19 the adequacy of the study to compare the diagnostic
20 utility of Thyrogen and withdrawal scanning and
21 thyroglobulin testing.

22 CHAIRMAN MARCUS: May we have the lights,

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1 please. Thank you, Dr. Castillo. Are there
2 questions. Dr. Braunstein?

3 DR. BRAUNSTEIN: I have a very simplistic
4 question on the analysis of the data. Ten nanograms
5 per ml. as a cutoff point is sort of an arbitrary
6 cutoff point, to begin with, and it's based on older
7 studies using different assays, not the assay that was
8 used in this particular study.

9 If one just looks at the patients who have
10 clinically important disease, as defined by scan or
11 defined by withdrawal Tg levels that are very high --
12 let's say, much greater than ten -- and the looks at
13 the data from Thyrogen stimulated Tg -- looks at
14 Thyrogen stimulated Tg levels and tries to arrive at
15 a cutoff point that will pick up all the patients with
16 clinically relevant disease, why could not that cutoff
17 point plus the scan data after Thyrogen be used as
18 diagnostic criteria for clinically relevant disease,
19 which is what we're interested in?

20 Having said that, isn't using the ROC
21 curve to generate this just another way of doing that?

22 DR. CASTILLO: The ROC curve is a way of

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1 doing that, but the way that this was carried out is
2 not an orthodox way of doing it. Like I mentioned,
3 typically you have an external standard of truth.

4 It's difficult for me as a statistician to
5 understand. If you have something like withdrawal as
6 part of the reference standard, standard of truth, and
7 it was also the comparator. When you assign something
8 as the reference standard, you assign it 100 percent
9 to the specificity. Yet you're also saying that it's
10 not 100 percent sensitive or specific when you use it
11 as a comparator.

12 DR. BRAUNSTEIN: Okay. Well, let me go
13 back to the first part, not being a statistician.
14 Let's just get rid of the ROC curve altogether. Let's
15 just look at the post-therapy scan data or the post-
16 withdrawal scan data that shows metastatic disease.

17 I'm not all that interested in patients
18 who have had a thyroidectomy and are getting their
19 first post-therapy scan afterwards, because I venture
20 to say that 100 percent of those will have positive
21 uptake if you use a high enough scanning dose.

22 So I'm not interested in that group. I'm

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1 only interested in the group who have already been
2 ablated, who you're trying to pick up clinically
3 relevant disease to treat. So in that group of
4 patients who have had radioactive iodine treatment
5 post scans or withdrawal scans that show metastatic
6 disease, can you not go over the Thyrogen data on
7 thyroglobulin levels after Thyrogen and pick a
8 Thyrogen level that will pick up the vast majority of
9 those patients -- or a thyroglobulin level after
10 Thyrogen that will pick up the vast majority of those
11 patients who have positive scans and use that in
12 conjunction with the post-Thyrogen scan to pick up 97-
13 99 percent of the patients who have clinically
14 relevant disease?

15 DR. CASTILLO: David, would you like to
16 take that?

17 DR. ORLOFF: Can I address that question?

18 DR. BRAUNSTEIN: Please, Dr. Orloff?

19 DR. ORLOFF: The fact is that, in looking
20 at this dataset, you can take a look at those patients
21 who have the absolute definition of metastatic
22 disease, based upon their withdrawal or post-therapy

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1 scan data, as well as elevated thyroglobulins by those
2 techniques.

3 You can make a cut, basically, in the
4 Thyrogen thyroglobulin data in that group of patients
5 and capture all of them, if you make it low enough.
6 If you put it down to 2 or at the limits of detection
7 of the assay, then, obviously, you're not going to
8 miss anybody in a retrospective fit of the data; but
9 the significance of that, to me, is questionable when
10 it comes to actual use of this technique, because are
11 you then proposing on the basis of this demonstrated
12 efficacy in detecting extensive disease that in any
13 given patient who happens to have a negative Thyrogen
14 scan or a low level Thyrogen scan, as we saw in this
15 database, some patients with metastatic disease were
16 significantly underdosed by Thyrogen scan.

17 Are you then proposing that in that
18 patient, whoever he or she is, if the thyroglobulin on
19 Thyrogen is detectable, that that patient has
20 metastatic disease? I think the answer is no.

21 So it's possible to fit, to look at the
22 database and make a cut and say we didn't miss

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1 anybody, if we use this as the fit, but the patient
2 has come to you and is in your office and all you have
3 in front of you is the Thyrogen data. You don't have
4 the withdrawal data, and only God knows at that point
5 what the patient actually has.

6 What I maintain is the data on Thyrogen
7 are different than the data after withdrawal, and you
8 cannot impute what the withdrawal data would be, had
9 you withdrawn that patient.

10 CHAIRMAN MARCUS: Dr. Sherwin, then Dr.
11 Molitch.

12 DR. SHERWIN: Just in that patient faced
13 with that problem, you would probably then withdraw
14 the patient. Right?

15 DR. ORLOFF: You would, but -- Yes.

16 DR. SHERWIN: And then make a decision
17 based upon your judgment of the numbers.

18 DR. ORLOFF: Right. What I would submit
19 to you is, insofar as you withdrew the patient, the
20 patient derived no benefit from having a Thyrogen
21 test.

22 DR. SHERWIN: That's correct.

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1 CHAIRMAN MARCUS: That patient may not,
2 but the patient who had a thyroglobulin of 8 or 9 in
3 whom maybe you have better confidence and they didn't
4 need to have the withdrawal did benefit.

5 DR. ORLOFF: Why did he benefit?

6 CHAIRMAN MARCUS: Because he got saved the
7 trouble of the withdrawal.

8 DR. ORLOFF: Are you going to treat him?

9 CHAIRMAN MARCUS: That's a different
10 issue.

11 DR. BRAUNSTEIN: Or the majority of
12 patients who have less than 2 and have a negative scan
13 really did benefit from that.

14 DR. ORLOFF: That's right. That's a
15 screening test.

16 DR. BRAUNSTEIN: Well, and the scan. I
17 added the scan in there.

18 DR. ORLOFF: What's that?

19 DR. BRAUNSTEIN: I said less than 2 and
20 the scan -- and a negative scan, because personally I
21 would use this along with a scan, not just Tg level.

22 DR. ORLOFF: Right. I think, actually,

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1 Dr. Mazzaferri raised this concept, that in essence in
2 a group of patients with a low pretest probability of
3 disease, one can in effect feel confident in the
4 negative with the Thyrogen test.

5 The problem is that one likely -- I mean,
6 obviously, there are vagaries of clinical judgment and
7 instinct, but in essence as a general rule one must
8 always follow up a positive Thyrogen test, because one
9 really does not know whether that, if the patient has
10 a class 1 scan, he could well have metastatic disease.
11 We saw that in our database here.

12 DR. BRAUNSTEIN: But couldn't the follow-
13 up be another --

14 DR. ORLOFF: If he has a thyroglobulin
15 level -- excuse me -- at the limits of detection of
16 the assay on Thyrogen, that could be a 100
17 thyroglobulin level on withdrawal, and so in essence
18 what I'm saying is, if you really -- If you're willing
19 to a priori accept a negative test and say to the
20 patient, you're okay, I'm pretty sure, because overall
21 I had a low sense of, you know, suspicion that you had
22 disease, I'll see you next year -- that's fine. But

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1 if you really want to know for sure that you're not
2 missing anything, you need to withdraw the patient,
3 because once you get a -- because you don't -- In that
4 sense, you can't rely on the negative, because it
5 could be a false negative.

6 CHAIRMAN MARCUS: Dr. Molitch.

7 DR. MOLITCH: I think that this discussion
8 that you're just now having with the patient is
9 exactly what we do, where we might talk to the patient
10 about the absolute necessity to know perhaps the
11 uncomfortableness of hypothyroidism in the withdrawal,
12 and so that we as clinicians would use this in a
13 dialogue with the patient, which is exactly why I
14 would rather, as a clinician, be the one to make this
15 decision in this dialogue rather than to have this as
16 an algorithm developed by the FDA.

17 DR. ORLOFF: I am getting ahead, and I was
18 going to say this at the podium, but we don't
19 fundamentally disagree that this should be available
20 for use, but we are discussing how it should be -- how
21 the data should be interpreted and what place it
22 should take.

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1 All I'm saying is that one really should
2 not consider this as the substitute for withdrawal.
3 Withdrawal is a definitive diagnosis and decision
4 guiding modality. This does not give the same kind of
5 information.

6 CHAIRMAN MARCUS: Are there any other
7 questions of Dr. Castillo? Dr. Sherwin?

8 DR. SHERWIN: Related to the issue of
9 interpreting scans, because I thought, you know,
10 fundamentally, to me, that was the most important
11 point that was raised -- to me, at least -- and I just
12 want to be sure I understand exactly how this was
13 done, because my sense is that you had some concerns,
14 from the slides you showed.

15 Was it that the -- Were the scans read in
16 an order where you knew the effect or did I
17 misinterpret what you were saying? Maybe I -- In
18 other words, you implied there was a bias in the
19 reading of the scans.

20 DR. CASTILLO: Typically, in medical
21 imaging when we have studies and we have scans, we
22 take -- basically put everyone's scan in a pot and mix

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1 it up and have the blinded readers look at them. They
2 have no idea which patient the scans belong to.

3 In this setting, the blinded readers
4 received both the Thyrogen and withdrawal scans from
5 the same patient. They evaluated the patient's total
6 number of scans first before going on to the next.

7 What I'm saying is, if you evaluate one
8 scan -- you don't know what it is. You evaluate it.
9 That's going to have some effect on the way you're
10 going to judge the next scan. I don't know which way
11 the bias went, but there's the potential for bias to
12 be there.

13 Another point that I bring up is that the
14 same three blinded readers were used in both studies.
15 Again, from medical imaging we don't typically accept
16 that, because we want two independent trials,
17 especially if they're similar in protocol. They may
18 know the intent of the study, and that's where
19 problems of potential bias may be creeping in.

20 CHAIRMAN MARCUS: Dr. Simpson, and then
21 Dr. Burman.

22 DR. SIMPSON: I just wanted to comment

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1 that, in fact, I was involved in a study where the
2 scans were mixed up and also pair to pair. They were
3 before and after, and there were quite different
4 results, and these were experienced readers.

5 So that, in fact, it does -- I suspect
6 that it does make a difference if you have them -- you
7 know, one after the other.

8 The other thing I wanted to say was that
9 one thing that was not done in this study was actually
10 to check whether in fact, if they read them again,
11 that they would get the same results, whether they
12 were the Thyrogen or the other.

13 DR. CASTILLO: I guess the other point I
14 would like to bring up, too, is the way the scans are
15 read, there really is no information on what the
16 clinical merit is of a Thyrogen scan alone. There
17 were two sets of scans. One could have influenced the
18 other.

19 CHAIRMAN MARCUS: Dr. Simpson.

20 DR. SOBEL: Just for interest in this, we
21 have two postulates which the potential bias could
22 work in either direction, toward concordancy or toward

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1 discordancy, depending on whether there's a curmudgeon
2 or a jolly fellow involved in this. Which way did the
3 bias go, just out of interest? In the one you
4 described?

5 DR. SIMPSON: When they were before and
6 after, they tended to be -- the two readers were more
7 in agreement than when they were all mixed up.

8 CHAIRMAN MARCUS: Dr. Burman.

9 DR. BURMAN: Just a quick question of
10 clarification which I thought I understood, but then
11 maybe I don't.

12 When the scans were read by the three
13 reviewers, they knew that they were the same patient
14 when they were reading the scans together. Did they
15 know the date order of the scans? Did they know which
16 ones were first or which ones were second?

17 DR. CASTILLO: No. They knew which
18 scanned pair belonged to which patient, but they
19 didn't know which was the Thyrogen scan, which was the
20 withdrawal scan.

21 CHAIRMAN MARCUS: Dr. Temeck, was that the
22 point you wanted to make?

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1 DR. TEMECK: Yes.

2 CHAIRMAN MARCUS: Okay. Dr. Molitch.

3 DR. MOLITCH: Another point along the same
4 thing for clarification. You said not all the scans
5 were sent for reading by the independent reviewers.
6 Maybe we can ask the sponsor why that was the case.

7 DR. MEEKER: Actually, that's not correct.
8 We reviewed all the scans for completeness. In fact,
9 there was only one set of scans that did not have the
10 complete set and, therefore, was not sent. So out of
11 the 220 scans that were -- or 221, 220 actually went
12 and were read and were evaluated.

13 DR. MOLITCH: Every scan was sent, and no
14 particular view was left out or something?

15 DR. MEEKER: Genzyme's review was for
16 completeness only, to make sure that all scans were
17 available. They were then sent out to blinding, and
18 then those --

19 CHAIRMAN MARCUS: Thank you. Dr.
20 Critchlow.

21 DR. CRITCHLOW: Yes, two protocol
22 clarification questions. One is: What was the

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1 original rationale for reading the scans in pairs?
2 And the other is: Was there a protocol derived
3 decision in terms of initiating treatment?

4 CHAIRMAN MARCUS: Dr. Meeker, would you
5 like to answer -- address that?

6 DR. CRITCHLOW: The first one was what was
7 the original rationale in the protocol for reading the
8 scans in pairs -- patient pairs?

9 DR. MAXON: Let me just say one thing, as
10 one of the ones who slogged through all these scans.
11 We were -- Ralph Ketler and Dave Becker and I were the
12 three who read them. In the first study, the 1992
13 study, it is true that we got envelopes of scans, but
14 I did not know they were the same patient until this
15 morning.

16 They did not tell us they were the same
17 patient. They came with totally different numbers.
18 We could not see anything on any of the scans that
19 would identify center, date, administered activity,
20 patient name, anything. They were all covered, both
21 front and back, with real heavy sticky electrician's
22 tape.

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1 So in that first study we had no idea
2 whatsoever that they were paired. Okay? That's
3 number one.

4 CHAIRMAN MARCUS: They all came at once?

5 DR. MAXON: They came in different
6 envelopes. They came at once. We would just get a
7 box of so many scans, and we had forms to fill out.
8 We had no idea whether they were the same patient,
9 whether a different patient, same centers, different
10 centers or whatever.

11 It was just -- I told them that I really
12 couldn't do more than 20 at a time, because at that
13 point it takes pretty much of the day anyway, and your
14 eyeballs are crossed, and you just want to go home.
15 But the fact is they would come in batches of about
16 that size, and we would simply get -- They sent us
17 that whole big box of these blue books that we were to
18 record information in.

19 We agreed that we would follow things in
20 a precise manner. We read them alone and privately,
21 with no residents or any other doctors around or any
22 other interruption or anything, and we sent back the

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1 books.

2 So I had no idea in the first study that
3 they were the same patient until this morning. That's
4 number one.

5 In the second study, my understanding of
6 why the paired reading was done was it was requested
7 by the FDA, and I guess it was because they wanted to
8 give us two chances to render a discordant reading.
9 I have no idea. You'll have to ask whoever made that
10 recommendation within the FDA, but that was done for
11 that reason.

12 When we did get those studies, again we
13 would read one and record it in the book. We would
14 read another and record it in the book. If they were
15 discordant, we quit. If they were concordant, we did
16 the side by side, and in the second protocol we had
17 asked that, if there were additional scans available
18 for both of them.

19 In other words, you couldn't have a 72-
20 hour scan for just one, because in clinical nuclear
21 medicine you find radioiodine in saliva. You find it
22 in gastric contents, in a lot of different places, and

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1 you can get artifact.

2 So most of us get sequential imaging over
3 time, if there's any question whatsoever. In my lab,
4 we do it over 72 hours routinely, on every patient,
5 anyway.

6 Now the other difference between the two
7 protocols was that, when we looked at the first group
8 of scans, we were not invited to look at protocols or
9 help set up imaging protocols or anything in advance,
10 and we were, frankly, distressed at some of the
11 difficulties we were having reading them.

12 So when Genzyme came back -- and frankly,
13 I was delighted. I thought I was done with the whole
14 bit, and that was it. But then they, unfortunately,
15 came back and said the FDA wants a second study. So
16 I took a deep breath and said, all right, but if we're
17 going to do a second one, we need to have a
18 standardized imaging protocol, and it needs to be one
19 that is based on good nuclear medicine practice where
20 we make sure that count densities are appropriate,
21 imaging times are appropriate, the right labels are
22 there so we're not saying, my gosh, is this the chest

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1 or the pelvis or where in the heck are we, and so
2 forth.

3 That also is why we came up with a 4
4 millicurie diagnostic administered activity. We did
5 know the kinetics were different on Thyrogen. We
6 thought with 4 millicuries we would end up with at
7 least a 2 millicurie activity to image, which in our
8 experience with the protocol that we recommended was
9 adequate, and we went on from there.

10 Now as far as the other uncertainties, I
11 don't know of studies in nuclear medicine imaging per
12 se of this type that show the type of bias you're
13 talking about, and I certainly don't know which way it
14 would go.

15 I did ask Genzyme if they could put
16 together some data to compare outcomes in terms of
17 concordance/discordance on the second study, depending
18 on which one we looked at first. If that would help
19 answer the question, I can ask them to show those
20 slides. If it's not relevant to the question, then I
21 won't. It's your call.

22 DR. SHERWIN: I think it would be

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1 interesting.

2 CHAIRMAN MARCUS: Yes. Thank you. That's
3 been very helpful. It sounds like you're more one of
4 the jolly fellows than the curmudgeons.

5 DR. MAXON: My wife would probably
6 disagree.

7 CHAIRMAN MARCUS: Is there going to be a
8 slide. Dr. Sherwin, did you ask to see that material?

9 DR. SHERWIN: I think it would be
10 worthwhile.

11 CHAIRMAN MARCUS: While they're doing
12 that, Dr. Temeck, did you want to --

13 DR. TEMECK: Yes. I just wanted to
14 emphasize that --

15 CHAIRMAN MARCUS: Would you use the
16 microphone, please.

17 DR. TEMECK: Sure. I'm sorry. -- that
18 with the first Phase III study we understand that the
19 -- This is the first time I'm hearing this, that the
20 independent reviewers did not know which scanned pair
21 belonged to which patient; because the information
22 that we received was that the independent reviewers

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1 did know which scanned pair belonged to which patient.

2 What our understanding was, was that in
3 that first study that they didn't know, though, which
4 was the Thyrogen scan and which was the withdrawal
5 scan -- If I could just please finish what our
6 understanding of the situation was and what we were
7 told -- and that the Thyrogen scan -- You know, one of
8 the scanned pairs was read independent of the other,
9 and then a third read was done, a side by side
10 comparison, and that we were told that on the side by
11 side comparison this was the concordant, and this was
12 the discordance rate. It was based on the side by
13 side comparison -- okay -- in the first Phase III
14 study.

15 So, clearly, there's some miscommunication
16 here in what our understanding was about the scans.

17 DR. McELLIN: In the first study they
18 were--

19 CHAIRMAN MARCUS: What is your name,
20 please?

21 DR. McELLIN: Kevin McEllin, clinical
22 affairs from Genzyme.

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1 In the first study the reviewers were
2 provided with two separate scans, both for the same
3 patient, the Thyrogen scan which was assigned a random
4 number, the withdrawal scan that was assigned a random
5 number. They did make a technical evaluation,
6 classify what type of uptake they did see on the first
7 scan.

8 In the first study there was -- That
9 classification was not part of the formal definition
10 of concordance. The formal definition was the side by
11 side comparison. We did not inform the independent
12 reviewers that those were the same patient, but you
13 know, they were, basically --

14 CHAIRMAN MARCUS: How could they do a side
15 by side comparison --

16 DR. McELLIN: They rated the first -- They
17 evaluated the first scan. They evaluated the second
18 scan for technical quality, and tried to identify what
19 type of uptake did they see, thyroid bed, whatever.
20 Then when that was completed, they did a side by side
21 comparison, and they --

22 CHAIRMAN MARCUS: Not knowing that they

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1 were the same patient? That doesn't make sense.

2 DR. McELLIN: Yes. They were the same
3 patient. Evidently -- I don't know if Harry knew that
4 they were, but they were the same patient. We didn't
5 prospectively identify them.

6 CHAIRMAN MARCUS: I don't know that we're
7 going to bring this to closure. I'd like to have Dr.
8 Orloff give his presentation, and then we will switch
9 the machinery and get the answer to Dr. Sherwin's
10 question.

11 DR. ORLOFF: We're going to need the
12 lights down.

13 As I said a few minutes ago, as we were
14 finding this slide, we really don't have a fundamental
15 disagreement here. I think that one of the confusing
16 things -- Certainly, this discussion is more than
17 worthwhile to try to iron out what the limitations of
18 the Thyrogen stimulation tests are and what, if any,
19 ramifications that has for its use; but I think one of
20 the confusions is that, to some extent, when we think
21 about placing it in the armamentarium for the follow-
22 up of these patients, is that some people -- and this

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1 may be a little bit confusing here -- Some people are
2 talking about it -- and that's really what my point is
3 going to be, is addressing it as a substitute for
4 withdrawal; that is, as a definitive test, replacing
5 withdrawal.

6 Others are talking about it when they say
7 a substitute for withdrawal, basically placing it in
8 the course of follow-up in lieu of withdrawal. So
9 that in the patient who might be withdrawn every year
10 or every two years or every five years, depending upon
11 the willingness of that patient, the approach of the
12 physician, the assessment of risk, the question is
13 whether this can in essence either completely obviate
14 the need for withdrawal or simply increase the
15 interval between obligatory withdrawals.

16 Anyway, I'm going to try to be brief,
17 because I think just about everything has been said.
18 My point here was to try to summarize and get to
19 really the place for Thyrogen in clinical practice.

20 Could you give me the first slide, please.

21 In patients with residual or recurrent,
22 well differentiated thyroid cancer, I think you've

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1 seen from the data presented here that Thyrogen
2 stimulation testing as performed in the clinical
3 trials yields scan and thyroglobulin data that are
4 different than those obtained after withdrawal of
5 thyroid hormone suppressive therapy.

6 Thyrogen derived scan and Tg data do not
7 provide the same information as withdrawal data with
8 regard to the presence of cancer, the location of
9 cancer, or the total burden of residual or recurrent
10 disease.

11 So we come to a discussion then of where
12 to place Thyrogen in the armamentarium. To address
13 this issue, I'm going to start by characterizing what
14 would constitute an ideal substitute for withdrawal;
15 that is, in the form of an exogenously administered
16 TSH preparation. Then in the context of a discussion
17 of the clinical trial data, and a very brief one at
18 that, I will show you how I see Thyrogen sizing up to
19 withdrawal and to that ideal.

20 This will lead me to enumeration of some
21 very basic considerations that I think go into the
22 interpretation of the Thyrogen test for the purposes

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1 of clinical decision making, and finally I'll finish
2 with the assessment of where I think Thyrogen should
3 be placed in clinical practice.

4 So what's the ideal substitute? Next
5 slide, please. Ideally, we'd like to see an
6 exogenously administered TSH preparation and a
7 protocol for that administration that achieves
8 pharmacodynamic equivalence. That is to say, equal
9 degrees of thyroglobulin elevation compared to
10 withdrawal and scan equivalence.

11 Short of that, the next best thing would
12 be a consistent thyroglobulin elevation relative to
13 the withdrawal, so that we could in essence be able to
14 convert from one to the other, but always scan
15 equivalence; because we can never impute what the
16 withdrawal scan would show. We can't divine it. We
17 can only know it.

18 Finally, we'd like to see intra-patient
19 reproducibility.

20 Next slide. Well, the bottom line for the
21 performance of Thyrogen in clinical trials is, I
22 think, that it's an inconsistent and generally less

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1 potent stimulator as administered of follicular cell
2 derived tissue than is withdrawal.

3 Thyrogen scans, as you saw, tended to
4 underdetect disease relative to withdrawal, and
5 Thyrogen thyroglobulin levels tended to be
6 significantly lower than withdrawal thyroglobulin
7 levels and, importantly, no mathematical constant or
8 simple mathematical constant described the
9 relationship of the twos.

10 I've put "significantly" in quotes in
11 order to point out the fact that, if one were taking
12 thyroglobulin values on face, they are discordant
13 enough in this database that they would be perceived
14 of as clinically significantly different.

15 Next, please. Well, before I tell you
16 what the data -- Before I summarize some of the
17 important data, let me say a few things about the
18 overall trial designs.

19 I want to emphasize that these were not
20 comparative diagnostic utility studies, and by the
21 same token, they were not comparative clinical
22 decision guiding studies.

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1 There was nothing in the design or conduct
2 of these trials that included -- There was no aspect
3 that included the independent use of Thyrogen scan and
4 thyroglobulin data, on one hand, and withdrawal scan
5 and thyroglobulin data, on the other hand, for
6 rendering a clinical decision with regard to any of
7 those patients.

8 What these were, and what, I think, we
9 really are limited to when we look at the data from
10 these trials, is comparing scan to scan and
11 thyroglobulin level to thyroglobulin level.

12 Next, please. So what were the scan
13 results? One should not be surprised that the FDA
14 takes the negative look, of course. So we have
15 focused on the problem of false negatives or
16 underdiagnosis.

17 As you heard from Dr. Temeck, the nominal
18 concordance rate of 84 percent in the first study is
19 weighted by the fact that -- and again, we shouldn't
20 be surprised -- that there was very high concordance,
21 nearly 100 percent, for the withdrawal -- among pairs
22 where the withdrawal class showed no disease.

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1 Half the patients had either remnants or
2 metastatic tumor. Most of them did have remnant,
3 admittedly, on withdrawal scan. There was only 68
4 percent concordance in those patients and, of the 21
5 concordance scans, withdrawal showed more tissue,
6 we'll say, than did Thyrogen in the majority of cases.

7 Importantly, she called your attention to,
8 and I do again, that there were 12 false negative
9 scans. That is, the Thyrogen -- the false negative
10 Thyrogen scans. The withdrawal scan of the pair
11 showed evidence of residual tumor, residual thyroid
12 tissue localized to the bed, and/or metastatic
13 disease; and the Thyrogen scan was negative.

14 Now one might say in the nine of 50 Class
15 1 scans -- that is, remnant tissue; this really
16 doesn't raise any clinical fears on your part for
17 those particular patients, but we did have a small
18 number of patients of the total cohort who had
19 metastatic disease and, while this is a poor estimate
20 of what might be expected in practice, suffice it to
21 say that there were actual false negatives, patients
22 who had significant disease by withdrawal, and indeed

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1 that was confirmed by other data, who had nothing on
2 the Thyrogen scan.

3 Next, please. The '95 study results are
4 quite similar with regard to scan. I won't go through
5 it, but suffice it to say, most of the withdrawal
6 scans of the discordant pairs -- in fact, most of the
7 overall positive scans in this trial were class 1, but
8 among the pairs where the withdrawal scan was
9 positive, 12 to 15 percent of the Thyrogen scans were
10 falsely negative. So you missed disease or remnant
11 altogether. There were -- Thyrogen did miss
12 metastases in five cases in this study.

13 What about thyroglobulin? Next, please.
14 Well, you've heard about how thyroglobulin is used in
15 follow-up. To briefly summarize, when it's measured,
16 really, in essence as a screen on thyroid hormone
17 suppressive therapy, -- for the sake of this
18 discussion, let's just say that, all else being equal,
19 that the general protocol would be to follow up a
20 detectable thyroglobulin level.

21 When it's measured on withdrawal,
22 particularly in the setting of a negative or low level

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1 withdrawal scan -- so no suspicion of significant
2 disease on withdrawal scan -- in that instance we rely
3 on the thyroglobulin level to give us additional
4 important clinical information.

5 This really comes from Schlumberge's
6 article earlier this year. A generally applicable
7 approach would be that in that setting, if it's
8 undetectable, the thyroglobulin level, that is taken
9 as assurance that there is no significant disease or
10 minimal disease.

11 When it's detectable but less than or
12 equal to ten, most physicians who practice in this
13 field, I think, would -- that would, you know, light
14 the bulb in their head to increase their vigilance,
15 perhaps doing more frequent follow-up with
16 thyroglobulin on suppressive therapy, perhaps calling
17 in some cases for a withdrawal scan and thyroglobulin
18 measurement at that point.

19 In many people's minds and in practice, a
20 level that goes above ten is presumptive evidence of
21 metastatic disease, significant tumor burden, and
22 calls for an empiric ablative dose of radioiodine,

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1 regardless of the finding on the scan.

2 I emphasize that thyroglobulin is
3 evaluated as a continuous variable. We keep talking
4 about cuts, but for any individual patient within the
5 range of variability of the assay, there is a
6 difference between a rising level, a falling level,
7 and a stable level.

8 Next, please. What about the
9 thyroglobulin data from TSH-95? Dr. Temeck showed you
10 that overall there was a poor and not apparently
11 clinically useful correlation between thyroglobulin
12 levels on Thyrogen and after withdrawal, and she
13 called your attention to the group of patients who had
14 a scan on Thyrogen where there was minimal to no
15 evidence of tissue disease and where the Thyrogen
16 thyroglobulin was less than ten.

17 So that would have been a patient where
18 you would have said I feel comfortable this patient
19 doesn't have significant residual tumor or recurrent
20 tumor, and I can send him or her home and see them in
21 six months or next year.

22 In that relatively small cohort of

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1 patients, some 33, I think, in arm 1 of that trial,
2 fully 25 percent of them had thyroglobulin levels on
3 withdrawal that were greater than ten, and 20 percent
4 of them had levels greater than 20.

5 So again, without going into some of the
6 details of those individual cases, this is evidence
7 that one can be misled by Thyrogen based data.
8 Importantly, I say again that prospectively we can --
9 There's nothing in the database that tells us how we
10 can predict a withdrawal Tg from a Thyrogen Tg or vice
11 versa, the point being, if our understanding of this
12 disease and our current approach is sort of based upon
13 a gestalt of how we use withdrawal data, Thyrogen
14 thyroglobulins -- we don't know how to relate them to
15 withdrawal.

16 Next, please. Let me just say a few
17 things about the diagnostic utility analysis, which --
18 I made some points when I was sitting at the table a
19 few minutes ago. These were at best retrospect best
20 fit manipulations of the Thyrogen data in order to fit
21 those after withdrawal. As such, at best they
22 describe and apply only to the present dataset.

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1 I would submit to you that they do not
2 support comparable utility of Thyrogen data and
3 withdrawal data in actual use. That indeed has not
4 been studied here.

5 I think the other way of looking at it is
6 that they really don't provide any guidance on the
7 interpretation of Thyrogen data in isolation. As I
8 pointed out earlier, these are the data that the
9 physician will have before him or her for a given
10 patient, just the Thyrogen data.

11 I used as the example the cutoff analysis
12 for detection of metastatic disease. Yes, we can go
13 back in the database and pick a cutoff point that
14 allows us to capture, in essence, all of the patients
15 with metastatic disease, but how do we then apply that
16 in practice?

17 Are we to then say that, if you have a
18 thyroglobulin on Thyrogen of greater than two, that
19 you have metastatic disease? No.

20 Next, please. So what are the
21 considerations in the interpretation of Thyrogen test
22 data? These really are, in essence, I think, the

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1 shortcomings of Thyrogen testing at this time as a
2 substitute for withdrawal -- in other words, as a
3 replacement of that as a definitive test.

4 These are the considerations: A positive
5 Thyrogen scan has a significant chance of
6 underestimating the extent of disease. A negative
7 Thyrogen scan has a significant chance of being a
8 false negative, even in patients with extensive
9 disease; and a thyroglobulin level after Thyrogen is
10 frequently not reflective of the extent of disease,
11 and as I said, there's no conversion to a
12 corresponding level after withdrawal.

13 Next, please. So where -- I've thought
14 about this so many times in the last couple of hours.
15 Let me just make sure.

16 Okay. When we consider replacing
17 withdrawal altogether with Thyrogen in the course of
18 follow-up of this disease, what must we think about?
19 Well, withdrawal testing is used currently to
20 definitively assess the presence and extent of
21 disease. It is considered the gold standard.

22 For example, it's employed in patients

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1 periodically perhaps, depending upon overall risk
2 assessment, who might have a persistent negative Tg on
3 thyroid hormone suppressive therapy. In the example
4 that Dr. Mazzaferri gave of the sports writer status
5 post excision of a single brain metastatic lesion, he
6 raised the issue in that case. That is to say, that
7 patient has been followed with a persistent low or
8 negative thyroglobulin level on suppressive therapy,
9 and he's raising the issue that it's really time to
10 look more definitively.

11 Another place, obviously, when it's used
12 for the definitive assessment is in patients with a
13 newly detectable or rising thyroglobulin on thyroid
14 hormone suppressive therapy. This is all with the
15 premise that more and more people are followed by
16 being screened periodically in order to -- on
17 suppressive therapy in order to avoid withdrawal.

18 Well, it turns out that, if that's the
19 gold standard, what I can tell you about Thyrogen
20 scans and Tg levels is that they are unreliable as
21 measures of the presence of extent of disease. You
22 saw that they missed in a significant number of cases

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1 the presence of metastatic disease or they
2 underdiagnosed it.

3 So I would say that Thyrogen testing, as
4 performed using the protocol of administration in
5 these trials, does not yield definitive information.
6 So I would not recommend to people that, if they feel
7 the need to do a withdrawal test, that they instead do
8 a Thyrogen test.

9 So could I have the last slide, please.
10 The place for Thyrogen in the follow-up of patients
11 with thyroid cancer then is, most importantly, as a
12 screening test. That is, although this wasn't
13 formally studied in these trials, it makes complete --
14 it has complete logical sense based upon the
15 physiology and the demonstrated effect of Thyrogen to
16 stimulate follicular cell derived tissue, that in
17 patients who would otherwise be followed solely by
18 thyroglobulin on thyroid hormone suppressive therapy,
19 clearly, one has to believe that this is going to be
20 a more sensitive measure of recurrent disease.

21 I would submit, as I did a few months ago,
22 that, really, as a screening test one must in most

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1 instances seriously consider following up a positive
2 result with withdrawal, because as you've seen in the
3 data, the positive Thyrogen test results not
4 infrequently underestimate the extent of disease, and
5 they certainly don't accurately reflect extent of the
6 disease most of the time, at least if one believes
7 that the withdrawal data do.

8 The final indication that I would put in
9 italics here, simply because it's sort of the no-
10 brainer of the whole bunch, is for general follow-up
11 in patients who can't mount an adequate TSH response,
12 who have some medical contraindication to withdrawal.

13 Thank you very much.

14 CHAIRMAN MARCUS: Thank you, Dr. Orloff.
15 Are there questions for Dr. Orloff? Dr. New.

16 DR. NEW: Dr. Orloff, there was one option
17 that you didn't include, and that is that you heard
18 this morning that there were a number of patients who
19 don't know whether they can mount a TSH test or have
20 a medical contraindication who just won't do
21 withdrawal because it's so painful and so disabling.

22 I just want to say another thing. I'm a

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1 pediatrician, and I would not do a withdrawal test on
2 a young child, because I think it would damage his
3 function and development.

4 So there are all sorts of situations in
5 which the option isn't withdrawal, Thyrogen. The
6 options are withdrawal, Thyrogen or nothing. In that
7 situation, I would say that the Thyrogen test is
8 indicated.

9 DR. ORLOFF: And I don't disagree with you
10 at all. That's called clinical judgment and taking
11 care of the patients.

12 CHAIRMAN MARCUS: Thank you. Are there
13 any other questions at the table for Dr. Orloff? Yes,
14 sir?

15 DR. CHINCHILLI: Dr. Orloff, in your last
16 slide here where you're suggesting it be used as a
17 screen, you are saying then that you want to make the
18 net very large with Thyrogen, and so you're going to
19 have a high proportion of false positives. Is that --

20 DR. ORLOFF: No. What I'm saying is that
21 most -- and the experts here will confirm this, but
22 more and more, because of the availability of very

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1 sensitive thyroglobulin assays and the, in essence,
2 trust, therefore, in that measurement -- more and more
3 patients are being followed chronically, irrespective
4 of their overall assessed risk, to a greater or lesser
5 degree, depending upon the patient and his risk, by
6 this screen of thyroglobulin on thyroid hormone
7 suppressive therapy; because it's cruel and unusual to
8 keep withdrawing people, and they just won't tolerate
9 it.

10 DR. CHINCHILLI: But the information is
11 not available --

12 DR. ORLOFF: When patients are screened
13 with that method, as Dr. Mazzaferri pointed out,
14 depending upon the pretest probability of disease
15 within the group that you're studying, you are going
16 to be inclined as a physician to more or less
17 frequently employ a definitive test like withdrawal
18 to, in essence, check on the validity of your negative
19 tests. Okay?

20 So -- and that's how the issue of false
21 negatives for that is really addressed in practice.
22 People who -- if you're more worried that -- In a

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1 group of people who have a higher pretest probability
2 of disease, you are less willing to tolerate then or
3 to believe, I guess, negative results, at least over
4 the long haul.

5 So those are the patients in whom you
6 might choose to withdraw the patient or do a
7 definitive test every two years. Patients who really
8 you're very relaxed about, you would go longer.

9 I'm saying, where you would have otherwise
10 used thyroglobulin on suppressive therapy, use
11 Thyrogen; but depending upon pretest probability of
12 disease -- and we don't really know how much more
13 sensitive Thyrogen stimulated thyroglobulin is, but
14 likely a lot more. But when you have a persistent
15 negative value on Thyrogen or a newly detectable or
16 rising value, you need to further investigate that.

17 Persistent negative means -- Persistent
18 negative in that case, once in a while you may want to
19 be sure that it's truly negative, and I'm saying the
20 only way to really be sure is to withdraw the patient.

21 CHAIRMAN MARCUS: Thank you. We are going
22 to do the following. We have somehow managed to be

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1 exactly one hour behind time. I don't know how that
2 happened.

3 We are going to take, if everyone at the
4 table is agreeable, a 45-minute lunch break. On
5 completion of that, I hope that the projectors can be
6 switched so that the very first order of business will
7 be to address Dr. Sherwin's question.

8 Secondly, I understand there are a couple
9 of members of this panel who have airport priorities
10 here which demand that they leave by some arbitrary
11 time. I'm going to ask them in particular to have
12 their questions as soon as we finish Dr. Sherwin's --
13 the answer to Dr. Sherwin's question, so that we can
14 then have them fill out the paper with the questions
15 and submit them to Kathleen Reedy. Then they can feel
16 comfortable about leaving when they need to.

17 So without any further objection to that,
18 we'll declare a lunch recess for 45 minutes. We'll
19 reconvene at 1:15.

20 (Whereupon, the foregoing matter went off
21 the record at 12:30 p.m.)

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1 withdrawal was better. There was no statistically
2 significant difference.

3 So please kind of ferment this in your
4 memory, and let's go to the next slide. All right.
5 Now this is where the withdrawal scan was first, and
6 once again you see that the numbers are very, very
7 similar in terms of Thyrogen better or equal to
8 withdrawal, withdrawal equal to Thyrogen or better.

9 Then down below again there was no
10 statistically significant difference in terms of the
11 discordances. To the extent that that would answer
12 the question, I think at least it shows that, if there
13 were any sort of bias that we're not aware of or can't
14 quantify, it's not a huge number. It doesn't have a
15 huge impact on the data. Thank you.

16 CHAIRMAN MARCUS: Thank you. Bob, is that
17 satisfactory to you?

18 DR. SHERWIN: Yeah, I guess so. But the
19 issue is with respect to the FDA's point. I still am
20 a little confused as to how you -- It was obviously a
21 difference of opinion about the bias level. Has
22 anything come out from this discussion that's changed

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1 anything in your mind or not, because it seemed as if
2 you were hearing something different than you had
3 first learned about.

4 I'm just a little confused perhaps as to
5 whether anything has been clarified or is any new
6 information available or is it really where we were
7 before?

8 DR. TEMECK: My opinion is we're where we
9 were before. I'm still -- because we keep hearing
10 different things. So I'm really not honestly sure
11 what exactly happened. That's all I can really say.

12 DR. MEEKER: Can I offer an additional
13 thought? We've had this discussion with the FDA, and
14 by virtue of the fact that the scans were read in a
15 pair, albeit one first and the other following that,
16 the potential for recall bias exists. Of course,
17 we've acknowledged that.

18 Then the question is how big was it, and
19 in which direction did it go? I think we can't answer
20 that. So to the extent that you say that's a hurdle
21 we can't get over, then we can't evaluate the data.
22 We would obviously disagree with that, and I think the

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1 FDA has reached a point -- I don't want to put words
2 in their mouth -- where they're comfortable moving
3 beyond that, and we would leave it at that point.

4 CHAIRMAN MARCUS: Good. Thank you.

5 What I propose now, that we have a series
6 of discussion points where it is stated that FDA seeks
7 our advice and opinion. Many of these are points that
8 we have already discussed, to one degree or another,
9 and then we have three questions. You actually only
10 have two questions written down, but Dr. Orloff has
11 asked me to expand that by one question.

12 I think the most expeditious way to do
13 this is for me just to give you an indication of the
14 discussion points that FDA is interested in, and then
15 I'll go around the table for members of the panel,
16 asking them if they have any particular comments on
17 one or another of those points that they wish to add
18 to what has already been said.

19 Once we have gone around the table, I'll
20 ask for any other general questions, and then we can
21 go directly to answering the posed questions.

22 So the first discussion point concerns the

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1 adequacy of the Thyrogen Phase III studies to address
2 the overall utility of Thyrogen as an alternative
3 diagnostic agent to withdrawal, the diagnostic utility
4 of Thyrogen versus thyroglobulin, and the
5 acceptability of the false negative rate for the
6 Thyrogen scans.

7 The others are sort of redundant. Also,
8 I guess, at the end, the place for Thyrogen testing in
9 the follow-up of patients with well differentiated
10 thyroid cancer.

11 Please don't feel the need to respond to
12 each one of these points, because much of this has
13 already been stated; but if there is something about
14 any of them that you wish to place into the record, I
15 invite you now to do it. Let's begin with Dr.
16 Braunstein.

17 DR. BRAUNSTEIN: I have a few comments, in
18 addition to the points that you asked.

19 First of all, I want to congratulate both
20 Genzyme and the FDA for wonderful presentations, and
21 the documents that they sent ahead of time were
22 excellent, and I think both groups have done their job

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1 very well.

2 I, for one, appreciate that, and I think
3 that this is the type of session that is
4 extraordinarily useful, because you have one -- you
5 had the data presented by the company. You have a
6 very critical analysis by the FDA, and then certainly
7 we have the panel who are trying to weigh the evidence
8 on both sides and come up with some reasonable
9 conclusions. So I think this has been a wonderful
10 session.

11 First of all, I would say that in my own
12 experience with dealing with a large number of thyroid
13 cancer patients who go through withdrawal protocol,
14 these patients are uniformly miserable, maybe not the
15 first time around when they have enough thyroid
16 remnant to provide enough thyroxine to keep them
17 feeling relatively well, but certainly after that
18 these patients are miserable.

19 What Mr. Smith said this morning, I know
20 a lot of my patients would vouch for. So anything
21 that we can do to prevent that misery would be great.

22 Also, many of my patients do not want to

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1 go through withdrawal, and are willing to, as Dr.
2 Mazzaferri said, nickel and dime you to prolong the
3 time when they have to go off.

4 So many patients are not getting follow-up
5 according to our established protocols in the
6 established time period, because of lifestyle -- you
7 know, the need to really take virtually six weeks to
8 two months out of their lives in order to go through
9 this before they can function again at a 100 percent
10 level.

11 I think the Thyrogen, in addition to
12 avoiding the hypothyroidism, does have an additional
13 advantage in that potentially one can avoid the
14 stunning effect for subsequent treatment dose.

15 That is, if a patient gets a scan on
16 Thyrogen and it's positive, one could wait for a while
17 before withdrawing them to get through the radiation
18 thyroiditis that occurs in some individuals, and then
19 withdraw them and treat them, and potentially get more
20 radioactive iodine into their lesion.

21 I think that the data that has been
22 presented convinces me that, although Thyrogen

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1 stimulation, at least according to the present
2 protocol, the two-day protocol or the three-day
3 protocol that was used, is not as good, not as
4 sensitive as the withdrawal protocol.

5 It does provide the clinicians with
6 sufficient information to treat the high risk patient
7 or to make a judgment as to which of the high risk
8 patients or which of the patients should get
9 subsequent either withdrawal and scan or withdrawal
10 and treatment.

11 So from that standpoint, I think this is
12 very useful. I think that what we would see is, once
13 this material is on the market, it will go the way of
14 other materials that have been released -- for
15 instance, ceredase which, certainly, Genzyme knows
16 about quite well -- that the protocol that was used to
17 approve ceredase subsequently has been changed after
18 it's been on the market, because clinicians found that
19 one could get away with lower doses and a lower
20 frequency of administration.

21 Similarly with growth hormone. The dosage
22 regiment and the type of treatment regiment has

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1 changed since release of these drugs, and the same
2 thing will happen here, and there are ways of
3 potentially improving the retention of radioactive
4 iodine, such as giving lithium or other agents to
5 euthyroid individuals after they've been on a iodide
6 deficient diet.

7 So having said all that, I do think that
8 this is an agent that will be quite useful. Also, the
9 individuals that need to be educated about the use of
10 this agent really is actually a rather small group of
11 individuals, because we're talking about
12 endocrinologists and nuclear medicine physicians, who
13 take care of the majority of these patients.

14 So we aren't talking about trying to
15 educate a large number of general practitioners,
16 obstetrician/gynecologists, etcetera. We're really
17 talking about a relatively small group of individuals
18 who already treat these patients.

19 So based on that, I think that this is a
20 very useful drug. I do think that -- I don't think
21 that I would use this for following up low risk
22 patients who are already on thyroid suppressive

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1 therapy, who have undetectable Tg.

2 I wouldn't use this to try to stimulate
3 the Tg on a repeated basis, because I follow the Tg
4 relatively frequently in those patients anyway, but I
5 would use it periodically in those patients because of
6 late follow-ups.

7 I do think that Thyrogen, when it's
8 administered, should be -- Tg should be measured
9 afterwards, and a scan should be done. If the Tg is
10 greater than 2 in a very sensitive assay and the scan
11 is negative, then I would withdraw that patient and
12 then scan the patient afterwards, and then decide on
13 treating the patient and getting a Tg, obviously,
14 after withdrawal.

15 If the Tg is greater than 2 and the scan
16 is positive or if the scan was positive and even if
17 the Tg was less than 2, I would go ahead and just
18 withdraw that patient and treat the patient.

19 So I think that there is a place for
20 Thyrogen testing. There is a place, certainly, that
21 endocrinologists and nuclear medicine physicians will
22 be educated about, and the indications and the way of

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1 doing this will probably change over time; but I, for
2 one, am in favor of having this released.

3 CHAIRMAN MARCUS: Thank you. Dr.
4 Chinchilli.

5 DR. CHINCHILLI: Yeah, I think
6 unconditionally we can't say that the Thyrogen is a
7 substitute for the withdrawal scan or the Tg, but Dr.
8 Orloff, I thought, presented -- before lunch presented
9 something which I think is intriguing and will have
10 some use, and that is as a screen; but I would like to
11 see some of the details talked about that, because,
12 obviously, the studies weren't designed to look into
13 it in that particular mode.

14 So I think there's a place for this
15 somewhere in the market, but I think that it's going
16 to have to be very specifically stated in the label.

17 CHAIRMAN MARCUS: Thank you. Dr. Molitch.

18 DR. MOLITCH: I agree with Dr. Braunstein.
19 I think that I would perhaps not have it quite so
20 specifically stated in the label. I think that
21 clinicians who do this type of treatment are going to
22 use it with their clinical judgment, will not use it

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1 entirely as a substitute for withdrawal but use it as
2 a substitute on selected occasions, perhaps intermix
3 total withdrawal versus this in various years and
4 follow patients over time.

5 I think that sort of the strategies for
6 doing so will evolve with increased experience. I do
7 agree with the FDA that the thyroglobulin data as such
8 are very a post hoc analysis of the data that's been
9 collected and, as such, is useful to at least start
10 from.

11 It does indeed need to be validated by
12 subsequent studies, but in the meantime the guidelines
13 that they have suggested can be used as a starting
14 point for further studies and for clinicians as we
15 await validation of that data. I don't think it makes
16 that stuff invalid. I just think it needs to be
17 validated better.

18 So I think that it may be very useful to
19 patients, in addition to the listings that Dr. Orloff
20 had, in a variety of circumstances that I think need
21 to be individually decided upon.

22 CHAIRMAN MARCUS: Thank you. Dr. Simpson.

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1 DR. SIMPSON: I think that it's pretty
2 clear that the Phase III studies really don't address
3 the issues of whether the scan with Thyrogen is going
4 to be useful as an alternative diagnostic agent. In
5 fact, it's not clear that the scans would be useful at
6 all in connection with Thyrogen.

7 As far as for screening, I think I agree
8 totally with Dr. Chinchilli, that needs to be looked
9 at further, because there was -- there is a mention in
10 part 2 about the false negative rate, but if you took
11 a cutoff of, say, 2, then you wouldn't have any false
12 negative rate; but there would be other implications.

13 So I think that that needs looking at
14 further.

15 CHAIRMAN MARCUS: Thank you. Dr.
16 Illingworth.

17 DR. ILLINGWORTH: I endorse Dr.
18 Braunstein's comments about the excellent background
19 information by both the agency and the sponsor.

20 I think, really, assuming it doesn't
21 really deal with thyroid disorders in terms of cancer,
22 but it strikes me that this is -- It allows

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1 specialists potentially another approach for
2 evaluation and assessment.

3 One question I have, and perhaps the
4 sponsor would know this, is the big difference strikes
5 me as being the longer exposure to a high TSH when you
6 withdraw thyroxine versus giving Thyrogen. Is there
7 any data on the time course of response in thyrogen --
8 in thyroglobulin in response to increase in levels of
9 TSH? Is there any data, for instance, that would say,
10 if you give Thyrogen once a week for a month, do you
11 get similar scans or similar thyroglobulin results as
12 if you give it just for two days?

13 CHAIRMAN MARCUS: Let's find out. Dr.
14 Meeker.

15 DR. MEEKER: We don't have the data you
16 specifically ask for in terms of looking at
17 thyroglobulin levels with differing doses. What we do
18 -- I mean, it's a different question. We know how
19 long the TSH was elevated or the duration of TSH
20 elevation in the patients who were withdrawn. That's
21 useful. For the patients who were on T-3 it was
22 approximately 18 to 19 days, and for patients who were

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1 withdrawn from T-4 it was 31 days.

2 CHAIRMAN MARCUS: Can we address this
3 question from the old bovine TSH literature?

4 DR. MEEKER: No.

5 CHAIRMAN MARCUS: On this point? Okay,
6 Dr. Davidson, you wanted to --

7 DR. DAVIDSON: One question. You know,
8 the patients continue the suppressive therapy. You
9 know, have you done anything where you stop, you know,
10 thyroxine for just a week or a short period of time to
11 see if just stopping the thyroxine will give you
12 better therapy -- better Tg levels?

13 DR. MEEKER: We have not done that, no.

14 DR. DAVIDSON: Thank you.

15 CHAIRMAN MARCUS: Mark, did you have --

16 DR. MOSCICKI: Just to continue with Dr.
17 Meeker's comments, though, I might just suggest that
18 the levels of the three-dose regimen probably cover
19 approximately nine days at levels at 20 or above.
20 That would not be out of the ballpark of what one
21 might suspect with a two-week withdrawal from T-3. It
22 would clearly take a few days to get the TSH level up

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1 to there.

2 So we're not entirely on the ballpark of
3 what might be observed.

4 DR. ILLINGWORTH: Can I just take that one
5 step further. Are there any cell culture models where
6 you could look at the effects of, say, a high TSH
7 inducing thyroglobulin production compared to a high
8 TSH in the presence of thyroxine, because there are
9 two different -- There really are -- The situation is
10 different.

11 Scientifically, this may be something to
12 pursue.

13 DR. MOSCICKI: I am afraid I'm unaware of
14 such a system, but perhaps Dr. Pacini.

15 DR. PACINI: There is no cell culture
16 system in which the cell is able to secrete
17 thyroglobulin at the rates that the human thyroid
18 cells can do. So this model would be very nice, but
19 is not available, not either the FRT cell which are of
20 rats. Also in these cells which are normal thyroid
21 cell rats, cannot do thyroglobulin.

22 CHAIRMAN MARCUS: Dr. Temeck.

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1 DR. TEMECK: Dr. Illingworth, I don't know
2 if this would be helpful at all, but on the three-dose
3 regimen, although there was approximately six to nine
4 days where the TSH was elevated at 20 or above, but it
5 was not a consistent elevation. You see you had these
6 peaks and these valleys, while with withdrawal what
7 was happening is that -- We'll, I'm sorry. Withdrawal,
8 you would expect that it would be a continuous rise.

9 So that -- I don't know if that helps
10 answer the concern that you have.

11 CHAIRMAN MARCUS: Thank you. Roger, is
12 that okay?

13 DR. ILLINGWORTH: Thank you.

14 CHAIRMAN MARCUS: Dr. Sherwin.

15 DR. SHERWIN: Well, I think from the
16 clinical perspective the agent, the recombinant TSH is
17 a useful clinical tool for an experienced clinician
18 managing people with thyroid disease.

19 Now it's not a substitute for withdrawal.
20 That's clear, because it's not as sensitive a test in
21 some specific instances where you have high risk
22 patients; but on balance, I think that one can learn

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1 to use this agent in an appropriate way.

2 I don't think that I agree with what was
3 said before. It's unlikely that the protocol we're
4 using today is the end-all. I can think of many
5 different approaches one could take to optimize, but
6 to limit physicians and their ability to manage their
7 patients with an agent that is a step above everything
8 but withdrawal, I think, would be a mistake.

9 So my own view is that it's a useful
10 clinical tool that is not a substitute, but is a
11 valuable addition, and I think, if I was going to
12 manage patients, for the most part, I would begin to -
13 - It would allow me to reduce the frequency with which
14 I would withdraw patients.

15 I would use this test in between as a way
16 of keeping track of what's going on. I probably
17 wouldn't substitute it totally, but at the same time
18 it would allow me to reduce the frequency, so that I
19 could withdraw patients less frequently. That's the
20 way I would use it.

21 CHAIRMAN MARCUS: Dr. Critchlow.

22 DR. CRITCHLOW: I agree with the FDA in

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1 that one cannot answer the question of what is the
2 true sensitivity and specificity of these tests with
3 the present -- with using Thyrogen with respect to the
4 true disease state. But the issue is, given the
5 representativeness of -- or the assumed
6 representativeness of the study population and the
7 target population, are the figures that we can derive
8 from these tests close enough to what might be
9 considered reality in order for the physician in
10 practice to make reasonably informed decisions as to
11 how they might incorporate this into their repertoire
12 with respect to -- in terms of making informed
13 decisions based upon knowledge of the strengths and
14 limitations of the test or of using this, as well as
15 knowledge of the particular laboratories where the
16 assays might be done or the radiology center.

17 So in that sense, it's going to be
18 incumbent upon Genzyme, I think, in terms of
19 educational efforts in that direction, as well as the
20 FDA in the labeling, but also just the acquisition of
21 experience in practice, that if it's not available,
22 then that experience will not be -- will not come.

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1 CHAIRMAN MARCUS: Dr. Davidson.

2 DR. DAVIDSON: Davidson. You know, I see
3 patients every day, you know, and I have many patients
4 that, you know, we follow for thyroid cancer. I don't
5 know how many of you have seen patients that are
6 hypothyroid for the period of time that we require.

7 That's a lot of suffering. I know that
8 the agent that we're discussing today is not 100
9 percent specific, is not 100 percent sensitive, but is
10 a very good alternative. It's a very good
11 alternative, because we have so many patients that
12 refuse to do what we ask them to do because they did
13 it once, and they don't want to see that again the
14 rest of their lives.

15 I believe that this is an alternative that
16 physicians that practice good medicine can use, can
17 learn and, hopefully, with the help of the FDA, some
18 surveillance after we start using the agent in
19 clinical practice, that we may learn more about Tg,
20 you know.

21 What will be really the Tg value of
22 somebody that has, you know, continuous thyroid

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1 suppression therapy, which is, you know, something we
2 couldn't answer today, you know, because we're not
3 comparing the same type of patients. One is totally
4 suppressed, and one is not totally suppressed.

5 You know, I find that, you know, the agent
6 will be clinically very useful for us.

7 DR. HIRSCH: I agree with what's been
8 said. First of all, let me just say a few things that
9 shape my views at this moment.

10 One is we clearly need a source of TSH
11 that isn't from extracted cows or human pituitary. So
12 we've got one now. This is a -- It's going to be a
13 very helpful kind of thing to have.

14 Now the withdrawal thing is -- People sort
15 of vary on how bad it is, but it is a kind of --
16 Fundamentally, it's a primitive way of doing this
17 thing. It's the best we have right now, but it is a
18 kind of primitive approach, like bloodletting or
19 something. It's not a very appetizing way to treat
20 human beings, and I think we can do better than that.

21 The question is what do we have to learn?
22 The other thing that worries me is prolonged TSH

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1 stimulation in withdrawal. Maybe that's not so good
2 for neoplasia either.

3 I have no proof of that, but I don't think
4 that's a happy thing, to take someone who has had a
5 thyroid malignancy and say, let's give them a four to
6 six-week jolt of TSH. We ought to be able to do
7 better in that sense as well.

8 So I'm left, however, with the fact that
9 the particular protocol that was tested is not exactly
10 as good at this moment in some respects as the TSH
11 elevation by withdrawal. I accept the statistical
12 issues, although it's not bad. I mean, the 2 nanogram
13 level plus the scan is awfully damn good, it seems to
14 me. It's a hell of a lot better than many other
15 clinical tests we have around.

16 Be that as it may, it may not be quite as
17 exact or perfect as the withdrawal thing. So the
18 question we have now is you got to do some more
19 testing of this thing and arrive at absolutely the
20 optimal way of doing it.

21 So who is going to do it? So the issue is
22 do you get it out to the endocrine public and people

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1 who can do a wide set of studies with this and evolve
2 a better form of treatment, or do we stop everything
3 now for another specific specified kind of thing, of
4 four days at this level or five at that or something?

5 I think the latter is kind of silly. I
6 think at this point it's a good thing to -- In my
7 view, we've done enough to get this thing out. Let
8 people start using it creatively.

9 Now that means, however, that the
10 particular information we give to clinicians has to be
11 very carefully crafted by FDA to let them know exactly
12 what is known and what the good and bad side of this
13 thing is at the present time.

14 CHAIRMAN MARCUS: Dr. Burman.

15 DR. BURMAN: Thank you. I also wanted to
16 take this opportunity to make my appreciation known to
17 both sides, Genzyme and the FDA, for really a
18 thoughtful, contemplative approach, and it just really
19 shaped my view as well.

20 To be succinct, I think that the drug
21 medication ought to be approved, that I think the
22 studies are sufficient to show the most important

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1 aspect, as far as I'm concerned, which is safety.
2 There is really very little evidence that it has any
3 adverse effect.

4 I think that, when you combine the
5 withdrawal scan plus a thyroglobulin level at a level
6 of 2 as a marker, you picked up over 95, and I think
7 maybe even more than that, percentage of patients who
8 had disease, and that's very impressive to me.

9 I think this will allow the physician and
10 the patient flexibility, as Dr. Mazzaferri said, to
11 use this in their armamentarium and to use their best
12 clinical judgment to treat the patient most
13 appropriately.

14 So I'm certainly in favor of it being
15 approved. I would echo the sentiment that it would be
16 important to have post marketing studies, especially
17 looking at -- of interest, thyroglobulin antibodies to
18 make sure they are not there in these longer term
19 studies, and to better define the exact circumstances
20 when we might want to use this medication.

21 One issue that hasn't been stressed enough
22 perhaps is that thyroglobulin is used, I think -- At

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1 least in my practice, 80-90 percent of the
2 thyroglobulins I measure are while somebody is on
3 thyroid medication, and it's only, let's say, two or
4 three times in the first five years after surgery that
5 a patient is off thyroid medication.

6 So that a question that hasn't been raised
7 sufficiently enough in my mind and needs to be studied
8 a little more is: Every time we're going to measure
9 a thyroglobulin level in someone on thyroid
10 medication, are we going to measure that after TSH or
11 not?

12 I think my view would be we need more
13 information, but probably we're not going to use TSH
14 in that circumstances, but when will we, and what
15 would be the indications?

16 In brief, I wanted to echo the sentiments
17 that I think this is a useful agent, and appreciate
18 the arguments on both sides.

19 CHAIRMAN MARCUS: Thank you. I think I
20 agree with virtually --

21 DR. ORLOFF: Could I ask a question?
22 Could one of the thyroid cancer experts tell me, how

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1 frequently do you measure those thyroglobulin levels?
2 Every month? Every six months?

3 DR. BURMAN: I think everybody -- This is
4 my view, if you want me to answer for the moment. I
5 think everybody measures it differently, but in all
6 patients, regardless of the risk, outside of the very
7 small percentage of people that have a microscopic
8 papillary that we might not treat very aggressively at
9 all or use diagnostic procedures, in the vast majority
10 of patients with thyroid cancer, which means papillary
11 cancer, more than one to 1.5 centimeters papillary,
12 and all follicular cancers, we measure thyroglobulins
13 frequently.

14 I would say, in our offices we measure
15 them every three to four months for the first five
16 years, although others might do it every six months;
17 and if it's an aggressive tumor with a lot of poor
18 prognostic features at the beginning, we might measure
19 it even more frequently, especially for the first year
20 or two.

21 CHAIRMAN MARCUS: That is very helpful.
22 Actually, I would like to just ask a question in

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1 follow-up to Dr. Orloff's question.

2 We've heard many people talking about low
3 risk and high risk, as though that is an assumed body
4 of knowledge. Would you define for me what you would
5 call a low risk as opposed to a high risk patient, Dr.
6 Burman?

7 DR. BURMAN: Sure. A lot of my views on
8 this were formed by Dr. Mazzaferri's studies. So if
9 he wanted to add anything to correct anything or
10 modify it, I'd appreciate it.

11 We divide them up into several
12 characteristics, and they are more qualitative rather
13 than quantitative. But they include gender, history
14 of radiation, size of the original tumor, whether
15 there's vascular invasion in the tumor or whether
16 there's vascular invasion outside of the tumor, is the
17 tumor outside of the capsule invading into surrounding
18 tissues, and are lymph nodes present.

19 You put all of those together, and there
20 are various ways that various clinics have tried to --
21 reports have tried to put that and make it more
22 quantitative, but let me, if I can, just for

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1 illustrative purposes, very succinctly give two case
2 reports.

3 If it was, on one hand, a one centimeter,
4 well circumscribed papillary carcinoma that there was
5 no evidence of invasion outside the tumor and no other
6 poor prognostic factors, and it was completely excised
7 apparently at the time of a near-total thyroidectomy,
8 that patient would be a very low risk. I think some
9 of us may or may not even give radioactive iodine, and
10 we would measure thyroglobulin infrequently, maybe
11 once every six months or something like that.

12 On the other hand, if it's a 6 centimeter
13 papillary carcinoma with vascular invasion invading
14 into the surrounding tissue with lymph nodes and
15 hoarseness because of nerve involvement, we would be
16 much assiduous in trying to pick up tumor earlier.

17 CHAIRMAN MARCUS: Is that what everybody
18 who has talked about risk today can live with? Is
19 that pretty much what we've all been hearing? Good.

20 DR. SHERWIN: Does histological type have
21 anything to do with it?

22 CHAIRMAN MARCUS: Sorry. Dr. Robbins.

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1 Microphone, please.

2 DR. ROBBINS: I just want to add one
3 important factor, which I think Ken left out, is the
4 age at the onset of the disease, one of the most
5 important.

6 CHAIRMAN MARCUS: Thank you, Dr. Robbins.
7 Dr. Sherwin, and then Dr. Braunstein.

8 DR. SHERWIN: I was just saying, it's also
9 the type of tumor.

10 CHAIRMAN MARCUS: Histological type, yes.
11 Follicular as opposed to papillar.

12 DR. SHERWIN: I think so.

13 CHAIRMAN MARCUS: Okay.

14 DR. BURMAN: To be complete, there might
15 be some disagreement on that. Follicular used to be
16 taught, at least in my view, that it was more
17 aggressive, but papillary can be just as aggressive,
18 depending on the prognostic factors at the beginning.

19 DR. SHERWIN: Sure.

20 CHAIRMAN MARCUS: Well, the nice thing
21 about going last is that I don't really have to
22 stretch too far to find new things to be said, because

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1 there's nothing new to say.

2 I agree fundamentally with everybody, but
3 I do not want to let pass the somewhat disparate view
4 that Dr. Simpson and some of the statistical opinions
5 have been. I think it is true that you cannot use the
6 post hoc analysis without -- as a representation of
7 truth without independently recruiting prospectively
8 another population to test it.

9 I would ask that a surveillance study, a
10 Phase IV study be done to test the concept that the
11 scan plus a thyroglobulin level of 2 actually is as
12 predictive as the post hoc analysis would have
13 suggested.

14 I think we can now go on to -- Is there a
15 question?

16 DR. MOSCICKI: Dr. Marcus, could I just
17 make one comment on that?

18 CHAIRMAN MARCUS: Sure. Certainly.

19 DR. MOSCICKI: I would just like to remind
20 the panel that, in fact, the cutoff levels of 2, 5,
21 and 10 for analysis were, in fact, prospectively
22 defined, both for use in combination with the whole

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1 body scan, as well as for thyroglobulin alone.

2 The analyses are not based only on a post
3 hoc analysis. That was an additional analysis
4 requested by the investigators.

5 CHAIRMAN MARCUS: Dr. Simpson?

6 DR. SIMPSON: I think that there is -- For
7 me, there's a problem with this, in the sense none of
8 the -- neither of the studies were done in a way
9 where, if you're going to use Thyrogen in clinical
10 practice, you're going to use it.

11 In other words, from these studies we
12 still don't know how it would work in clinical
13 practice. So there is a need for another study, at
14 least one more. In fact, by the sound of it, it
15 sounded as if many people will be doing many studies.

16 CHAIRMAN MARCUS: I hope so. I hope so.

17 Okay. We are now ready to address the
18 questions, and I would like to go from most specific
19 to general. So the sequence will not necessarily be
20 what you have.

21 The first question I would like to pose is
22 the one that Dr. Orloff added to the list, and so you

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1 haven't seen it. I will read it to you right now.

2 Taking into account the risks and benefits
3 associated with its revised proposed use, should
4 Thyrogen be approved in patients who otherwise would
5 be followed with thyroglobulins alone while on
6 suppressive thyroid hormone therapy?

7 Should I repeat that? Taking into
8 account, etcetera, etcetera...should Thyrogen be
9 approved for use in patients who would otherwise be
10 followed with thyroglobulin concentrations alone while
11 taking suppressive thyroid hormone replacement?

12 We will begin with Dr. Burman and proceed
13 around the table. Would you refresh me. Who is not
14 voting? Everybody is voting. Okay. Dr. Burman.

15 DR. BURMAN: Sure. I tend to think and
16 lean toward yes. To just reiterate to make sure I
17 understand it: Should thyroglobulin be approved for
18 use in conducting thyroid scanning of thyroglobulin
19 testing in the follow-up of patients who are either
20 unable to mount an adequate --

21 CHAIRMAN MARCUS: No, no. No. No.

22 DR. BURMAN: I was reading one.

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1 CHAIRMAN MARCUS: Yes. People who are --
2 People who would otherwise be followed only with a
3 measurement of thyroglobulin, while taking thyroid
4 hormone replacement.

5 DR. BURMAN: That's, obviously, a harder
6 question. I would -- and I don't know whether the
7 answer has to be totally yes or no or it could be in
8 the middle with some caveats. I think I would be in
9 favor that, with some caveats, if the patient refused
10 or if there were other extenuating circumstances, that
11 perhaps in my mind it should not be a total
12 alternative to withdrawal scanning.

13 CHAIRMAN MARCUS: We're not asking whether
14 -- You have a patient who has, for one reason or
15 another, or a physician, for one reason or another,
16 who has made a decision that he's just going to follow
17 that patient with thyroglobulin while staying on
18 thyroid hormone.

19 DR. BURMAN: He would never give them
20 anything else?

21 CHAIRMAN MARCUS: Never getting anything
22 else. Should Thyrogen be used in that?

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1 DR. BURMAN: Thank you for clarifying
2 that.

3 DR. HIRSCH: To what end? I mean, after
4 Thyrogen you would then follow the Thyrogen and scan
5 or not?

6 DR. SHERWIN: No. Some people have low
7 risk.

8 DR. HIRSCH: I mean, but what's the
9 question? The question is what -- You didn't --

10 DR. BRAUNSTEIN: Just measuring the Tg
11 before and after suppression.

12 DR. HIRSCH: I understand that, but I mean
13 one way of saying it is that's a wonderful thing, but
14 they also ought to be scanned while you're giving them
15 this EG. Is that out of the question?

16 CHAIRMAN MARCUS: No. Thyrogen scan.
17 That's part of the question.

18 DR. BURMAN: And people with physicians
19 who would not recommend usually anything except
20 thyroglobulin in that circumstance.

21 CHAIRMAN MARCUS: Right.

22 DR. BURMAN: If it was done with scan and

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1 thyroglobulin level, I think that's a reasonable
2 approach.

3 CHAIRMAN MARCUS: Your answer is yes?

4 DR. BURMAN: Yes.

5 CHAIRMAN MARCUS: Thank you. Dr. Hirsch?

6 DR. HIRSCH: Exactly the same, with the
7 scan.

8 CHAIRMAN MARCUS: Yes.

9 DR. HIRSCH: But I assume that what they
10 said was --

11 CHAIRMAN MARCUS: Thyrogen plus scan.

12 DR. HIRSCH: Well, ask Dr. Orloff. What
13 did you mean, Dr. Orloff? With scan or without?

14 DR. ORLOFF: You got it right. I was
15 expecting comments on the scan, but the idea would be
16 again, if thyroglobulin testing on suppressive therapy
17 is in essence the sort of usual easy follow-up of
18 patients, do we know enough about this to say use it
19 sometimes or all of the time in that setting, in
20 patients whom you would otherwise only be doing that?

21 DR. HIRSCH: Well, I'm saying yes, but
22 with scan, following Tg plus scan.

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1 DR. ORLOFF: Right.

2 CHAIRMAN MARCUS: Yes. Dr. Davidson.

3 DR. DAVIDSON: Yes.

4 CHAIRMAN MARCUS: Thank you. Dr.

5 Critchlow.

6 DR. CRITCHLOW: Yes.

7 CHAIRMAN MARCUS: Dr. Sherwin.

8 DR. SHERWIN: Yes.

9 CHAIRMAN MARCUS: Dr. Illingworth?

10 DR. ILLINGWORTH: Yes, but with the caveat
11 that there probably needs to be more seriously looking
12 at the effects of just Thyrogen on thyroglobulin
13 without the scan.

14 DR. HIRSCH: I'm sorry. You said without
15 scan?

16 DR. ILLINGWORTH: There needs to be more
17 data on that.

18 CHAIRMAN MARCUS: On the Thyrogen level.
19 Sure. Dr. Simpson?

20 DR. SIMPSON: Yes.

21 CHAIRMAN MARCUS: Dr. Molitch.

22 DR. MOLITCH: Yes.

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1 DR. CHINCHILLI: Yes.

2 DR. BRAUNSTEIN: Yes, with scan.

3 CHAIRMAN MARCUS: Yes. Terrific. Okay.

4 Next question you have in front of you.

5 We'll do question 2 next.

6 Taking into account the risks -- I'm
7 taking the one that's labeled 2. We're going upwards
8 from specific to more general.

9 Taking into account the risks and benefits
10 associated with its revised proposed use, should
11 Thyrogen be approved for use in conducting thyroid
12 scanning and thyroglobulin testing in the follow-up of
13 patients with well differentiated thyroid cancer who
14 are either unable to mount an adequate endogenous TSH
15 response after withdrawal or for whom withdrawal is
16 medically contra-indicated?

17 We'll begin with Dr. Braunstein.

18 DR. BRAUNSTEIN: Yes, but that wouldn't be
19 my only indication.

20 DR. CHINCHILLI: Yes, I agree with that.

21 DR. MOLITCH: Yes.

22 DR. SIMPSON: Yes.

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1 DR. ILLINGWORTH: Yes.

2 DR. SHERWIN; Yes.

3 DR. CRITCHLOW: Yes.

4 DR. DAVIDSON: Yes.

5 DR. HIRSCH: Yes.

6 DR. BURMAN: Yes.

7 CHAIRMAN MARCUS: Dr. New's answer is yes,
8 and I say yes. Okay.

9 Third: Taking into account the risks and
10 benefits associated with its revised proposed use,
11 should Thyrogen be approved as a definitive test for
12 use in conducting thyroid scanning and thyroglobulin
13 testing in the follow-up of patients with well
14 differentiated thyroid cancer as a general substitute
15 for withdrawal?

16 Dr. Burman.

17 DR. BURMAN: No.

18 CHAIRMAN MARCUS: I have added those words
19 at the request of FDA, "as the definitive test."

20 DR. MOLITCH: Where is the word
21 definitive?

22 CHAIRMAN MARCUS: I just added them a

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1 short time ago at request of the agency. I'm keeping
2 you on your toes.

3 DR. MOLITCH: Are we going to have yet a
4 fourth question?

5 CHAIRMAN MARCUS: No.

6 DR. MOLITCH: For selected patients or a
7 little bit more qualifying -- Here you're taking a
8 total substitution, but I think many of us would agree
9 that something in between those would be appropriate.

10 CHAIRMAN MARCUS: The Chair will entertain
11 a motion to have a fourth question. Let's vote on
12 this one first, and then you can formulate that.

13 DR. MOLITCH: Thank you.

14 CHAIRMAN MARCUS: Or you can make
15 comments. I mean, I think these are advisory
16 opinions, and the agency will be delighted to hear you
17 explicate your vote. So let's begin with Dr. Burman.

18 DR. BURMAN: Thank you. I think, as
19 written, my answer would be no; but with the
20 precautions as perhaps an adjunct in the diagnosis of
21 thyroid cancer is a fourth question or modification
22 that I would be in favor of.

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1 CHAIRMAN MARCUS: Thank you. Dr. Hirsch.

2 DR. HIRSCH: I say no, too, but I'm not
3 sure I know what "a definitive test" is.

4 CHAIRMAN MARCUS: The gold standard.

5 DR. HIRSCH: Well, come on. No. The
6 answer is no.

7 DR. DAVIDSON: The way the question is
8 posed, no; but, you know, I agree with Dr. Molitch.
9 We need to get another question.

10 DR. CRITCHLOW: No.

11 DR. SHERWIN: No, but with all the
12 caveats, obviously, this is an extreme question.

13 DR. ILLINGWORTH: The definitive test, no.

14 DR. SIMPSON: No.

15 DR. MOLITCH: No, and since nobody else
16 has been commenting, I will reserve my right to add a
17 fourth.

18 DR. CHINCHILLI: No.

19 DR. BRAUNSTEIN: No.

20 CHAIRMAN MARCUS: Dr. New actually didn't
21 have a chance to respond to the specific words. All
22 right.

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1 Dr. Molitch, would you like to -- and I
2 say no also.

3 DR. MOLITCH: I think we could add a
4 fourth question with the preamble of the first part of
5 all these questions, and then I guess in the follow-up
6 of patients with well differentiated thyroid cancer,
7 or selected well differentiated thyroid cancer as a
8 substitute for withdrawal, depending upon clinical
9 circumstances. I'd leave it as vague as that.

10 CHAIRMAN MARCUS: Okay. Does everybody
11 understand the question?

12 DR. HIRSCH: If you don't mind my making
13 suggestions, keep it exactly the way number 1 was
14 here, but take the word general out. I hate those
15 words like that. Definitive, general don't mean
16 anything.

17 DR. DAVIDSON: Can I make another comment?
18 Instead of -- substitute alternative.

19 CHAIRMAN MARCUS: Let's vote on that,
20 beginning with Dr. Braunstein.

21 DR. MOLITCH: Well, let's get the
22 question.

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1 CHAIRMAN MARCUS: Read it again. Let's
2 see.

3 DR. MOLITCH: How about, "the follow-up of
4 patients with well differentiated thyroid cancer as an
5 alternative for withdrawal -- to withdrawal?"

6 DR. BRAUNSTEIN: Yes.

7 DR. CHINCHILLI: Are you going to specify
8 the selection criteria or -- You're going to leave it
9 general.

10 DR. MOLITCH: Leave it up to clinical
11 discretion.

12 DR. CHINCHILLI: Well, being a
13 statistician, I have to vote no.

14 DR. MOLITCH: Yes.

15 DR. SIMPSON: I am a statistician, too.
16 No.

17 CHAIRMAN MARCUS: Okay. Enough said.
18 Roger.

19 DR. ILLINGWORTH: Given the fact that this
20 is going to be used by specialists, not family
21 practitioners and people with no specialized
22 knowledge, I vote yes.

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1 DR. SHERWIN: I would say yes, too, being
2 a physician.

3 DR. CRITCHLOW: I don't know how to answer
4 this. To the extent that the trials were conducted to
5 specifically answer that, I'd say no, but -- I'll
6 leave it at that.

7 DR. DAVIDSON: Yes.

8 DR. HIRSCH: Yes.

9 DR. BURMAN: I am going to vote yes, but
10 with an asterisk. The asterisk is, if I can mention
11 it, that the word alternative is a bad word.

12 DR. HIRSCH: I don't like any adjective
13 there. There's no need for an adjective.

14 DR. BURMAN: Because an alternative means
15 -- implies you're going to do one and not the other.

16 DR. SHERWIN: That's why I was laboring,
17 actually.

18 DR. BURMAN: Adjunct or --

19 CHAIRMAN MARCUS: You propose adjunct.
20 Okay. Being a country practitioner, I'll vote yes as
21 well.

22 DR. SHERWIN: Now do we all agree what we

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1 voted on? Could you be sure that we have the question
2 so that it's final, because we changed the question.

3 CHAIRMAN MARCUS: Dr. Molitch will read
4 the question.

5 DR. ORLOFF: Excuse me. The FDA has the
6 idea.

7 CHAIRMAN MARCUS: You have the idea?
8 Okay, good.

9 Then that concludes today's business. I
10 think we have set a new land speed record for an FDA
11 hearing. I congratulate both the sponsor and the
12 agency.

13 Meeting is adjourned.

14 (Whereupon, the foregoing matter went off
15 the record at 2:01 p.m)

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CERTIFICATE

This is to certify that the foregoing transcript in the
matter of: 70TH MEETING

Before: ENDOCRINOLOGIC AND METABOLIC DRUGS
 ADVISORY COMMITTEE

Date: MAY 15, 1998

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.

John Mangoren