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8 PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

9 ADVISORY COMMITTEE

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11

12 Wednesday, November 13, 2013

13 8:00 a.m. to 5:00 p.m.

14

15

16

17 Sheraton Silver Spring Hotel

18 Cypress Ballroom

19 8777 Georgia Avenue

20 Silver Spring, Maryland

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22

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4 Division of Advisory Committee &

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6 Office of Executive Programs, CDER, FDA

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21 Clinical Reviewer, DNP
22 ODE-I, OND CDER, FDA

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

2 **Call to Order**

3 **Introduction of Committee**

4 DR. FOUNTAIN: Good morning and welcome.
5 We'll begin the meeting. I'd first like to remind
6 everyone to please silence your cell phones,
7 smartphones, and any other device if you've not
8 already done so. I'd like to identify the FDA
9 press contact, Stephen King. If you are present,
10 would you please stand?
11 Not here. Okay. All right, behind the
12 pillar in the back.
13 DR. FOUNTAIN: I'd like to go around the
14 room and have everyone introduce themselves, so
15 I'll know who we are and the context for things.
16 Why don't we start on this end of the room with Dr.
17 Kramer?
18 DR. KRAMER: Lynn Kramer. I'm a
19 neurologist, and I'm the industry representative on
20 the committee.
21 DR. WOODS: Good morning. My name is Mark
22 Woods. I'm the clinical coordinator and residency

1 program director in the pharmacy department at
2 Saint Luke's Hospital in Kansas City, Missouri.
3 MS. SITCOV: Good morning. My name is
4 Cynthia Sitcov. I'm the patient representative. I
5 was diagnosed with MS 40 years ago, in the dark
6 ages as I like to say, when there were no
7 treatments. I personally have experienced probably
8 six or seven severe flare-ups during the course of
9 this illness and have benefitted from
10 disease-modifying treatment.
11 DR. HOFFMANN: I'm Richard Hoffmann, and I'm
12 a pharmacist and medical writer, and I'm the
13 consumer representative on this committee.
14 DR. WALLIN: My name is Mitch Wallin. I'm a
15 neurologist based at the VA MS Center and also on
16 staff at Georgetown and the University of Maryland.
17 DR. LU: I'm Ying Lu, a biostatistician.
18 I'm a professor of biostatistics at Stanford
19 University Medical Center School of Medicine and
20 also a director at the VA Cooperative Studies
21 Program, Palo Alto Coordinating Center.
22 DR. KRYSCIO: Dick Kryscio, University of

1 Kentucky. I'm a biostatistician, chair of
2 biostatistics, and I do a lot of work in
3 neurodegenerative diseases.
4 DR. BAGIELLA: Emilia Bagiella. I'm a
5 professor of biostatistics at Mount Sinai School of
6 Medicine.
7 DR. KLASSEN: I'm David Klassen. I'm a
8 nephrologist at University of Maryland, and
9 primarily a transplant nephrologist.
10 DR. SMITH: I'm Roy Smith. I'm a professor
11 of medicine, and I do benign hematology and
12 specialize in coagulation disorders.
13 DR. ASCENSAO: Good morning. My name is
14 Joao Ascensao. I am a professor of medicine and
15 immunology at George Washington University, and I
16 practice at the DC VA Medical Center.
17 DR. BLUMENTHAL: David Blumenthal,
18 rheumatologist at the Cleveland VA Medical Center
19 in Case Western Reserve University.
20 DR. FOUNTAIN: Nathan Fountain. I'm a
21 neurologist at the University of Virginia and chair
22 of the committee.

1 LCDR: Good morning. I'm Glendolynn
2 Johnson. I'm the DFO for the Peripheral and
3 Central Nervous System Drugs Advisory Committee.
4 DR. ROSENBERG: I'm Paul Rosenberg. I'm a
5 geriatric psychiatrist at Johns Hopkins Bayview
6 Medical Center and an Alzheimer's trialist.
7 DR. ALEXANDER: Good morning. Caleb
8 Alexander. I'm an associate professor of
9 epidemiology and a practicing general internist at
10 Johns Hopkins. And I co-direct the Center for Drug
11 Safety and Effectiveness there.
12 DR. CLANCY: I'm Robert Clancy. I'm a
13 professor of neurology and pediatrics at the
14 University of Pennsylvania and The Children's
15 Hospital of Philadelphia.
16 DR. ZIVIN: I'm Justin Zivin. I'm professor
17 emeritus at the University of California, San
18 Diego, in the neurosciences department.
19 DR. YEH: I'm Ann Yeh. I'm associate
20 professor of pediatrics in neurology at University
21 of Toronto, and I direct the pediatric MS center at
22 Hospital for Sick Children in Toronto.

1 DR. MIELKE: I'm Michelle Mielke, associate
2 professor of epidemiology and neurology at the Mayo
3 Clinic.
4 DR. MARLER: I'm John Marler. I'm a
5 clinical reviewer at the Division of Neurology at
6 FDA.
7 DR. MENTARI: I'm Evelyn Mentari. I'm
8 safety reviewer in the Division of Neurology at
9 FDA.
10 DR. DUNN: My name is Billy Dunn. I'm the
11 acting deputy director, Division of Neurology
12 Products.
13 DR. BASTINGS: Eric Bastings, acting
14 director of the Division of Neurology Products.
15 DR. UNGER: I'm Ellis Unger. I'm director
16 of Office of Drug Evaluation I at Office of New
17 Drugs, FDA.
18 DR. FOUNTAIN: Thank you.
19 For topics such as those being discussed at
20 today's meeting, there are often a variety of
21 opinions, some of which are quite strongly held.
22 Our goal is that today's meeting will be a fair and

1 open forum for discussion of these issues, and that
2 individuals can express their views without
3 interruption. Thus, as a gentle reminder,
4 individuals will be allowed to speak into the
5 record only if recognized by the chairperson, by
6 me. We look forward to a productive meeting.
7 In the spirit of the Federal Advisory
8 Committee Act and the Government in the Sunshine
9 Act, we ask that the advisory committee members
10 take care that their conversations about the topic
11 at hand take place in the open forum of the
12 meeting.
13 We are aware that members of the media are
14 anxious to speak with the FDA about these
15 proceedings. However, FDA will refrain from
16 discussing the details of this meeting with the
17 media until its conclusion. Also, the committee is
18 reminded to please refrain from discussing the
19 meeting topic during breaks or lunch. Thank you.
20 Now, I'll pass it to Lieutenant Commander
21 Glendolynn Johnson, who will read the Conflict of
22 Interest Statement.

1 **Conflict of Interest Statement**

2 LCDR JOHNSON: The Food and Drug
3 Administration is convening today's meeting of the
4 Advisory Committee for the Peripheral and Central
5 Nervous System Drugs under the authority of the
6 Federal Advisory Committee Act of 1972. With the
7 exception of the industry representative, all
8 members and temporary voting members of the
9 committee are special government employees or
10 regular federal employees from other agencies and
11 are subject to federal conflict of interest laws
12 and regulations.

13 The following information on the status of
14 this committee's compliance with federal ethics and
15 conflict of interest laws covered by, but not
16 limited to, those found at 18 USC Section 208 is
17 being provided to participants in today's meeting
18 and to the public.

19 FDA has determined that members and
20 temporary voting members of this committee are in
21 compliance with federal ethics and conflict of
22 interest laws. Under 18 USC Section 208, Congress

1 has authorized FDA to grant waivers to special
2 government employees and regular federal employees
3 who have potential financial conflicts of interest
4 when it is determined that the agency's need for a
5 particular individual's services outweighs his or
6 her potential financial conflict of interest.
7 Related to the discussion of today's
8 meeting, members and temporary voting members of
9 this committee have been screened for potential
10 financial conflicts of interest of their own, as
11 well as those imputed to them, including those of
12 their spouses or minor children and, for purposes
13 of 18 USC Section 208, their employers. These
14 interests may include investments, consulting,
15 expert witness testimony, contracts, grants,
16 CRADAs, teaching, speaking, writing, patents and
17 royalties, and primary employment.
18 Today the committee will discuss a
19 supplemental biologics license application 103948-
20 5139 for alemtuzumab injection, proposed trade name
21 Lemtrada, submitted by Genzyme Corporation, a
22 Sanofi company. The proposed indication is for the

1 treatment of patients with relapsing forms of
2 multiple sclerosis to slow or reverse the
3 accumulation of physical disability and reduce the
4 frequency of clinical exacerbations.
5 This is a particular matters meeting during
6 which specific matters related to Genzyme's
7 alemtuzumab will be discussed. Based on the agenda
8 for today's meeting and all financial interest
9 reported by the committee members and temporary
10 voting members, no conflict of interest waivers
11 have been issued in connection with this meeting.
12 To ensure transparency, we encourage all standing
13 committee members and temporary voting members to
14 disclose any public statements that they have made
15 concerning the product at issue.
16 With respect to FDA's invited industry
17 guest, we would like to disclose that Dr. Lynn
18 Kramer is participating in this meeting as a
19 nonvoting industry representative, acting on behalf
20 of regulated industry. Dr. Kramer's role at this
21 meeting is to represent industry in general and not
22 any particular company. Dr. Kramer is employed by

1 Eisai.

2 We would like to remind members and

3 temporary voting members that if the discussion

4 involves any other products or firms not already on

5 the agenda for which an FDA participant has a

6 personal or imputed financial interest, the

7 participants need to exclude themselves from such

8 involvement, and their exclusion will be noted for

9 the record. FDA encourages all participants to

10 advise the committee of any financial relationship

11 that they may have with the firm at issue. Thank

12 you.

13 DR. FOUNTAIN: We'll now proceed with

14 Dr. Bastings' introductory remarks.

15 **FDA Introductory Remarks**

16 DR. BASTINGS: Good morning. I would like

17 to welcome the members of the advisory committee,

18 and in particular, the invited guests who are here

19 today to offer expertise to the committee and to

20 the discussion. I also would like to welcome the

21 members of -- the patients with multiple sclerosis

22 in the room who came here today to participate in

1 the open hearing session. So my goal right now is
2 to give you a brief overview of what we think are
3 the main issues that we would like the committee to
4 discuss.
5 As you know, alemtuzumab is a monoclonal
6 antibody that binds to the surface antigen CD52 and
7 produces a prolonged depletion of T cells and
8 B cells with some pharmacodynamic effect extended
9 up to one year after administration, and in some
10 occasions, beyond. That prolonged duration of
11 action allows for the administration cycle
12 separated by one year, but also means that there is
13 no opportunity to interrupt the drug effect once
14 the drug has been administered beyond skipping the
15 next cycle one year later.
16 In support of the application, Genzyme
17 submitted the result of two phase 3 studies, 323
18 and 324, as well as one supported phase 2 study,
19 223. All of these studies used Rebif as an active
20 control and had relapse rate and six-month
21 sustained disability as primary outcomes.
22 There was extensive discussion between FDA

1 and Genzyme during the development program about
2 the study design. And as early as 2002, FDA
3 expressed concerns about the potential bias that
4 could be introduced by an open-label design and
5 repeated that concept during meetings or
6 communications in 2004 and 2006.
7 In 2007, Genzyme submitted requests for two
8 special protocol assessments for Study 323 and 324.
9 As you know, a special protocol assessment is a
10 mechanism under which a sponsor and FDA can reach a
11 binding agreement on the design and size of pivotal
12 trials intended to support the efficacy in a
13 marketing application. An agreement could not be
14 reached on these special protocol assessments
15 primarily because of the open-label design. In the
16 non-agreement letter, FDA strongly advocated for a
17 double-dummy design and also stated that the
18 acceptability of the open-blind, rater-blinded
19 study would be a matter of review.
20 As you have read in the meeting package, the
21 review team has significant concerns about the
22 safety profile of alemtuzumab. Dr. Mentari, who

1 conducted the safety analysis, will describe to you
2 an array of secondary autoimmune disorders that
3 appear to be triggered by alemtuzumab. Among them,
4 one of the most notable is immune thrombocytopenia
5 that was seen in 2 percent of patients treated with
6 alemtuzumab in pivotal trials.
7 Among the thyroid disorders, Graves' disease
8 was seen in over 3 percent of patients treated with
9 alemtuzumab in controlled trials, with Graves'
10 ophthalmopathy in 1.3 percent. Also, 1.3 percent
11 of patients required thyroidectomy in the
12 controlled trial in patients treated with
13 alemtuzumab. Dr. Mentari will also describe
14 nephropathies and autoimmune hemolytic anemia and
15 pancytopenia that were associated with alemtuzumab,
16 and there were also other autoimmune disorders that
17 will be described.
18 There were other safety issues identified by
19 Dr. Mentari; among them, a signal for pneumonitis,
20 thyroid cancers, infusion reactions, and also
21 increased rates of some infections. And
22 Dr. Mentari emphasizes that these safety concerns

1 cannot be prevented by monitoring or prophylactic
2 measures. And again, the long duration of actions
3 of the drug is also to be taken into consideration.
4 This slide shows the primary efficacy
5 outcome results. It shows that in both studies,
6 alemtuzumab had on face a significantly lower
7 relapse rate than Rebif. And in Study 324, the
8 sustained disability was significantly lower for
9 alemtuzumab, but that was not the case in
10 Study 323. However, Dr. Marler and Dr. Yan, who
11 conducted the review of the efficacy data,
12 questioned the reliability of these estimates
13 because they believe that both studies did not
14 constitute adequate and well-controlled trials.
15 The evidentiary standards for approval
16 described in the Federal Food, Drug, and Cosmetic
17 Act state that a drug product must be found to be
18 effective and safe before it can be approved for
19 marketing. And the Act explicitly gives the legal
20 definition of the evidence necessary for the agency
21 to determine that a drug product has been found to
22 be effective. And in that definition is a

1 requirement that the evidence has to come from
2 adequate and well-controlled investigations.
3 In his presentation, Dr. Marler will
4 describe the characteristics of adequate and
5 well-controlled trials and report how he believes
6 the alemtuzumab studies met these characteristics.
7 And Dr. Yan, who is the statistical reviewer for
8 this application, will also describe why she
9 believes bias may have played a pertinent role in
10 the alemtuzumab trials, and why, in her opinion,
11 effectiveness on disability has not been
12 established. Dr. Yan is requesting the accuracy of
13 the relapse rate estimates because of study bias.
14 So our first question to the committee will
15 be to vote as to whether trials 323 and 324 are
16 adequate and well controlled. I want to emphasize
17 the question is specific to alemtuzumab and
18 specific to the clinical trials that were conducted
19 by the applicant. We are not asking the committee
20 to vote as to whether generically open-label trials
21 can constitute adequate and well-controlled
22 studies.

1 The next question is to ask whether the
2 applicant has provided substantial evidence of
3 effectiveness of alemtuzumab for the treatment of
4 patients with relapse in forms of multiple
5 sclerosis. And if you vote no, we ask that you
6 indicate whether it is because the studies were not
7 adequate nor well-controlled, or it is because
8 there is no substantial evidence of effectiveness.
9 The next question, we ask whether the
10 applicant has provided substantial evidence that
11 alemtuzumab has a beneficial effect on disability,
12 and here again ask that you pay special attention
13 to Dr. Yan's presentation on this topic.
14 Question 4, we ask whether, in the context
15 of the purported benefits of alemtuzumab, the
16 safety concerns preclude approval. So here we ask
17 you not to take into consideration the open-label
18 design issues that will be discussed, and that you
19 consider the alemtuzumab as they appear on face.
20 Question 5, we ask whether -- if you believe
21 that alemtuzumab should be indicated as a
22 first-line therapy if you have concluded that the

1 available data support approval. And finally, we
2 ask the community to discuss whether there are
3 strategies that may mitigate the autoimmune serious
4 adverse events and the malignancies. We ask
5 whether the proposed REMS can be modified to ensure
6 adequate monitoring, follow-up, and reporting of
7 adverse events. And we ask the committee to
8 discuss the appropriate infusion setting and
9 duration of post-infusion monitoring.
10 Then we finish by saying that even if you
11 have seen in our documents that some of the
12 reviewers have taken some firm positions on the
13 issues that will be discussed, the agency has not
14 taken a final position on these issues. That's why
15 we're here, and that's why we're very interested to
16 get your input on the issues.
17 So again, welcome to the committee, and I
18 give it back to Dr. Fountain.
19 DR. FOUNTAIN: Thank you. Now I'll proceed
20 with the sponsor presentation.
21 Both the Food and Drug Administration and
22 the public believe in a transparent process for

1 information-gathering and decision-making. To
2 ensure such transparency at the advisory committee
3 meeting, FDA believes that it is important to
4 understand the context of an individual's
5 presentation.
6 For this reason, FDA encourages all
7 participants, including the sponsor's non-employee
8 presenters, to advise the committee of any
9 financial relationships that they may have with the
10 firm at issue, such as consulting fees, travel
11 expenses, honoraria, and interests in the sponsor,
12 including equity interests and those based on the
13 outcome of the meeting.
14 Likewise, FDA encourages you at the
15 beginning of your presentations to advise the
16 committee if you do not have any such financial
17 relationships. If you choose not to address this
18 issue of financial relationships at the beginning
19 of your presentation, it will not preclude you from
20 speaking, though.
21 We'll now proceed with the sponsor
22 presentations.

1 **Sponsor Presentation - Jennifer Panagoulias**

2 MS. PANAGOULIAS: Good morning. I'm
3 Jennifer Panagoulias, senior director of regulatory
4 affairs at Genzyme. And I'd like to thank the
5 chairman, members of the committee, and
6 representatives of FDA for the opportunity to
7 present an overview of the development of
8 alemtuzumab.
9 Alemtuzumab was approved in 2001 as a
10 third-line agent for the treatment of B-cell
11 chronic lymphocytic leukemia under the trade name
12 Campath. Pilot investigation in multiple sclerosis
13 began in 1991, and led to an eventual IND filing
14 for a phase 2 study. A risk management plan
15 involving monthly blood monitoring and education
16 was implemented in phase 2 after an index case of
17 immune thrombocytopenia occurred. And the product
18 was very recently approved in the EU as a
19 first-line agent for the treatment of MS and is now
20 available to European patients.
21 The proposed indication is for the treatment
22 of patients with relapsing forms of MS.

1 Alemtuzumab is a humanized, IgG1 monoclonal
2 antibody targeting the CD52 cell surface antigen.
3 CD52 expression varies with cell type. It's
4 present at high levels on T and B lymphocytes and
5 at lower levels on other cell types. Alemtuzumab
6 lyses T and B lymphocytes but has minimal or
7 transient effects on components of innate immunity.
8 Its effect on lymphocytes allows for
9 application in various diseases, and the dose used
10 is then influenced by the patient population and
11 therapeutic goal of treatment. The proposed dose
12 for MS is 12 milligrams per day administered for
13 two short courses one year apart. The regimen was
14 designed in consideration of a goal to modulate
15 immune response through depletion and re-population
16 of lymphocytes.
17 The MS dose is tenfold lower than the
18 approved dose of Campath, which is 30 milligrams
19 per day, administered three times per week for up
20 to 12 weeks, the goal in CLL being different, as
21 alemtuzumab is repeatedly administered in an effort
22 to eliminate as many leukemic cells as possible.

1 Ultimately, differences in dose, administration,
2 and patient profile has likely given rise to
3 distinctions in the safety profile in MS as
4 compared to CLL.
5 With that background in mind, it brings us
6 to a key question for discussion today. Why was it
7 that Genzyme chose to pursue a rater-blinded design
8 for the clinical studies in MS? In phase 2,
9 efficacy was seen after just two courses of
10 treatment. With this came an emerging safety
11 signal related to autoimmunity. So while
12 placebo-controlled studies had been the norm in MS
13 development, Genzyme believed it would be important
14 to evaluate alemtuzumab effects as compared to an
15 effective first-line therapy.
16 At that time, high-dose Rebif was arguably
17 considered the most effective of available
18 therapies. It was approved on the basis of two
19 pivotal studies, 1 placebo controlled and 1
20 rater-blinded study versus Avonex. In fact, it was
21 that rater-blinded study that was considered
22 sufficient to overcome Avonex's orphan exclusivity.

1 Genzyme sought parallel advice in the U.S.
2 and EU on the proposed phase 3 program. FDA
3 strongly recommended a double-dummy placebo
4 control. Using a rater-blind would be a matter of
5 review but potentially acceptable depending on the
6 results. To the contrary, European regulators
7 supported a rater-blinded design because of the
8 difficulties in conducting a study with two drugs
9 that had different modes of administration and
10 well-known side effects.
11 We carefully considered the feedback from
12 both agencies and ultimately decided a rater-
13 blinded study was the best option. During this
14 time, the IND was on hold due to the index case of
15 ITP. FDA advised Genzyme that the hold could be
16 lifted after a positive review of a well-designed
17 and well-controlled randomized study to assess
18 benefit-risk. And in fact, FDA listed the hold
19 with the submission of Protocols 323 and 324.
20 Throughout our presentation, we'll cover the
21 reasons why these rater-blinded were well
22 controlled. Rebif was an effective active

1 comparator, and study design features were
2 carefully developed to allow comparisons across
3 arms. Procedures were designed to minimize bias.
4 The primary disability endpoint was measured by a
5 blinded clinician using an objective neurological
6 scale. This scale is the most widely used measure
7 of disability in MS trials to date.
8 Relapses were determined by a panel of
9 blinded neurologists following an accepted
10 definition. An MRI was assessed with a central
11 blinded reading facility. Statistical analyses
12 followed a prospective plan as agreed with FDA.
13 Alemtuzumab demonstrated robust effects on relapse
14 and disability as compared to Rebif. These
15 clinical effects were supported by MRI data. Taken
16 together, the totality of data established
17 substantial evidence of efficacy.
18 There's a long history of use of
19 alemtuzumab, and the safety profile has been well
20 characterized from clinical studies and over
21 12 years postmarketing experience with Campath.
22 The MS trial database includes over 1400 patients

1 with a median of almost four years follow-up. Use
2 of alemtuzumab increases the risk of autoimmunity,
3 and there's a need to monitor for these events in
4 the long-term. Risk management activities
5 implemented during phase 2 will form the basis of
6 Genzyme's proposed REMS. These efforts will help
7 ensure that the benefits of use outweigh the risks.
8 What you'll hear from our presenters today
9 is the following: MS remains a serious disease,
10 and despite the existence of several therapies, a
11 need for more effective treatment remains.
12 Clinical studies establish credible evidence of
13 efficacy. The safety profile is informed by
14 Campath experience. There are serious risks, but a
15 strong commitment to implement comprehensive risk
16 mitigation measures. And finally, there are
17 limited options for patients with active MS, and
18 the benefit-risk supports use of alemtuzumab.
19 We have the experts listed here with us
20 today, who are available to answer questions during
21 discussion. These are their disclosures.
22 Thank you. I'll ask Dr. Rudick to address

1 the existing needs of MS.

2 **Sponsor Presentation - Richard Rudick**

3 DR. RUDICK: Good morning. I'm Richard

4 Rudick. I'm a neurologist, MS expert, and clinical

5 investigator. I've been working in the MS field

6 since 1981, and I've played key roles in the

7 development of MS disease-modifying drugs,

8 especially interferon, beta, and natalizumab. I'm

9 here at the request of Genzyme to give my opinion

10 on the current unmet need for MS treatments. My

11 institution is being compensated for my time today.

12 I've had no role in the alemtuzumab clinical trial

13 program.

14 I'll discuss three main points. First,

15 despite available treatments, MS is still a serious

16 condition for many patients. Second, many of these

17 patients continue to experience brain inflammation

18 even while on treatment, so there's still a

19 significant unmet need. Third, MS therapy needs to

20 be individualized. Let me expand on the points,

21 starting with my first point.

22 These are the cardinal features of MS. It's

1 relatively common. It occurs mostly in women with
2 an onset in the prime of life. Here are common MS
3 symptoms. Individually, these symptoms often lower
4 a person's quality of life, interfere with the way
5 a person feels or functions, and limit
6 participation in normal activities. However, these
7 symptoms occur in variable combinations in many
8 patients, resulting in an extreme symptom burden
9 for many. And in a significant portion of patients
10 with early relapsing MS, the underlying disease is
11 severe, even though there may be little or no
12 disability. And in those cases, the patient will
13 eventually suffer severe disability, which could be
14 delayed for many, many years.
15 These are some of the consequences faced by
16 patients. I see these all the time at the Mellen
17 Center. Living with MS always means a lifetime of
18 uncertainty and too often results in devastating
19 consequences for patients and the family.
20 Unfortunately, these complications are not rare.
21 For example, in a study published in 2008,
22 58 percent of 8,000 MS patients in the NARCOMS MS

1 database were not gainfully employed, and MS
2 severity was the strongest correlate of this.
3 So let me explain why this happens. We now
4 know that the pathologic process in MS is active
5 from disease onset even though patients may have
6 few or even no symptoms. This conclusion comes
7 from MRI studies showing that lesions occur far
8 more frequently than MS relapses, and showing that
9 brain atrophy begins at the earliest stage of MS,
10 worsening steadily with time. While much of this
11 brain pathology is subclinical, eventually the
12 severity of brain injury reaches a threshold after
13 which patients become increasingly disabled. I'll
14 show you some evidence to support this view.
15 As part of our NIH supported MS brain
16 donation program, we studied 18 lesions from five
17 people who died from MS. This picture was shocking
18 to me because this young woman died from MS from a
19 brain stem lesion at the young age of 18. She had
20 MS for less than one year.
21 Each of the arrows points to a nerve fiber
22 that's been transected by the inflammatory process

1 within this lesion. These neurons will degenerate
2 and never function again. Importantly, this shows
3 that axonal transection occurs at sites of brain
4 inflammation and is not dependent on disease
5 duration.
6 The table shows that there were thousands of
7 these transected axons per microliter of lesion
8 tissue, and high numbers of transected axons were
9 even found in normal appearing brain tissue from
10 the MS patients. The consequences of this
11 pathology is brain tissue loss or brain atrophy, as
12 I'll show you in the next slide.
13 These examples come from our NIH
14 longitudinal study of brain atrophy in MS patients.
15 We use the brain parenchymal fraction BPF to
16 measure whole brain atrophy precisely. The time
17 row shows a young healthy control. There's no
18 brain atrophy and no change over five years. The
19 bottom row shows a young, relapsing-remitting MS
20 patient. She has significant atrophy at baseline,
21 and this worsens, as you can see, from the
22 expanding ventricles.

1 So this diagram shows what we now know is
2 happening within MS. During the
3 relapsing-remitting disease stage on the left,
4 patients have only periodic relapses from which
5 they usually recover. But this is the tip of the
6 iceberg because brain atrophy accumulates over the
7 years, leading to secondary progressive MS later
8 on, and at that stage, there is no known effective
9 treatment.
10 This slide shows that brain atrophy in early
11 MS predicts future severe disability. The data is
12 from an eight-year follow-up of the phase 3 Avonex
13 trial. Bars 1 to 4 show groups of
14 patients -- they're quartiles of patients -- with
15 increasing rates of brain atrophy during the
16 two-year clinical trial. The patients with the
17 most atrophy, the worse quartile, are on the right,
18 and the least atrophy on the left. The height of
19 the bar shows the proportion of these patients in
20 each group who develop severe disability eight
21 years later. The patients with the highest rates
22 of brain atrophy had more than a 50 percent chance

1 of severe disability at the eight-year follow-up.
2 The data shows that brain atrophy in early MS
3 patients is very important because it predicts
4 severe disability.
5 Let me move to my second point. Even while
6 on approved drugs, over 50 percent of the patients
7 have clinical or MRI evidence for brain
8 inflammation. We call this breakthrough disease.
9 This references to a paper now in press in
10 Neurology that reviews 20 published studies that
11 all document the same thing, poor outcome for
12 patients with breakthrough disease. And even a few
13 MRI lesions in a patient with relapses is a poor
14 sign.
15 I'll show a case to illustrate what this
16 breakthrough disease actually looks like and to
17 highlight some of these points. I'm going to show
18 a move from the brain of a 42-year-old patient with
19 relapsing-remitting MS who is currently enrolled in
20 our NIH prospective study. Brain MRI scans done
21 every six months were co-registered in order to
22 create this movie. The movie will show the course

1 of this person's disease over six and a half years,
2 and during this time, he cycled through the various
3 disease-modifying drugs, ending up on Tysabri. The
4 movie will play on the right.
5 (Video played.)
6 DR. RUDICK: The first thing you will see is
7 the bright T2 lesions coming and going over six and
8 a half years.
9 Now, the next thing I'm going to show you is
10 what happens to his brain volume. I'd like you to
11 concentrate on the brain ventricles in the center,
12 and I'll play this movie again. After six and a
13 half years, he's lost a substantial part of this
14 brain volume despite being on existing medications.
15 So what's happened to him? In his last visit in
16 2012, this is his brain. He's now 55 years old,
17 remains on Tysabri. He can no longer work as an
18 engineer, and he was just divorced. He has
19 significant cognitive impairment, and he clearly
20 illustrates the importance of breakthrough disease
21 and the unmet medical need in some patients with
22 MS. The implications to me are obvious. We need

1 to prevent this by inhibiting brain inflammation
2 early in the MS disease process.
3 The last point I want to make is about
4 individualized treatment. Relapsing MS patients
5 with a poor prognosis should be identified early,
6 and highly-effective treatment should be
7 considered. Poor indicators include the high
8 relapse frequency, poor relapse recovery, high T2
9 lesion burden, and evident brain atrophy. I
10 evaluate these factors in every patient and engage
11 the patient and her family as a partner because
12 each patient has individual concerns about MS and
13 individual views of risk tolerance. I believe this
14 approach is important because it results in better
15 treatment decisions, better compliance, and better
16 outcomes.
17 In summary, there's a continuing unmet
18 medical need in relapsing MS, so we need more and
19 better options. And we need to treat patients
20 early in the disease in selected cases to prevent
21 the worst outcomes in patients with relapsing MS.
22 Lastly, after reviewing the alemtuzumab clinical

1 and imaging results, particularly the brain atrophy
2 results, I believe alemtuzumab is highly effective
3 in MS and should contribute meaningfully to better
4 outcomes for our patients. Thank you.
5 **Sponsor Presentation - David Margolin**
6 DR. MARGOLIN: Good morning. I'm Dr. David
7 Margolin, a senior medical director of clinical
8 research at Genzyme and the global medical lead for
9 alemtuzumab development. I will describe the
10 clinical development program and present efficacy
11 results from two adequate and well-controlled,
12 phase 3 studies supported by a comprehensive
13 approach designed to minimize the potential for
14 bias.
15 The alemtuzumab clinical development program
16 included three randomized controlled studies as
17 well as an ongoing extension study. Study 223 was
18 the phase 2 study in treatment-naive patients. We
19 conducted two phase 3 studies, one again in
20 treatment-naive patients, Study 323, and the other,
21 Study 324, in patients with breakthrough disease
22 having relapsed despite treatment with an approved

1 disease-modifying drug.
2 Each study followed patients for at least
3 two years. All were head-to-head superiority
4 trials versus high-dose subcutaneous, interferon
5 beta-1A, the approved MS treatment marketed under
6 the brand name Rebif. The primary endpoints
7 relapse rate and the six months sustained
8 accumulation of disability were the same as in
9 other MS studies, and none of these design elements
10 have been contested by FDA. The primary efficacy
11 endpoints were analyzed with adjustment for
12 multiple comparisons, so the criterion for success
13 in each study was to observe a significant
14 treatment effect in either or both endpoints.
15 The Expanded Disability Status Scale, or
16 EDSS, is the most widely used measure of MS-related
17 disability. It is determined by findings from a
18 standardized neurological examination. The scale
19 ranges from zero, a normal exam, through half-point
20 steps of increasing impairment up to 10. The
21 sustained accumulation of disability primary
22 endpoint, abbreviated SAD, was defined as an

1 increase of at least one EDSS point that was
2 repeatedly documented at three consecutive visits
3 spanning six months or one and a half points if the
4 baseline were zero. We also evaluated a 1-point
5 improvement in EDSS score using the sustained
6 reduction in disability.
7 A secondary endpoint disability was
8 additionally assessed using the Multiple Sclerosis
9 Functional Composite. The MSFC includes three
10 objective subscales that evaluate ambulation and
11 eye coordination and dexterity and cognition. And
12 the scores for these three components are combined
13 to create an overall MSFC Z score.
14 Genzyme's first alemtuzumab study was the
15 phase 2, head-to-head rater-blinded trial versus
16 Rebif in treatment-naive patients. Alemtuzumab
17 12 milligrams, shown in blue, strongly and
18 significantly reduce both the MS relapse rate,
19 shown in the column plot on the left, and the risk
20 of six months sustained accumulation of disability,
21 shown in the Kaplan-Meier plot on the right, over
22 three years of follow-up.

1 To confirm these phase 2 results, Genzyme
2 sought advice from MS clinical trial experts and
3 formed a neurology steering committee for these
4 trials and also from regulatory authorities, as you
5 heard, on the design of the phase 3 program. Since
6 distinctive side effects for both drugs are seen in
7 roughly 90 percent of patients, even in a
8 double-blinded study, almost everyone would know
9 which treatment they were taking. So we viewed our
10 challenge as how to conduct an even more
11 rigorously, well-controlled rater-blinded study of
12 alemtuzumab versus Rebif.
13 In consideration of FDA concerns that
14 patients and some site staff knew which treatment
15 was assigned by randomization, we developed a
16 comprehensive approach to minimize the potential
17 for bias. As a first step, patients underwent
18 blinded assessment by EDSS raters who had no
19 knowledge of treatment assignment. These scores
20 were the sole basis for the disability primary
21 endpoint SAD and brought blinded and objective
22 evidence to the determination of relapse events.

1 Blinded raters were trained and certified to
2 assess EDSS with the widely used standardized exam
3 and rating scale called Neurostatus. EDSS blinded
4 raters had to attest to their blinding status for
5 every assessment they performed. Blinding was
6 effectively maintained in both studies. Less than
7 1 percent of all EDSS assessments were unblinded.
8 Protocol provided a definition for MS
9 relapse, the essential features being new or
10 worsening of neurological symptoms that must be
11 attributable to MS, last at least 48 hours, be
12 present at a normal body temperature, and be
13 preceded by at least 1 month of clinical stability.
14 And importantly, symptoms must be accompanied by an
15 objective chain on neurological exam.
16 Patients were instructed to report any new
17 or changing symptoms within 48 hours of onset.
18 Those symptoms might be from an adverse event or
19 could indicate an MS relapse. We knew it was
20 important to reduce subjectivity in relapse
21 reporting, so patients had to present for a
22 complete relapse evaluation unless it was very

1 clear their symptoms were unrelated to MS. A
2 broken ankle was the example given in study
3 documents.
4 The first step of a relapse evaluation visit
5 was the blinded-rater assessment of EDSS. And
6 next, the patient would see the treating
7 neurologist. Why would an unblinded treating
8 neurologist have any role in relapse evaluation?
9 Neurostatus guidelines explicitly prohibit the
10 blinded rater from conversation with patients,
11 except as necessary, to conduct their exam. That
12 is why brief description of patient symptoms
13 potentially signaling a relapse or other adverse
14 event had to be collected by the treating
15 neurologist.
16 Also, the treating neurologist was
17 responsible for patient care and might need to
18 provide treatment for the event. Protocol
19 specified a standard steroid regimen if a relapse
20 needed treatment. Case dossiers for each event
21 were submitted for independent review to a relapse
22 adjudication panel. The RAP included six

1 neurologists with expertise in MS. They conducted
2 a blinded review of all events evaluated as
3 potential relapses regardless whether the site
4 believed it was truly an MS relapse. And
5 importantly, only events affirmed by this blinded
6 panel were counted in the primary relapse analyses.
7 A key element of the relapse dossiers was
8 the EDSS scored by the blinded rater to support
9 that requirement for an objective change in
10 neurological examination. The RAP didn't just get
11 the overall EDSS score zero, 1.5, or whatever.
12 They got the complete record of the blinded rater's
13 detailed neurologic exam performed at three time
14 points, from the time of the relapse and for
15 comparison, also the most recent prior and
16 baseline. The blinded rater's exam extended for 10
17 pages in the dossier for each event.
18 Highlighting the importance of these data, a
19 lack of objective neurological change was the
20 reason most often cited by the RAP for rejecting
21 potential relapse events. The RAP was also
22 provided with a brief description of each event as

1 I mentioned, including whether it met other
2 elements of the relapse definition. This
3 information collected by the treating physician was
4 largely structured using drop-down menus or check
5 boxes to limit subjectivity. As an additional
6 precaution, dossiers were prescreened by a blinded
7 CRO using programmatic checks on free text fields
8 to minimize potential for unblinding.
9 Collectively, these measures helped ensure the
10 validity of the clinical efficacy endpoints, which
11 could therefore provide substantial evidence of
12 efficacy.
13 Let's look now at the phase 3 studies'
14 design and results. Study 323 followed 581
15 treatment-naive patients with early stage, active
16 relapsing MS over two years. The alemtuzumab
17 group, again shown in blue, received the regimen
18 proposed for licensing with two annual courses of
19 treatment. The comparator group, shown in gray,
20 self-administered subcutaneous Rebif three times
21 weekly throughout the study period. There were no
22 incentives to influence patient reporting of

1 relapse or performance on EDSS. There was no
2 rescue arm for patients who worsened, and this was
3 clearly stated in the consent form. There was no
4 crossover from Rebif to alemtuzumab allowed during
5 the pivotal studies.
6 EDSS assessments were performed at quarterly
7 visits and MRI done once a year. Collection for
8 samples for lab testing was monthly for both
9 groups, and Rebif patients did have an extra visit
10 at month 1 to assess success in completing the
11 Rebif dose escalation. And this was the only
12 difference between the treatment arms and visit
13 schedule.
14 EDSS assessments. Disposition
15 post-randomization is shown here. A high
16 percentage of patients on both arms completed a
17 two-year study. Dropout in the Rebif arm was
18 similar to or lower than in most interferon
19 studies. Treatment groups were balanced across all
20 major MS and demographic characteristics.
21 Now, note the MS duration. Median time
22 since first MS symptoms was only 1 and a half

1 years. As Dr. Rudick explained, such early stage
2 patients often seem to recover well after a relapse
3 even though their brains show accumulating damage.
4 And as you'll see, this was true in Study 323.
5 Efficacy results from that study are shown
6 here and on the next few slides. The annualized
7 relapse rate was reduced by 55 percent in
8 alemtuzumab patients as compared with Rebif, a
9 highly significant effect. Superior efficacy on
10 relapse was apparent early and was sustained
11 through the second year of study. According to our
12 prespecified statistical plan having met the
13 relapse primary endpoint, 323 is a positive study.
14 Secondary and supportive analyses of relapse
15 outcomes provide evidence that conclusions from the
16 primary relapsed endpoint are robust. Alemtuzumab
17 patients were significantly more likely to remain
18 relapse free. Also, we specifically examined
19 relapse events that are less likely to go
20 unreported; in particular, severe relapses with a
21 high change in EDSS. Also, relapses that were
22 treated with steroids and relapses that were

1 detected at scheduled quarterly visits. And in
2 each case, alemtuzumab led to a significant result
3 in the relapse risk.
4 Results for the primary disability endpoint
5 are shown here. The results were numerically in
6 favor of alemtuzumab. Fewer alemtuzumab patients
7 worsened over time, and separation between the
8 curves widens over time, with a 30 percent
9 reduction in the risk of SAD for alemtuzumab
10 compared with Rebif. However, the group difference
11 did not reach statistical significance.
12 The sample size calculations had assumed
13 that 20 percent of Rebif patients would worsen
14 during the two-year study. The lower observed
15 rate, 11 percent, diminished statistical power for
16 this endpoint. However, the MSFC, the disability
17 secondary endpoint, did show a difference between
18 groups. Alemtuzumab patients had better MSFC
19 scores after treatment.
20 Now, let's turn to Study 324, which enrolled
21 patients who had at least one relapse on their
22 prior MS drug. The study design was identical to

1 323, except the 324 study included also a higher
2 24 milligram alemtuzumab dose arm. In addition to
3 rater blinding, this study featured dose blinding
4 for patients, and again, there was no rescue arm
5 for patients who worsened. Recruitment into the
6 24 milligram arm was discontinued early in order to
7 accelerate recruitment into the other arms. And
8 thus to ensure timely completion of this study, the
9 decision was not taken for safety reasons.
10 Statistical comparisons for that 24-milligram group
11 were deemed exploratory, and the primary analyses
12 in my presentation focused on the comparison of
13 alemtuzumab 12 milligrams to Rebif.
14 Patient disposition, shown here, more than
15 95 percent of patients randomized to alemtuzumab
16 completed this study. More patients randomized to
17 Rebif discontinued prior to treatment. Only
18 12 percent of Rebif patients discontinued after
19 initiating treatment, which is similar to or lower
20 than in other interferon studies.
21 Treatment groups were balanced across all
22 major demographic and MS disease-related

1 categories. Compared to the treatment-naive
2 studies, patients in 324 had longer MS duration and
3 more disability at baseline. Their prior therapies
4 reflect those available at the time. The typical
5 324 study patient that had MS for close to five
6 years had been using an improved therapy for nearly
7 three years, but had continued to relapse more than
8 once a year and was still developing new enhancing
9 lesions.
10 The relapse primary analysis in Study 324
11 found a 49 percent reduction in the annualized
12 relapse rate compared with Rebif, a highly
13 significant effect. As in our other studies,
14 alemtuzumab's superior relapse efficacy was
15 apparent early and sustained through both years of
16 study. The secondary endpoint, percent
17 relapse-free and supportive analyses, again showed
18 the relapse reduction to be robust. Importantly,
19 this study also found a significant alemtuzumab
20 treatment effect on the primary disability
21 endpoint. Twenty-one percent of the Rebif group
22 had SAD versus 13 percent on alemtuzumab, for a

1 42 percent reduction in the risk of six-month SAD.
2 So both primary endpoints were met in this study.
3 Subgroup analyses indicated that alemtuzumab
4 was more effective on both endpoints across a
5 variety of demographic and baseline
6 characteristics. Results were not attributable to
7 enrollment of patients who had failed interferon
8 since a prespecified subgroup analysis, shown here,
9 found that alemtuzumab was more effective on both
10 primary endpoints, even among patients with no
11 prior history of Rebif use, and similar results
12 were seen in a subgroup also with no prior use of
13 any interferon.
14 An alemtuzumab treatment effect was also
15 seen on disability related secondary and tertiary
16 endpoints. Notably, the alemtuzumab groups' mean
17 disability score were significantly improved
18 post-treatment, and this difference was
19 substantially larger than the small between-group
20 differences seen either at screening or baseline.
21 And by contrast, mean disability in the Rebif group
22 significantly worsened over time.

1 The Kaplan-Meier plot shown here depicts the
2 percentage of patients who had a 1 point
3 improvement in EDSS score that was then sustained
4 for at least six months. This effect was seen in
5 more than a quarter of alemtuzumab treated patients
6 and that alemtuzumab were more than twice as likely
7 than Rebif patients to have a sustained improvement
8 in pre-existing disability. Significantly greater
9 improvement with alemtuzumab was also seen on the
10 MSFC in this study.
11 Alemtuzumab treatment effects at two years
12 were largely maintained through a third year of
13 follow-up in extension Study 03409, suggesting
14 durable efficacy after two treatment courses. The
15 relapse rate stayed low, shown on the left, and
16 70 percent of patients had a disability score that
17 was unchanged or improved compared to their
18 original entry baseline. During that third year
19 study, only 20 percent of alemtuzumab patients
20 received a third treatment course, and less than
21 3 percent received another disease-modifying
22 therapy.

1 In summary, Studies 323 and 324 were
2 adequate and well controlled. Rater-blinding was a
3 necessary choice and effectively maintained, and
4 was supported by a comprehensive approach to
5 minimize the potential for bias. These studies
6 provide substantial evidence of alemtuzumab
7 efficacy superior to that of the approved treatment
8 Rebif, with significant effects on relapsed and
9 disability endpoints.
10 Alemtuzumab efficacy was seen across patient
11 populations. With alemtuzumab, fewer
12 treatment-naive patients suffered breakthrough
13 disease activity. And those who had relapsed on
14 their prior drug could better control their
15 disease. We conclude that alemtuzumab outperforms
16 standard therapy and could benefit many patients
17 with MS.
18 Dr. Steve Lake will next present analyses
19 that affirm the robustness of our efficacy
20 conclusions. Thank you for your attention.
21 **Sponsor Presentation - Stephen Lake**
22 DR. LAKE: Hello. I'm Steve Lake, head of

1 Genzyme biostatistics. As with any clinical trial,
2 we perform sensitivity analyses to confirm the
3 results, and many were included in our briefing
4 document. In their review, the FDA also performed
5 analyses, and based on those, takes the position
6 that the efficacy results are not interpretable due
7 to bias, with an emphasis on three topics:
8 pretreatment dropout in Study 324 and the
9 difference between screening and baseline EDSS.
10 FDA has performed a sensitivity analysis where the
11 time to SAD result is not significant when the
12 screening EDSS score is used instead of baseline.
13 The third topic is under and over-reporting of
14 relapses.
15 I will review each of these and demonstrate
16 the FDA position is not supported by the data.
17 After me, Dr. Cutter will discuss these in the
18 context of other MS studies. Let's start with
19 pretreatment dropout.
20 As was shown, in the 324 study, more
21 patients randomized to Rebif withdrew from the
22 study before treatment than in the alemtuzumab

1 12-milligram arm. This dropout can cause
2 imbalances between the patient groups that go on to
3 receive randomized treatment. We used various
4 approaches to understand what happens to the
5 treatment effect estimate when we take this
6 pretreatment dropout into account.
7 This forest plot shows the result for time
8 to SAD. It has the hazard ratios for the Cox model
9 and the associated 95 percent confidence intervals
10 for the primary efficacy analysis and the
11 sensitivity analyses. These methods address
12 pretreatment dropout by weighting the observed data
13 or imputing missing data. The results of these
14 analyses are similar to the primary efficacy
15 analysis.
16 Additionally, we simulated the SAD rates for
17 the patients who dropped out prior to treatment
18 using increasingly conservative assumptions: half
19 the estimated treatment effect, no treatment
20 effect, and most conservatively, no Rebif dropouts
21 experiencing SAD over two years of follow-up.
22 These results are also consistent with the primary

1 efficacy analysis. We performed a similar set of
2 analyses for relapse rate and conclude that the
3 primary efficacy analyses are robust to
4 pretreatment dropout.
5 Let's move on to the difference between
6 screening EDSS, which was used to qualify patients
7 for the study, and baseline EDSS, which was used to
8 determine if patients had SAD for the primary
9 analysis. In their review, the FDA suggests that
10 difference between screening and baseline EDSS
11 suggests bias. So let's look at these changes and
12 see what they show us.
13 This table summarizes the screening and
14 baseline EDSS by treatment group for Study 324.
15 The top portion presents the means and standard
16 deviations. As you can see, the change was
17 slightly greater for the Rebif arm. However, the
18 changes from screening to baseline are small,
19 especially with respect to the standard deviation;
20 that is, the signal-to-noise ratio is low. These
21 changes from screening to baseline are typical in
22 MS trials, as Dr. Cutter will present.

1 Additionally, if we look at the percentage of
2 patients with the same or different EDSS, as shown
3 on the bottom, we do not see any imbalance between
4 groups.
5 Next, I will show the summaries after
6 splitting the data into whether the baseline EDSS
7 was performed on the day of randomization or after.
8 Because patients who had their baseline EDSS after
9 the day of randomization could have known their
10 treatment assignment, FDA attributes differences in
11 the change from screening to baseline to bias.
12 Here is the summary. The largest change is
13 in the Rebif group that had their baseline EDSS
14 after the day of randomization. The argument for
15 bias is that the patients who might have known they
16 were randomized to Rebif artificially improved
17 their baseline EDSS scores. However, this logic
18 doesn't really hold up.
19 First, we expect differences of this
20 magnitude given the variability in a measure like
21 the EDSS. We performed a simulation that shows
22 across the treatment arms, we should see changes

1 distributed like this subset over 70 percent of the
2 time simply by chance alone. Second, the changes
3 go in the opposite direction for Study 323. Here
4 are the biggest decreases in the alemtuzumab
5 12-milligram arm that has EDSS performed at
6 randomization.
7 I mentioned earlier that when the screening
8 EDSS value is used instead of baseline, then the
9 time to SAD result is not statistically
10 significant. Let's look at this. This is a cross-
11 tabulation of SAD events using baseline EDSS and
12 SAD events using screening EDSS. The rows indicate
13 whether a patient had an SAD event in the primary
14 analysis, and the columns indicate whether a
15 patient had an event when screening is used. The
16 difference between the analyses is in the 7 percent
17 of patients whose SAD outcomes were discordant.
18 These differences can be attributed in part to some
19 major drawbacks of an analysis that uses screening
20 instead of baseline EDSS.
21 Here are the scores for a patient who has no
22 evidence of disease progression throughout the two

1 years of follow-up. However, since the screening
2 value is lower, if screening is used instead of
3 baseline, this patient is counted as having an SAD
4 event that started at month 3, even though the
5 initial increase occurred prior to treatment.
6 These types of SAD events account for 35 percent of
7 the events that were only counted in the screening
8 as baseline analysis.
9 There are other drawbacks that Dr. Cutter
10 will discuss. Using screening instead of baseline
11 also generated discordant results in the
12 statistical review of the Tysabri application.
13 When this same analysis was performed with the
14 treatment-experienced Sentinel trial, the time to
15 SAD outcomes also became non-significant.
16 There are appropriate ways to account for
17 differences between screening and baseline, and
18 those results are shown here. Here we include the
19 screening value. And the change from screening to
20 baseline as covariates in the model restrict the
21 analysis to patients who had the same or different
22 values, and restrict by whether the baseline EDSS

1 was performed at or after randomization. All of
2 these analyses show consistent treatment effect
3 estimates in favor of alemtuzumab.
4 Importantly, we can take the inherent
5 variability of the EDSS into account by requiring
6 an SAD event to be a sustained increase from the
7 maximum of screening and baseline. This analysis
8 yields a treatment-effect estimate that is
9 identical to our primary efficacy results. Based
10 on these analyses, and with the understanding that
11 the screening in its baseline analysis has
12 significant limitations, we conclude that the time
13 to SAD results are robust to differences between
14 screening and baseline.
15 Lastly, I would like to discuss under- and
16 over-reporting of relapse. Let's look at the data
17 and see if there is evidence of this. This table
18 summarizes the relapse severity as a percentage of
19 all potential relapses by treatment group for
20 Study 324. The definition of relapse severity is
21 based only on the changes in EDSS score as recorded
22 by the blinded rater.

1 If there was over-reporting of relapses in
2 the Rebif arm, we should expect to see an increase
3 in the percentage of the no-change or mild category
4 compared to alemtuzumab; that is, patients in the
5 Rebif arm would be more likely to report milder
6 events if there was a negative placebo effect. We
7 do not see that here. Conversely, if there was
8 under-reporting of relapses in the alemtuzumab arm,
9 or a positive placebo effect, then we should expect
10 to see an increase in the percentage in the
11 moderate and severe category. Again, that is not
12 the case. There also does not appear to be under-
13 or over-reporting of relapses since the Relapse
14 Adjudication Panel confirmation rates are the same
15 between the treatment groups.
16 Some analyses that further address this
17 issue are presented here. The estimated treatment
18 effect is the same when we analyze all potential
19 relapses regardless of RAP confirmation status or
20 if we restrict only to severe relapses. Even if we
21 do assume that there is some degree of under- or
22 over-reporting of relapses, then we must reduce the

1 treatment effect by 40 percent to get to the point
2 where it is not statistically significant.
3 Based on the data, we conclude the primary
4 efficacy results are robust to pretreatment
5 dropout. Differences between screening and
6 baseline EDSS are expected given variability. A
7 time to SAD analysis that uses screening has
8 significant limitations, and there is no evidence
9 of under- or over-reporting of relapses.
10 Dr. Cutter will now put these findings in
11 the context of other MS studies.
12 **Sponsor Presentation - Gary Cutter**
13 DR. CUTTER: Good morning. My name is Gary
14 Cutter. I am a professor of biostatistics at the
15 UAB School of Public Health. I have worked in the
16 field of MS for 20 years with a specific interest
17 in outcome measures. I direct the data center for
18 the National Patient Report Outcome Registry,
19 NARCOMS, and direct the coordinating center for the
20 recently completed CombiRx trial, a double-blind,
21 randomized trial of interferon, glatiramer acetate,
22 and their combination, which was funded by NINDS.

1 My role has been to ask questions relevant
2 to the data review by the FDA, and I started with
3 what would you expect to see and how would this
4 influence the results presented. Let me start with
5 a general point.
6 Blinded raters are the norm in both blinded
7 and unblinded MS pivotal trials. In 324, there
8 clearly were early dropouts, and they were
9 differential between the arms. The dropouts were
10 more likely to be on Rebif in the past, they had
11 taken more DMTs, and they were roughly the same
12 proportions in both the alemtuzumab and Rebif arms.
13 Thus, had these patients been participating in the
14 trial, we would have expected them to be more
15 likely to have outcomes.
16 When the sensitivity analyses were done,
17 specifically the one just presented by Dr. Lake,
18 assuming these individuals were included with no
19 contributing events, the hazard ratio was 0.68,
20 still favors the effectiveness of alemtuzumab.
21 Study 323 had the same design but had much lower
22 pretreatment dropout rates and has not raised

1 concerns.
2 Another point, I will strongly suggest that
3 the changes from screening to baseline result from
4 random variability and are expected. The
5 sensitivity analyses using the maximum EDSS of
6 screening and baseline removes progressions likely
7 due to noise. And finally, the sensitivity
8 analyses, and the analyses of relapse severity, and
9 the RAP confirmation rates support the lack of
10 biased reporting.
11 To begin, let me address the concerns around
12 the screening to baseline EDSS, which is commonly
13 seen in other MS studies. In the original
14 alemtuzumab statistical review of the Sentinel
15 trial by the FDA, the FDA raised concerns that
16 since approximately 40 percent of the subjects had
17 different EDSS scores between screening and
18 baseline, this was an issue. The alemtuzumab trial
19 was double-blinded, but as you can see in this
20 slide here, this is essentially what is shown in
21 the 324 study for alemtuzumab. In addition, as
22 Dr. Lake showed you before, the changes were very

1 similar in 323.
2 So to see if the differences identified by
3 the FDA were unusual, I used the data that I
4 presented at ECTRIMS in 2012 from the CombiRx
5 trial, where I examined the impact of these common
6 changes seen in EDSS from screening to baseline.
7 In the table presented, you'll see the average
8 change in EDSS between screening and baseline by
9 the CombiRx treatment groups. The differences
10 between the treatment groups are actually larger
11 than those seen in the 324 study, and none of the
12 pairwise differences shown in the table are
13 statistically different.
14 If the participants in Combi had the same
15 baseline EDSS distribution as the Rebif and
16 alemtuzumab groups, the differences seen from
17 screening to baseline in the current studies can be
18 reproduced using the Combi data. This suggests
19 that it is random variability and not due to bias.
20 Both Sentinel and 324 had similar patient
21 populations. In addition, they had about the same
22 percentage with screening to baseline differences,

1 and both lose about 25 percent of the SAD events
2 when calculating events from screening rather than
3 baseline. Further, the losses are the same within
4 each treatment arm within each trial. This is
5 consistent with the variability of the EDSS and not
6 unique to 324 or its lack of double-blinding.
7 If there were over- and under-reporting of
8 potential relapses as you've heard, it should show
9 in the proportions adjudicated if the Rebif arm
10 over-reporting would likely show more events not
11 confirmed by the RAP as relapses, and this was not
12 seen. In the alemtuzumab arm, under-reported would
13 likely show a higher proportion of severe relapse.
14 This also was not seen. The FDA asserted both
15 under- and over-reporting. It took a bias of
16 10 percent over-reporting and 6 percent
17 under-reporting to achieve a p-value greater than
18 P .05 for relapses. But even at that point, the
19 treatment benefit is nearly 30 percent.
20 So in conclusion, I think the expected
21 differences are due to EDSS variability, they're
22 seen in blinded as well as unblinded studies, and

1 the extensive sensitivity analyses confirm the
2 consistency of the results. And now Dr. Arnold
3 will provide the MRI results.
4 **Sponsor Presentation - Douglas Arnold**
5 DR. ARNOLD: Thank you. I'm Douglas Arnold.
6 I'm the professor of neurology at the Montreal
7 Neurological Institute of McGill University where I
8 direct a research imaging lab. I'm also the
9 president of NeuroRx Research, a CNS imaging CRO
10 that is doing the majority of MS clinical trials
11 sponsored by PhRMA in the world today.
12 MRI was performed in these trials to provide
13 objective biologic support of alemtuzumab's
14 efficacy. MRIs were obtained at baseline, and one
15 year, and two years using a standardized
16 acquisition, and the scans were read centrally,
17 blinded to treatment status. In these studies,
18 scans were performed at MRI facilities associated
19 with clinical sites and were sent to ICON Medical
20 Imaging. ICON Medical Imaging performed site
21 qualification oversight and quality control of the
22 images. They then transferred the identified scans

1 to NeuroRx. NeuroRx performed analysis, except for
2 brain atrophy, which was measured by Beth Fisher at
3 the Cleveland Clinic. Thus, all MRI analyses were
4 performed blinded to treatment status and without
5 any contact whatsoever with clinical sites.
6 The lesion-based MRI outcome measures
7 performed are illustrated on this slide. The left
8 panel shows a bright rim of gadolinium enhancement
9 surrounding a T1 hypointense lesion in the white
10 circle. Gadolinium enhancements last for about one
11 month and provide a snapshot of focal inflammatory
12 activity at a point in time. Focal inflammation
13 also produces new and enlarging T2 hyperintense
14 lesions on T2 weighted scans, which you can see in
15 the next panel. These tend to persist and
16 integrate focus inflammatory activity over time.
17 The panels on the right show the situation
18 six months later. The gadolinium enhancement has
19 resolved, leaving behind a T1 hypointense lesion,
20 which is associated with a relatively greater
21 tissue destruction. The associated T2 weighted
22 abnormality persists and adds to the chronic

1 accumulated burden of disease.
2 Now let's turn to the results. MRI results
3 from the 323 trial are shown in the left panel, and
4 from the 324 trial are shown in the right panel.
5 Because mean values for lesion activity are
6 sensitive to the effective outliers, I'll present
7 the results using the percent of patients with
8 active lesions.
9 Approximately 50 percent of patients had
10 active gadolinium-enhancing lesions at baseline, as
11 shown by the left-sided bars in the two graphs.
12 Both Rebif and alemtuzumab substantially reduced
13 the percentage of patients with
14 gadolinium-enhancing lesions. In the case of
15 patients who had relapsed on prior therapy,
16 alemtuzumab was superior at both year 1 and year 2.
17 In the case of the treatment-naive patients,
18 alemtuzumab was similar to Rebif in year 1 and
19 superior to Rebif in year 2 after the second
20 treatment course with alemtuzumab, a pattern that
21 will repeat itself. Thus, alemtuzumab
22 substantially reduced focal brain inflammatory

1 activity compared to Rebif, demonstrating that
2 alemtuzumab has a very strong anti-inflammatory
3 effect.
4 In this slide, we again see study 323 in the
5 left panel and 324 in the right panel. In
6 subsequent slides, for each panel, the left-hand
7 bars show the change over the entire two years of
8 the trial, the middle bars show the change in
9 year 1, and the right-hand bars show the change in
10 year 2. In untreated patients with MS, the volume
11 of T2 hyperintense lesions normally increases by
12 about 5 percent a year, so one would expect bars
13 reaching to the top of the chart area after two
14 years.
15 In these patients, all of whom were
16 receiving anti-inflammatory therapy, the treatment
17 succeeded in preventing the expected increase in
18 lesion volume; that is the total T2 hyperintense
19 lesion volume tended to decrease rather than
20 increase. This decrease in T2 hyperintense lesion
21 volume was probably due to the resolution of
22 low-grade inflammation in the chronic lesions. Not

1 surprisingly, this effect was greater in the
2 treatment-naive patients, shown on the left panel,
3 than in patients who had already been on
4 anti-inflammatory therapy, shown in the right
5 panel.
6 In both trials, alemtuzumab completely
7 prevented the expected increase in T2 lesion
8 volume. In the first year, alemtuzumab and Rebif
9 performed similarly, however, in the second year,
10 alemtuzumab was superior to Rebif in both trials.
11 Thus, alemtuzumab was more effective than Rebif at
12 preventing the accumulation of focal brain damage
13 over the longer term.
14 Here you see new or enlarging T2
15 hyperintense lesion activity over the two trials.
16 New or enlarging lesions tend to accumulate and
17 therefore integrate white matter lesional activity
18 over the early intervals and over the whole trial.
19 Alemtuzumab was superior to Rebif over all
20 intervals except for the first year in the
21 treatment-naive patients. These data confirm and
22 extend the observation made on gadolinium-enhancing

1 lesions, showing that alemtuzumab reduces focal
2 brain inflammatory activity more than Rebif and has
3 a very strong anti-inflammatory effect, which is of
4 course the goal of this sort of treatment.
5 Here we see the new T1 hypointense lesion
6 formation in the two studies. In previously
7 treated patients, alemtuzumab was more effective
8 than Rebif at suppressing T1 hypointense lesion
9 formation over all intervals. In naive patients,
10 this effect was demonstrated in year 2 after the
11 second course of therapy with alemtuzumab. The
12 differences in significance compared to the effects
13 on T2 hyperintense lesion volume may reflect the
14 fact that the T1 lesions are a subset of the T2
15 lesions with a much lower event rate. Thus,
16 alemtuzumab was more effective than Rebif at
17 preventing tissue destruction within newly formed
18 lesions.
19 We're now going to shift from anti-
20 inflammatory activity to potential neuroprotective
21 effects; in other words, preservation of brain
22 tissue. Alemtuzumab was superior to Rebif over all

1 intervals in naive patients and over the entire
2 two-year interval of the trial in previously
3 treated patients. Slowing of atrophy was not
4 significant over the individual years in Study 324
5 probably at least in part due to the fact that the
6 rates of atrophy in these patients, who were
7 already treated when they entered the trial, were
8 slower.
9 Recall that brain atrophy is a marker of
10 neurodegeneration and an important predictor of
11 long-term disability. Thus, the atrophy data
12 reinforced the clinical observation of
13 alemtuzumab's superiority over Rebif in slowing the
14 accumulation of disability.
15 In conclusion, MRI data provide objective
16 biological support for the efficacy of alemtuzumab.
17 Alemtuzumab was superior to Rebif on most MRI
18 endpoints reflecting reduction in focal
19 inflammation and slowing of neurodegeneration in
20 both treatment-naive and previously treated
21 patients. The pattern of MRI results supports the
22 superior clinical efficacy of alemtuzumab compared

1 to Rebif.

2 I'll now turn over the podium to Dr. Panzara

3 to provide the safety overview.

4 **Sponsor Presentation - Michael Panzara**

5 DR. PANZARA: Good morning. I'm Dr. Michael

6 Panzara, and I oversee MS in neurology clinical

7 development at Genzyme. It is my pleasure to be

8 here today to share with you the safety data from

9 the alemtuzumab clinical studies. There's a great

10 deal of information in the two briefing documents

11 that you've received, so due to time constraints, I

12 am unable to review everything. My intention

13 therefore is to discuss the most important

14 information regarding the safety profile in MS and

15 assist in the interpretation of this large volume

16 of data. We will of course be available throughout

17 the day for questions.

18 The safety database consists of three active

19 control studies in relapsing MS, the three-year

20 phase 2 study and the two phase 3 studies.

21 Patients in each can enroll following completion

22 into an open-label safety study, where those who

1 had received alemtuzumab were eligible for
2 additional courses of therapy, and those who had
3 received Rebif were eligible to receive alemtuzumab
4 for the first time. All patients were then
5 followed for a minimum of 48 months.
6 My presentation will focus on two analysis
7 groups. The first is the three-year active control
8 experience, or Pool E, comparing alemtuzumab to
9 Rebif. The second is the complete alemtuzumab
10 experience, or Pool C, which encompasses all
11 available safety follow-up regardless of dose
12 received. At the time of the data cutoff for this
13 presentation, which was 26 November 2012, there was
14 a total alemtuzumab exposure of 5400 patient years
15 in 1486 patients with a follow-up of up to nine
16 years.
17 The extent of exposure in this group is
18 further illustrated here. Focusing on the
19 right-hand side of the slide, patients were
20 followed for a median of 43 months with
21 three-quarters of the patients followed for three
22 years or more.

1 The safety profile on alemtuzumab is related
2 to its pharmacodynamic activity. After an
3 intravenous infusion, the drug is rapidly cleared,
4 as shown in green on top, and cannot be detected in
5 most patients one month following the first or
6 second course of treatment. However, following
7 dosing, there is a significant decrease in the
8 number of circulating lymphocytes and repopulation
9 of these cells occurring during the annual
10 treatment interval. Following the second
11 administration, a similar depletion in repopulation
12 is observed. Importantly, cells of the innate
13 immune systems such as neutrophils are only
14 transiently affected.
15 When looking at individual lymphocyte
16 populations, what has become apparent is that
17 during the repopulation process, there is a change
18 in the proportion and number of lymphocytes. As
19 shown on the top-half of the slide, following
20 depletion, CD19 positive B cells return to baseline
21 levels within three months. In comparison, on the
22 lower half of the slide, CD3 positive T cells

1 repopulate at a different rate.
2 In addition to changes in bulk lymphocyte
3 populations, specific subpopulations have also been
4 examined to help understand the mechanism of action
5 and its impact on specific cell types. Following
6 alemtuzumab administration, we've observed an
7 increase in the relative percentage of CD4 positive
8 T cells that display a regulatory phenotype, cells
9 known to be important in immunomodulation. Other
10 shifts in subsets observed include increases in
11 memory T cells as well as immature B cells.
12 It is likely that these shifts in lymphocyte
13 populations not only play an important role in
14 maintaining efficacy in alemtuzumab treated
15 patients, but also with the autoimmune risks that
16 we've seen. Therefore, the mechanism and the
17 pharmacology was one of the three critical factors
18 that informed our risk management program. The
19 second factor was the 12-year Campath experience
20 primarily with B cell leukemia, where severe
21 infusion-associated reactions and infections are
22 part of the known safety profile with the high-dose

1 regimen. Finally, there was the early experience
2 in MS where antibody-mediated immune disorders were
3 first described.
4 Now let's see how these factors relate to
5 the profile starting with adverse events.
6 Beginning with the first row, AEs were well
7 balanced overall. Events in the alemtuzumab group
8 were primarily due to infusion-associated
9 reactions, which were defined as any event
10 occurring within 24 hours after the end of an
11 infusion.
12 Serious adverse events were likewise
13 balanced, occurring in 19 percent of patients in
14 each treatment group. The most common SAE on Rebif
15 was serious MS relapse, while those SAEs on
16 alemtuzumab were related again to infusions as well
17 as infections and autoimmunity. More patients on
18 Rebif discontinued treatment and discontinued the
19 study due to an adverse event.
20 There were six deaths in the active control
21 experience, including one on Rebif, and the details
22 are shown here. Accidents were the most common

1 cause of death. There was one event reported as a
2 cardiovascular disorder in a woman with several
3 cardiac risk factors. There was one patient who
4 died from aspiration pneumonia in the setting with
5 severe MS-related disability, and another, the
6 index case of ITP whose symptoms went unrecognized
7 prior to implementation of our risk management
8 program.
9 There were three additional deaths in the
10 extension study. The first two were due to
11 accidents. The third developed pancytopenia with
12 initial response to treatment with corticosteroids,
13 but due to non-compliance led to recurrent
14 pancytopenia and sepsis.
15 The remainder of my presentation will focus
16 on these key areas of interest, beginning with
17 infections. This slide provides an overview of
18 common infections for the active-controlled
19 experience on the left and all available follow-up
20 for the pooled dose group on the right. Infections
21 were common in both groups, but more common on
22 alemtuzumab. The types of infections seen were

1 most types commonly seen in MS patients, namely
2 upper respiratory tract infections and urinary
3 tract infections. With continued follow-up, there
4 was no increase in the risk of infection over time
5 with additional courses of treatment.
6 Next, we carefully evaluated infections that
7 we've viewed as potentially important indicators of
8 immunocompromise, namely the herpes family of
9 viruses and tuberculosis. The overall incidence of
10 these types of infections were increased in the
11 alemtuzumab patient as compared with Rebif. There
12 were two cases of active TB in alemtuzumab
13 patients, one from Russia and the Ukraine, known to
14 be endemic areas, and one case of active TB in a
15 Rebif treated patient. There were two cases of
16 latent tuberculosis, both identified incidentally,
17 one by chest X-ray and one with a positive PPD on
18 the day of the first infusion. All patients
19 received treatment and recovered.
20 Herpes simplex infections were the most
21 common infection in this category, followed by
22 varicella zoster, and occurred mostly in proximity

1 to infusions. There was one patient who
2 experienced a flu-like illness and was found to be
3 PCR positive for CMV and was successfully treated
4 with ganciclovir. There were four patients who
5 developed mononucleosis. There were no EBV
6 positive, however, lymphoproliferative disorders.
7 The increased risk of herpes simplex and
8 proximity to infusions led to the recommendation by
9 the Data Safety Monitoring Committee that all
10 patients receive acyclovir, 200 milligrams, twice
11 daily, beginning at the first infusion and
12 continuing for 28 days after the last infusion.
13 Introducing acyclovir while the phase 3 studies
14 were ongoing allowed us to assess the effectiveness
15 of this approach. Patients who received acyclovir
16 saw a significant reduction in the risk of herpetic
17 infections and associated with infusions. As a
18 result of this observation, we are recommending
19 acyclovir prophylaxis with each treatment course.
20 Serious infections occurred in 3 percent of
21 alemtuzumab treated patients and approximately
22 1 percent of Rebif patients. The types of

1 infections seen were similar to those seen in
2 common infections. There were three patients who
3 developed sepsis all in the setting of
4 pancytopenia. The first patient was mentioned
5 earlier who died from sepsis. The second and third
6 patients were successfully treated with full
7 recovery. Sepsis in the third patient occurred in
8 the setting of pancytopenia following mitoxantrone.
9 Finally, similar to the overall infection rate,
10 there was no increase in the rate of infection with
11 extended follow-up or with additional courses of
12 treatment.
13 Moving on to malignancy. This slide lists
14 all the malignancies that we have seen up to
15 June 30, 2013. Given the significance of these
16 events, we have used a later date of cutoff than
17 that used in other analysis. Focusing on the
18 right-hand side f the slide, there are a total of
19 21 patients with malignancies in the combined
20 alemtuzumab treatment groups over all available
21 follow-up. Thyroid malignancies were the most
22 common likely do to issues with ascertainment,

1 which I will address in a moment.
2 The number of malignancies observed in their
3 incidence relative to that expected in the U.S.
4 population is shown on the next slide. This table
5 shows the results of a covert analysis using the
6 U.S. Clinformatics Data Mart to estimate age-gender
7 specific incidence rates of these types of tumors
8 in MS patients. Using this cohort of over 31,000
9 MS patients as the background population,
10 standardized incidence ratios adjusted by age and
11 gender were calculated to evaluate the observed
12 number of events versus expected for the most
13 common malignancies observed only in alemtuzumab
14 treated patients.
15 As we can see, all of the confidence
16 intervals for the SIR include one, and thereby do
17 not indicate excess risk of the indicated
18 malignancies and their total, although these
19 confidence intervals are wide. We will continue to
20 evaluate malignancy risk as part of the proposed
21 post-approval safety study that you will hear about
22 later today.

1 FDA has raised a specific concern in their
2 briefing document about the risk of thyroid
3 malignancy, as these were the most common
4 malignancies seen in our program. In consideration
5 of these events, it is first important to
6 understand a bit about the epidemiology. The
7 incidence of thyroid malignancy is rising in the
8 U.S. population and is more common in women. Most
9 of this increase are from nodules less than 1
10 centimeter that are detected incidentally and later
11 determined to be papillary microcarcinoma. This
12 suggests that the increased risk is due to
13 increased detection of subclinical disease.
14 Ultrasound has become increasingly common in
15 the diagnostic evaluation of hyper- and
16 hypothyroidism, especially in the U.S. What this
17 has shown is that about 50 percent of patients in
18 this setting have nodules, and 5 to 10 percent of
19 the nodules in this setting will be malignant. In
20 this context, it is helpful to review the
21 individual cases of thyroid malignancy that we have
22 seen.

1 Reviewing these cases, we can see the events
2 that occurred in women were discovered incidentally
3 during the evaluation of thyroid disease or on
4 pathology following thyroid surgery, and all were
5 determined to be papillary carcinomas, most less
6 than 1 centimeter, consistent with the literature
7 regarding increased incidence of ascertainment bias
8 in these patients.
9 The focus of the remainder of my
10 presentation will be autoimmunity. Beginning with
11 thyroid disorders, autoimmune thyroid disorders are
12 common in MS patients and in the general
13 population. An increased frequency of thyroid
14 disorders were observed in the pilot studies in
15 alemtuzumab treated patients throughout clinical
16 development. Thyroid disorders in our studies were
17 tested for using quarterly TSH as well as an
18 educational program implemented during development.
19 They were also defined as any thyroid adverse event
20 or laboratory abnormality reported by the
21 investigator. We then performed additional
22 analyses based on abnormal TSH.

1 Clinical thyroid events were common on
2 alemtuzumab, increasing to an incidence of
3 approximately 30 percent combining both dose groups
4 over all available follow-up. Events were mostly
5 mild to moderate in severity with a 2 percent of
6 patients reporting a serious event. This included
7 a case of thyrotoxic crisis with ophthalmopathy
8 treated with thyroidectomy and decompression.
9 Thyroid events rarely led to treatment
10 discontinuation, and none led to study
11 discontinuation.
12 We then sought to characterize these thyroid
13 abnormalities further, classifying events as hyper-
14 and hypothyroidism and incorporating TSH results
15 into the analysis. Clinical hypothyroidism
16 developed in 15 percent of patients overall with
17 approximately 6 percent developing hypothyroidism.
18 There were 14 patients reported with
19 ophthalmopathy.
20 When casting a wider net looking for all TSH
21 abnormalities, TSH proved to be highly sensitive,
22 although not very specific, with 23 percent of

1 Rebif patients and 30 to 40 percent of alemtuzumab
2 treated patients showing an abnormality. Results
3 were similar when combining both the laboratory and
4 clinical definitions of hyper- and hypothyroidism.
5 Regarding treatment over all available follow-up,
6 two-thirds of patients with reported thyroid
7 disorders were treated with oral medications with
8 22 percent requiring no treatment.
9 This slide shows the incidence of first
10 thyroid abnormality or first TSH abnormality
11 occurring by year post-treatment. Most events
12 occurred within the first three years of
13 observation with all but 22 events occurring within
14 five years of last dose. However, of these 22
15 events, only two occurred outside of the study's
16 monitoring period of 48 months after last dose.
17 And these two events were isolated TSH
18 abnormalities with no clinical manifestations.
19 These findings support the 48-month, post-dose
20 monitoring period in the proposed REMS.
21 ITP was the most common immune cytopenia
22 identified during MS clinical development. The

1 index case was identified during the phase 2 study,
2 and this led to monthly platelet monitoring, the
3 introduction of a patient survey, and other
4 educational tools implemented for detection of ITP
5 and other cytopenias. Medically confirmed ITP in
6 our analyses was based upon a standard definition.
7 There were a total of 31 patients who
8 developed cytopenia in the 12- and 24-milligram
9 groups throughout all available follow-up again
10 through June 30, 2013. The most common cytopenia
11 was medically confirmed ITP, the details of which I
12 will describe in a moment. In addition, there are
13 three cases each of autoimmune hemolytic anemia and
14 autoimmune pancytopenia.
15 Focusing on ITP, there are a total of 28
16 patients who developed medically confirmed ITP.
17 Following identification of the index case, an
18 implementation of our risk management program, all
19 27 cases were detected, allowing for prompt
20 treatment and prevention of major hemorrhage. Most
21 cases were detected with platelet monitoring with
22 the remaining patients identified by patient

1 recognition of signs and symptoms. No cases were
2 identified using the monthly patient survey. All
3 patients were identified within study's monitoring
4 period of 48 months after last dose, again
5 supporting the recommended monitoring interval.
6 Of the 28 patients with medically confirmed
7 ITP, 25 received treatment. Most only required
8 steroid treatment with or without IVIG with an
9 additional 14 percent requiring a second-line
10 treatment. One patient underwent splenectomy.
11 Three patients, including the index case, received
12 no ITP treatment. This included one patient whose
13 ITP resolved spontaneously, and one patient with
14 H. pylori-induced ITP who received antibiotics and
15 responded.
16 Of the 25 patients who received treatment,
17 initial response to treatment or a platelet count
18 greater than 100,000 was achieved within a median
19 of two weeks following disease onset, and 22
20 achieved complete response within three months.
21 The remaining three patients remained stable on a
22 steroid taper. Thus, early detection of ITP with

1 prompt treatment can result in a lasting response.
2 We continue to follow these patients to ensure that
3 this complete response is maintained.
4 Glomerulonephritis is rare in the general
5 population. The historical context as to why we
6 were interested in glomerulonephritis is that there
7 were three patients identified outside of clinical
8 trials early in development. In these patients,
9 since there was no monitoring, the symptoms went
10 undetected and progressed to renal failure.
11 Monthly monitoring of urinalysis and serum
12 creatinine, as well as an educational program, was
13 implemented as a result of this to enable early
14 detection.
15 It's been shown by the literature that early
16 detection and treatment allows for preservation of
17 renal function, and you will see that in our cases.
18 These diagnoses were made based on symptom
19 detection, an increase in creatinine, proteinuria
20 or hematuria, and the diagnoses were confirmed by
21 biopsy. There were four cases of
22 glomerulonephritis, three membranous

1 glomerulonephritis, and one Goodpasture's syndrome
2 without pulmonary involvement. All events were
3 detected by the risk management program identified
4 by proteinuria, hematuria, or an elevated
5 creatinine. All occurred within 48 months of last
6 dose, and all received treatment with full recovery
7 of renal function.
8 Finally, there were several isolated
9 autoimmune events described by FDA in their
10 briefing document as likely related to alemtuzumab.
11 We searched the cumulative Campath safety database,
12 which includes the experience in B-CLL, transplant,
13 and other off-label uses, including MS. The
14 results of the search are displayed here with the
15 MS clinical trial experience on the left and the
16 Campath experience on the right.
17 What we see is that even with this broader
18 search, these are isolated events not identified as
19 risks of Campath over the 12 years of safety
20 reporting from over 41,000 patients. Nonetheless,
21 these are potentially serious events, and we are
22 committed to monitor for these and other autoimmune

1 events with postmarketing surveillance as we've
2 always done for Campath enhanced by elements of the
3 REMS being proposed for MS.
4 So what has the safety experience in MS told
5 us about alemtuzumab's safety profile? First, the
6 safety profile is well characterized, albeit with
7 serious risks. There's an increase risk for
8 infusion-associated reactions, infections, and
9 autoimmunity. Autoimmune events were successfully
10 detected following the implementation of education
11 and our monitoring program.
12 Early detection in the treatment of
13 autoimmune events is very critical, but it enables
14 positive outcomes. Safety monitoring will continue
15 in the proposed postmarketing studies, and this
16 safety experience from the clinical program forms
17 the foundation of the proposed REMS, which we'll
18 now hear about. I thank you for your attention,
19 and I turn the podium over to Jennifer Panagoulias.
20 **Sponsor Presentation - Jennifer Panagoulias**
21 MS. PANAGOULIAS: Genzyme has piloted risk
22 management efforts over the past eight years. This

1 experience has formed the foundation of a
2 multifaceted risk mitigation strategy. Our goals
3 are as follows:
4 First, to provide educational tools to
5 patients and providers that promote awareness of
6 risks and foster symptom recognition; second, to
7 mitigate the severity and complications of events
8 through early identification by intensive lab
9 monitoring; and third, to continue surveillance
10 efforts post-approval in an effort to better
11 characterize the long-term safety profile.
12 To meet these goals, Genzyme has developed a
13 comprehensive program involving three key pillars:
14 labeling, a formal REMS program, and a
15 post-approval surveillance study. Looking first at
16 labeling, a boxed warning will educate prescribers
17 on the potential for serious autoimmune adverse
18 events. Labeling will also educate prescribers on
19 other warnings and precautions based on clinical
20 experience in MS and over 12 years postmarketing
21 experience with Campath. Among these warnings,
22 screening requirements and mitigation strategies

1 for the management of autoimmunity, infections, and
2 infusion reactions will be detailed.
3 Dr. Panzara noted that the testing used in
4 clinical studies was effective in detecting
5 autoimmune AEs, therefore labeling will require lab
6 testing following the same schedule used in
7 clinical trials. Monitoring should continue for
8 four years after last treatment. In their clinical
9 review, FDA also recommended that patients be
10 monitored for four years.
11 A REMS forms the second pillar of the risk
12 mitigation strategy. As we know, a REMS is used
13 when a strategy beyond labeling is required to
14 ensure that benefits of use outweigh risks. The
15 REMS proposed for alemtuzumab includes a medication
16 guide for patients and a communication plan for
17 prescribers, with tools to educate these
18 stakeholders about important identified risks. The
19 REMS also includes elements to assure safe use or
20 ETASU that I'll detail in the slides that follow.
21 Distribution of alemtuzumab will be restricted to
22 trained and certified prescribers.

1 Looking now at the ETASU provisions,
2 physicians will complete required training and
3 certification in order to prescribe alemtuzumab.
4 Certified prescribers will enroll each patient into
5 the REMS and provide patient labeling, taking care
6 to educate the patient on symptom recognition and
7 the need for monitoring. The key to this process
8 is the commitment to comply with program
9 requirements and monitor patients for four years
10 after last administration.
11 From their review, FDA proposes that Genzyme
12 add a requirement for a periodic patient status
13 report to be submitted by the physician. This
14 would further link lab compliance to product
15 distribution. And we agree, this could be a useful
16 addition and look forward to further discussing it
17 with the agency.
18 Looking at options to decrease the burden on
19 physicians and facilitate lab tracking for their
20 patients, Genzyme will offer additional support
21 services to certified prescribers. These include
22 access to a central lab service, web-based

1 platforms of patient compliance reports, and alerts
2 that notify the physician when a test has been
3 missed.
4 As an IV therapy, alemtuzumab will often be
5 dispensed in an outpatient infusion clinic setting.
6 These facilities must then be included under the
7 ETASU provisions so it can verify enrollment and
8 compliance before dispensing drug. Healthcare
9 facilities will be trained and certified on risks
10 and program requirements in order to dispense
11 alemtuzumab.
12 Given that MS patients in particular are
13 often self-advocates who take an active role in
14 their care, they'll be asked to acknowledge the
15 conditions for safe use. A patient will sign a
16 form in enrollment to acknowledge their commitment
17 to have lab tests performed on an ongoing basis.
18 They'll also need to acknowledge their
19 understanding of the medication guide, their
20 awareness of symptoms to look for, and the need to
21 immediately report these symptoms to their doctor
22 should they occur. While the monthly surveys

1 utilized in clinical trials didn't lead to
2 identification of any AEs, their educational
3 messages were still useful, and they've been
4 carried over into the medication guide. The
5 inevitable question is whether patients will
6 continue to have tests over four years.
7 While education on the importance of testing
8 is critical, we've spent considerable time thinking
9 about ways in which we can offer support to
10 patients to help them comply with monitoring. To
11 that end, Genzyme will offer patient support
12 services, including free lab tests, access to local
13 and home phlebotomy services, electronic tools and
14 test reminders, and outreach to nurse coordinators
15 to enhance compliance.
16 Moving now to the final pillar, a
17 post-approval safety study is planned to address
18 the goal of continued surveillance. Genzyme has
19 proposed a five-year postmarketing study to better
20 characterize the long-term safety profile with a
21 specific focus on the incidence of autoimmune
22 adverse events, serious infections, malignancies,

1 and other SAEs. The multicenter study will be
2 conducted in 5,000 patients worldwide, and its
3 implementation is already underway since
4 alemtuzumab is now available in Europe.
5 Through this comprehensive, risk-mitigation
6 strategy, which includes restricted distribution,
7 we believe that benefits of use outweigh the risks.
8 In fact, Genzyme has experience in conducting
9 restricted distribution programs for other products
10 with REMS, and it's this experience that's helped
11 us identify the infrastructure needed to
12 successfully support the program from its
13 initiation and will allow us to support such a
14 program for alemtuzumab. Thank you.
15 Dr. Fox?
16 **Sponsor Presentation - Edward Fox**
17 DR. FOX: Hello. My name is Edward Fox.
18 I'm here to provide you with my perspective on why
19 the research trial program presented today supports
20 a favorable benefit-to-risk profile for
21 alemtuzumab. I'm a clinical assistant, professor
22 of neurology at the University of Texas Medical

1 Branch and a director of an MS clinic at a private
2 practice group, Central Texas Neurology
3 Consultants. At present, I have over a thousand MS
4 patients under my care, and I've been in clinical
5 practice for over 20 years.
6 My alemtuzumab involvement began over 10
7 years ago as an investigator and a steering
8 committee member in the development of the phase 2
9 and 3 trials, in which I enrolled 50 patients, and
10 I co-authored the publications that reported the
11 results of these studies.
12 With the data from the phase 2 study, the
13 steering committee worked with the sponsor to
14 design phase 3 studies that would ensure rigorous
15 assessment of the effectiveness of alemtuzumab
16 relative to the standard of care at that time,
17 Rebif. It was critical for these studies to
18 demonstrate the magnitude of efficacy and to
19 further characterize the safety profile in order to
20 establish the true benefit-risk profile of
21 alemtuzumab.
22 The rationale for the selection of Rebif as

1 the comparator was simple. I still prescribe Rebif
2 frequently today. It has been studied in relapsing
3 MS, and it's demonstrated the ability to reduce
4 relapses and slow disability progression, the key
5 clinical endpoints in treating MS. Until the
6 alemtuzumab trials, no other treatment had shown
7 superiority to Rebif.
8 The head-to-head trial design presented a
9 challenge. It was clear that a truly blinded,
10 double-dummy design was not feasible, as the
11 tolerability profiles of each product are distinct.
12 The infusion reaction seen with alemtuzumab and the
13 obvious injection site reactions and flu-like side
14 effects, well known with beta interferon
15 administration, meant that all patients would
16 unambiguously know which treatment had been
17 received.
18 The use of a blinded rater and MRI reading
19 center is common practice in MS studies, given the
20 unblinding side effects encountered in all studies
21 of MS therapies approved to date. At our site, the
22 EDSS rate was not only fully blinded to treatment,

1 he was not even aware of which of the many clinical
2 trials the individual was enrolled in. The
3 steering committee remains convinced that this was
4 the best trial design to evaluate the efficacy and
5 safety of alemtuzumab. The evidence that we've
6 seen today I believe supports that view.
7 The most important task I'm confronted with
8 on a daily basis is making the right treatment
9 decisions for my patients. As I face the challenge
10 of trying to prevent progression of my patients'
11 disease and preserve the quality of life, I
12 currently have limited high efficacy options when
13 it comes to treating patients with active MS.
14 Available options are not appropriate for or
15 effective in all patients. The substantial
16 evidence of superior efficacy demonstrated over
17 Rebif in these trials establishes alemtuzumab as a
18 high efficacy product for active relapsing MS
19 patients irrespective of the duration of the
20 disease or treatment history. Furthermore, the
21 efficacy of alemtuzumab was maintained for most
22 patients throughout year 3 in the extension trial.

1 Only 20 percent of patients received another dosage
2 of alemtuzumab, and less than 2 percent were
3 treated with another disease-modifying therapy over
4 this period of time.
5 When we designed the studies, we understood
6 that alemtuzumab came with the potential for
7 serious risk. Therefore, we put measures in place
8 to allow for early detection of key side effects.
9 Infusion associated reactions were the most
10 commonly potentially serious risk. Alemtuzumab was
11 successfully administered in our outpatient
12 infusion center, and generally these were mild to
13 moderate reactions. But infusion centers must be
14 prepared to manage potentially serious
15 hypersensitivity reactions to alemtuzumab.
16 Risk management strategies focused on early
17 detection of autoimmune disorders and were
18 implemented even prior to the start of the phase 3
19 studies, and this implementation of the trials
20 allowed us to evaluate their effectiveness. Two of
21 my patients in the trials developed ITP, which was
22 detected by the patient recognizing the clinical

1 signs. The patients were rapidly treated,
2 responded to therapy, and now have normal platelet
3 counts that have been maintained for years without
4 further treatment.
5 Similarly, patients at my site who developed
6 thyroid disease were successfully treated due to
7 early detection of their laboratory abnormalities.
8 Therefore, laboratory monitoring and patient
9 education led to the early detection of autoimmune
10 events, allowing rapid implementation of
11 appropriate treatment, reducing the severity of the
12 event, and rendering these manageable.
13 As you've heard, there's also an increased
14 incidence of infection with alemtuzumab. Patients
15 must be informed about the potential for infection
16 to ensure prompt diagnosis and treatment. In fact,
17 though, this is no different than what I do in my
18 practice everyday when prescribing any of the
19 currently available immunomodulated or
20 immunosuppressant therapies.
21 I fully support the plan to restrict access
22 to treatment to those prescribers who have been

1 properly trained on how to administer alemtuzumab
2 and on appropriate safety monitoring. Patient
3 selection is critical, and it should be limited to
4 those patients who understand the risk of treatment
5 and commit to the prolonged monitoring under the
6 program even if no additional infusions are
7 required.
8 Although the safety measures for alemtuzumab
9 are unique, I have no doubt that the REMS program
10 can be properly adhered to because MS specialists
11 see their patients on a regular basis and will
12 continue to be able to reinforce the educational
13 component and the importance of ongoing monitoring.
14 In summary, the data we've seen today
15 confirm that the benefit-risk profile of
16 alemtuzumab is favorable in early active treatment
17 naive and previously relapsing MS patients. The
18 substantial evidence of efficacy versus an approved
19 treatment has been established in both populations.
20 Alemtuzumab's benefit comes with risks, some of
21 which are potentially serious. It is important,
22 however, to put these risks into a larger context.

1 First is the risk of MS itself, which is
2 serious and disabling. Most patients continue to
3 deteriorate despite current treatment, and there
4 are few options for those with breakthrough
5 disease. No product is appropriate or effective
6 for all patients. Higher efficacy products have
7 shown a greater tendency for increased risk. I
8 have seen PML on Tysabri and other serious
9 infections, congestive heart failure, and toxic
10 leukemia on mitoxantrone. Each of these cause
11 permanent impairment or death. I've also seen
12 serious adverse events within the alemtuzumab
13 trials. But autoimmune disorders including those
14 events you've heard about today fit into a more
15 manageable, albeit serious, category.
16 In closing, I'd like to say a few words
17 about the implications of the decision you will
18 make today. I have no doubt that when I return to
19 my clinic, there will be a young patient with
20 active MS who will be looking to me to provide the
21 best possible treatment. Currently, Tysabri offers
22 what I believe to be the most effective therapy for

1 active MS. But Tysabri is not the best option for
2 all patients. So should the patient try a safer
3 less effective therapy and risk disabling relapse
4 or progression? These are the options that we face
5 today. My patients need another option.
6 Alemtuzumab should be that option.
7 I greatly appreciate the opportunity I've
8 been given to speak to you today. This concludes
9 the sponsor's presentation. Thank you.
10 **Clarifying Questions**
11 DR. FOUNTAIN: Thank you.
12 Are there any clarifying questions for the
13 sponsor? Please remember to state your name for
14 the record before you speak. And if you can,
15 please direct questions to a specific presenter.
16 And recall that we'll have much time for discussion
17 later, so these should be specific questions
18 directed to clarify the information presented from
19 the sponsor. We'll also have time to ask of the
20 FDA later.
21 Dr. Hoffmann?
22 DR. HOFFMANN: I was wondering about the

1 patient medication guide. Will that be distributed
2 to the patient prior to administration in the
3 interest of patient disclosure?
4 DR. PANZARA: Jennifer Panagoulias can
5 answer that.
6 MS. PANAGOULIAS: Yes, it will. We propose
7 it be distributed at the time of enrollment into
8 the REMS prior to receiving treatment.
9 DR. HOFFMANN: Just in follow-up, I was
10 reviewing the patient leaflet from the European
11 Medicines Agency that was approved. And in that
12 leaflet for patient information, there was no
13 discussion about malignancy and the incidence of
14 possible malignancies with this drug. And I was
15 wondering why that was not in that patient
16 information leaflet.
17 MS. PANAGOULIAS: The regulatory assessment
18 in the Europe -- through that assessment, we felt
19 that there was no risk of malignancy. That was the
20 determination of the CHMP, that there was no risk
21 of malignancy, and therefore, it was not contained
22 in the materials given to patients.

1 DR. HOFFMANN: Would it be in the United
2 States if approved?
3 MS. PANAGOULIAS: Yes.
4 DR. HOFFMANN: Thank you.
5 DR. FOUNTAIN: Dr. Rosenberg?
6 DR. PANZARA: Just as a clarification, also,
7 though, as with what we're proposing in the United
8 States, the post-approval safety study will be
9 collecting those events, and as in Europe uses in
10 their risk management program, that's something
11 that we would be collecting, along with other
12 serious adverse events to better assess the risk.
13 DR. ROSENBERG: This is addressed to
14 Dr. Cutter. What would be the expected placebo
15 response rate for measures like SAD and relapse
16 rate, judging from other trials?
17 DR. CUTTER: That is of course dependent
18 upon the distribution of EDSS. If there are more
19 zeros and 1's in the patient population in a
20 placebo trial, which is common -- because moving
21 down to earlier -- you actually get a higher
22 progression rate. So I think there is -- if you

1 look at the plot of all the active and placebo
2 rates and trials done since 2000, you end up seeing
3 placebo rates inserted within the active arms.
4 DR. ROSENBERG: Is there a comparable trial?
5 DR. CUTTER: I don't think there is a
6 comparable trial in terms of taking a cross-trial
7 comparison of a placebo arm from one trial and
8 putting it in here to know where they are. I
9 actually have a slide of that. I don't have it
10 here, but there -- if you look at the placebo rates
11 across the trials for outcomes, they embed
12 themselves, even with the same drugs being
13 compared. So Avonex uses a comparator in a number
14 of trials, and the rates vary quite substantially.
15 DR. FOUNTAIN: Dr. Clancy?
16 DR. CLANCY: I have a question for Dr.
17 Douglas Arnold. First of all, I enjoyed the
18 animation of the patients' lesions and how dynamic
19 they were. And then you called our attention to
20 the second play of the movie, where the ventricles
21 enlarged. My question is, during this trial,
22 patients were also given steroids. If they had a

1 flare-up of their disease, they could also get
2 steroids of they developed -- for the 28 patients
3 who developed the ITP.
4 So how do you factor in this non-disease
5 factor that can also increase ventricular size or
6 reduce brain volume in the final calculations?
7 DR. ARNOLD: So patients were not supposed
8 to receive MRI within three weeks of obtaining
9 steroids. So that should have reduced the
10 effective anti-steroids on lesion activity-based
11 metrics and on brain volume measurements that were
12 made on MRI.
13 DR. ROSENBERG: And how was that period of
14 time decided?
15 DR. ARNOLD: I wasn't involved in this, but
16 it's the period of time during which the majority
17 of defective steroids is still present.
18 DR. ROSENBERG: All right. Thank you.
19 DR. FOUNTAIN: Dr. Lu?
20 DR. LU: This is Ying Lu. I have a question
21 for Dr. Cutter. You mentioned there are random
22 variations between the baseline and the screen EDSS

1 score. So in your review, how many previous
2 studies actually by changing the score actually
3 changes significant conclusions?
4 DR. CUTTER: Maybe I'll let Dr. Lake -- he's
5 familiar with a couple of others. I have looked at
6 several studies, and it has an impact.
7 Steve?
8 DR. LAKE: We've looked at the Sentinel
9 study for the Tysabri application. And there is
10 also another Sanofi-sponsored MS study, where we
11 also see that effect, where if you use screening
12 instead of baseline, the numbers of SAD events are
13 reduced, thus reducing study power.
14 DR. LU: But does that change the
15 significant conclusion or just still within the .05
16 level or whatever they use, the significant level?
17 DR. LAKE: It does reduce the study power,
18 but the treatment effect estimate is relatively
19 still preserved, as we've seen in our studies.
20 DR. FOUNTAIN: Ms. Sitcov?
21 MS. SITCOV: Yes. Thank you. I'm curious.
22 The sponsor states that over time, 70 percent of

1 those with relapsing, remitting develop secondary
2 progressive MS. And I wanted to know, is that even
3 with today's existing disease modifiers? I know
4 when I was diagnosed many years ago, before there
5 were even disease modifiers, I heard about
6 statistics. We didn't use terms like "secondary
7 progressive," but there were statistics that after
8 15 or 20 years -- this was based on a VA study -- I
9 think something like 75 to 80 percent of people
10 with MS remained ambulatory. And I'm just curious
11 about that 70 percent figure in light of the DMTs.
12 DR. PANZARA: Absolutely. I think the best
13 person to answer that question would actually be
14 Dr. Rudick.
15 DR. RUDICK: First of all, I think we have
16 clearly slowed the rate of progression in MS with
17 existing medication, so I certainly don't want to
18 give the impression that these are not effective
19 medications. In my own experience, we've followed
20 a cohort of patients in Cleveland with an NIH grant
21 over -- we're in the 14th year now. They're all on
22 the medications, and we're following their brain

1 size, and their brain atrophy, and their condition.
2 And what we see is that 75 percent of the patients
3 continue to have brain atrophy that's higher than
4 the healthy controls who are studied at the same
5 time, in the same protocol.
6 Now, about 25 percent of the patients in our
7 study have brain atrophy rates that are the same as
8 the healthy controls, and that may be related to
9 therapy. And about 25 percent do quite poorly, and
10 they deteriorate similar to the movie that I
11 showed. So it depends on how you define it, but we
12 have not stopped the disease with the existing
13 therapies, at least in my clinic.
14 DR. FOUNTAIN: Dr. Alexander?
15 DR. ALEXANDER: I wanted to ask -- no amount
16 of rigor, with respect to the analyses, can take
17 the place of double-blinding. So I'm a little
18 unclear. Was there a scientific rationale for not
19 pursuing a double-blinded study?
20 DR. PANZARA: The rationale that was decided
21 on was at that time, it was felt that given what
22 had been seen in the safety profile of alemtuzumab

1 in the pilot studies, the serious risk, that the
2 choice should be made to conduct the studies versus
3 what was viewed at the time to be the most
4 effective therapy. And there had been data,
5 studies done around the time of the initiation of
6 this study, that had shown that Rebif was superior
7 to Avonex, another interferon, on relapse and
8 imaging criteria. And it was those imaging and
9 relapse results that led to their superiority claim
10 in their labeling. So it was felt at the time that
11 the choice had to be made versus the most effective
12 comparator. And that's the choice that was made.
13 It was also thought about that all of the
14 study in MS that had been conducted to date had
15 issues with side effects, and thus the potential to
16 influence what was perceived to be true
17 double-blinding. And when thinking about it, we
18 wanted the most effective drug. The other studies
19 that had done rater blinding, because of unblinding
20 side effects, it was felt that this was the best
21 way to assess the benefit-risk.
22 DR. ALEXANDER: okay. Thank you. So if I

1 understood you correctly, one point is about an
2 active comparator, and then the other is about the
3 side effects, essentially, leading to some sort of
4 unblinding. So let me just ask about each of those
5 separately.
6 DR. PANZARA: Sure. One more. I'm sorry to
7 interrupt you. Just one more point is that we
8 couldn't get Rebif placebo because it was in
9 proprietary syringes, more of an operational point,
10 and we couldn't make it. So that was the other
11 point.
12 DR. ALEXANDER: So why would the use of an
13 active comparator preclude a double-blinded study?
14 DR. PANZARA: I'm sorry. I preempted your
15 question with the answer. So first is that we
16 couldn't get matching placebo that would allow us
17 to do it. And second, with the side effects of
18 alemtuzumab, namely significant rash on most
19 patients, and the other side effects at the time of
20 infusion, we could have thought the study was
21 double-blinded, but it really wouldn't be by the
22 actual profile.

1 DR. ALEXANDER: Well, wouldn't that be
2 better than the counter-factual, though? Or
3 wouldn't that be better than actually having it
4 unblinded?
5 DR. PANZARA: Again, we didn't -- the
6 operational things that were in our way precluded
7 us from doing it. And on top -- so that was the
8 first thing. And then the second element was we
9 put in place a lot of procedures that would
10 minimize any impact of doing that and then had
11 objective outcome measures like MRI that would
12 confirm objectively what we've seen in the
13 clinical.
14 So with all of these things together, the
15 view of the company and of our advisors was that
16 this study could be rigorously conducted, adequate,
17 and well controlled and yield interpretable
18 results.
19 DR. FOUNTAIN: Thank you. Dr. Zivin?
20 DR. ZIVIN: I'm going to ask this question
21 of both you and the FDA. But apparently there was
22 no agreement between the sponsor and the FDA about

1 the trial design prior to the beginning of this
2 study. Why was it allowed to proceed?
3 DR. FOUNTAIN: So we'll have an
4 opportunity -- just to interrupt you, though, we'll
5 have an opportunity to ask questions of the FDA
6 later, and so that might be a better time to ask
7 that question. But if you have one that the
8 sponsor can address from their perspective.
9 DR. ZIVIN: Yes, I want to hear it from
10 their perspective. Right.
11 DR. PANZARA: From our perspective was that
12 we had submitted protocols that described the
13 design, and that resulted in the lifting of the
14 clinical hold. And what we did as part of that
15 process, as part of the submission of the
16 protocols, we incorporated much of the agency's
17 feedback in terms of the other procedural elements
18 of the trial to achieve maximal reduction in
19 potential bias.
20 So there was no agreement in the SPA, as has
21 been pointed out, but the feedback received was
22 incorporated into the protocol. We sent the

1 protocols in as required, the requirement of
2 adequate and well-controlled studies be submitted
3 for the lifting of clinical hold. The clinical
4 hold was lifted, and we proceeded.
5 DR. ZIVIN: Then it's not a surprise to you
6 that they refused to accept your protocol design.
7 Is that correct?
8 DR. PANZARA: No, they didn't refuse to
9 accept it only under the SPA, and we couldn't come
10 to agreement as to the terms of the SPA. But the
11 protocol was allowed to proceed. And the
12 statistical analysis plan on how we were proposing
13 to analyze the studied was agreed to in 2010.
14 DR. FOUNTAIN: Okay. We'll have an
15 opportunity later to ask questions, even if they're
16 not clarifying questions.
17 Dr. Mielke?
18 DR. MIELKE: Yes. I have a clarification on
19 the study design. So you mentioned that there
20 weren't any crossovers. So are you saying that
21 none of the Rebif patients were allowed to take
22 alemtuzumab later on in the study or as an

1 open-label component?
2 DR. PANZARA: That's correct. Patients were
3 required to complete the two phase 3 studies to be
4 eligible to receive alemtuzumab in the extension
5 studies.
6 DR. MIELKE: Okay. So some of the -- after
7 the two years, though, they were -- you know, as
8 long as they completed the two years in Rebif, then
9 they were allowed to go on to the new drug.
10 DR. PANZARA: As long as they completed two
11 years on Rebif and had no safety issues that might
12 preclude them from entering into the extension
13 study -- we have listed criteria for that -- they
14 were allowed to enter the extension study and
15 receive alemtuzumab.
16 DR. MIELKE: Did that include relapse? So
17 if they relapsed on Rebif, they were still allowed
18 to --
19 DR. PANZARA: Yes. Yes.
20 Everybody -- clinical disease activity was not a
21 criteria for exclusion from the extension study.
22 Exclusion would include things like an abnormally

1 low CD4 count and those types of factors. ITP
2 would prevent them -- if they had developed ITP.
3 Things like that would prevent them from going into
4 the study.
5 DR. FOUNTAIN: Dr. Yeh, and I think this
6 will be probably the last question for the
7 clarifying questions. We'll have an opportunity to
8 clarify later.
9 DR. YEH: This is a question for Dr. Arnold.
10 I wonder if you could clarify -- thank you very
11 much for your detailed analysis of the lesion
12 volume. I was curious because in the published
13 studies, there were no differences between T2
14 lesion volumes at year 1 and -- sorry, at baseline
15 and year 2 between the groups, yet there's a
16 difference in atrophy measures. And I wonder if
17 you can clarify that a little bit more.
18 DR. ARNOLD: Specifically the difference
19 between what happens to lesion volume and atrophy?
20 DR. YEH: Well, I'm just interested to know
21 why you -- there was no detected real difference in
22 lesion volume in the published studies, the T2

1 lesion volume.
2 DR. ARNOLD: So the -- I mean, if I can
3 speak generally, in the past, lesion volume has
4 been used as a marker of the accumulated burden of
5 disease in patients who were on either no
6 treatment, or placebo, or even on some treatments
7 that were less than very effective. With
8 alemtuzumab -- and in fact in the current trials
9 with Rebif as well, instead of increasing over
10 time, the treated patients had a decrease in their
11 lesion volume associated with suppression of
12 inflammation in the pre-existing lesion. And it
13 was only after -- at least a year that the new
14 lesions, which continued to form, were sufficient
15 to actually result in some -- in a return of the
16 net lesion volume toward zero in the Rebif treated
17 patients.
18 So I think the negative results in the T2
19 lesion volume reflect the fact that both drugs were
20 very effective; there was no accumulation of lesion
21 in either group. And what we were really measuring
22 was not the intention of the outcome marker. It

1 wasn't a slowing in the accumulation of new
2 lesions. It was the anti-inflammatory effect on
3 the chronic lesion volume, which is necessarily
4 limited. There's only so much inflammation
5 present. And once you suppress that, you can't
6 really see -- there isn't much room to distinguish
7 between different treatments.
8 So I don't -- sorry, I'm not sure if I'm
9 answering your question.
10 DR. YEH: I guess -- so the additional
11 effect on atrophy -- although the inflammation was
12 suppressed due to factors that can't be established
13 through lesion volume?
14 DR. ARNOLD: Through lesion volume because
15 the lesion volume measurement in this case is
16 essentially non-informative because there is
17 no -- there's strong anti-inflammatory activity and
18 no accumulation in either group. It doesn't mean
19 there's no effect. It means it wasn't possible to
20 see a differentiation because both drugs had an
21 effect.
22 In contrast, atrophy continued, and it was

1 substantially slower in the patients treated with
2 alemtuzumab. So there we had an outcome measure
3 that did reflect on the efficacy of the drug, and
4 is dominated not so much by the lesions, but by
5 more diffuse nerve degeneration in the brain, so
6 probably measuring somewhat different biology as
7 well.
8 DR. FOUNTAIN: Okay. Thank you. We'll stop
9 questions now. I realize others may have
10 additional questions we can ask later. But in
11 fairness to the FDA, we'll take a five-minute break
12 instead of a 10-minute break. So we'll convene in
13 five minutes, and that will put us 10 minutes
14 behind. And then that means we'll break for lunch
15 10 minutes later. So we'll reconvene at 10:20.
16 (Whereupon, a recess was taken.)
17 DR. FOUNTAIN: Thank you for taking such a
18 short break. We'll now proceed with the FDA
19 presentations. Dr. Marler?
20 **FDA Presentation - John Marler**
21 DR. MARLER: Thank you. This morning I'll
22 be talking about the evidence submitted to support

1 the claim of effectiveness for alemtuzumab.
2 Dr. Sharon Yan will speak following me with a
3 discussion of statistical issues that have risen
4 during a review in the application. And then
5 Dr. Evelyn Mentari will speak about the safety
6 issues.
7 The background for this review is that the
8 applicant submitted results from two pivotal
9 phase 3 trials and a corroborating phase 2 trial.
10 This presentation will focus on the phase 3 trials,
11 especially on the fact that the trials used
12 subjective clinical outcome events -- relapse and
13 six months of sustained disability -- but did not
14 blind patients or treating physicians.
15 Genzyme asked FDA to review the trial
16 designs in 2007 before the trials started because
17 of concerns that the use of blinded EDSS raters
18 alone would not adequately control bias introduced
19 by unblinding patients and treating physicians.
20 FDA refused to agree to accept the results of any
21 trials without further review. So that review is
22 what you'll be hearing this morning.

1 At the time, FDA strongly recommended
2 double-blind designs that blinded both trial
3 subjects and treating physicians as well as for
4 EDSS raters. As the review proceeded, other
5 features of the trial became apparent that, in
6 conjunction with the unblinded design, may have
7 amplified the bias in reporting the primary events.
8 Review of the evidence presented to support the
9 applicant's claim of effectiveness for treating
10 multiple sclerosis finds substantial uncertainty
11 about the extent of any effectiveness.
12 This presentation does not stand alone. The
13 significance of the uncertainty about the
14 effectiveness of alemtuzumab must be considered in
15 the broader context of the certainty of many
16 unavoidable serious and life-changing toxicities
17 that will be described by Dr. Mentari in her
18 presentation of the safety data that follows my
19 discussion of the evidence for effectiveness.
20 The outline of my talk is a very brief
21 summary of the trial designs and the primary
22 outcome results. Then I'm going to look at the

1 results from three different perspectives. One
2 might be called an FDA regulatory, perhaps even
3 scientific, looking to ask the question, are the
4 studies in the application adequate and
5 well-controlled trials?
6 Another perspective is on the strength of
7 the results themselves and asks the question, is
8 the apparent treatment effect so large that any
9 placebo effect or bias would be overwhelmed? And
10 the third perspective is, is there consistency
11 between the two trials for the different primary,
12 secondary, and exploratory outcomes that suggest a
13 robust treatment effect despite bias in reporting
14 clinical events?
15 I think the sponsors already covered most of
16 the aspects of the trial design that are important.
17 I'll be going over some specific details about some
18 aspects of implementation of the protocol designs
19 later on, but I won't go through this slide in
20 detail.
21 I'll spend a little bit of time with the
22 primary outcome results. As you've heard several

1 times now, the trial results show an approximately
2 50 percent reduction in the annualized relapse rate
3 for both trials and, say, a 20 percent reduction in
4 the six-month SAD events in the 324 trial.
5 The results for the SAD in the 323 trial did
6 not achieve statistical significance. The reason
7 the sponsor supports the 323 as a positive trial is
8 because it met prespecified statistical Hochberg
9 criteria; essentially since even though the p-value
10 for SAD was quite high at .21 above .05, the
11 p-value for the relapse rate was below .025.
12 So let's move on to my first perspective:
13 are the 323 and 324 trials adequate and well
14 controlled? Given prior concerns about the trial
15 design and these results that are not entirely
16 positive, I proceed to answer the first of the
17 three main questions about the credibility of the
18 data submitted to support the applicant's claims of
19 safety and effectiveness.
20 Our requirements at FDA for approval are
21 that there be substantial evidence consisting of
22 adequate and well-controlled investigations that

1 the drug will have the effects suggested in the
2 proposed labeling. And the regulations go on to
3 say that the purpose of clinical investigation of a
4 drug is to distinguish the effect of the drug from
5 other influences such as spontaneous change in the
6 course of the disease, placebo effect, or biased
7 observation.
8 I'm going to go over our long-standing
9 concerns a little more from a different
10 perspective. As I said before, FDA did not agree
11 with the trial designs after special protocol
12 assessments in 2007, and the concern was that rater
13 blinding would not be an adequate compensation for
14 the unblinding of the trial patients and treating
15 physicians.
16 We did have a meeting with the applicant on
17 January 24th in 2011 and reiterated the concerns
18 about the lack of blinding, and requested that the
19 applicant submit a full discussion and analysis of
20 the impact of having the patients and treating
21 physicians unblinded. What we received in the
22 submission was a focused discussion of the blinding

1 on the relapse -- a discussion of blinding of the
2 Relapse Adjudication Panel and the success of rater
3 blinding without directly addressing the impact of
4 unblinding the patients and the treating
5 physicians.
6 FDA regulations list seven characteristics
7 of well-controlled trials. Three are most relevant
8 through this review, and I'll be discussing those
9 this morning. The first characteristic is that the
10 method of assigning patients to treatment and
11 control groups minimizes bias and is intended to
12 ensure comparability of the groups. The second
13 characteristic is that adequate measures such as
14 blinding are taken to minimize bias on the part of
15 the subjects, observers, and analysts of the data.
16 And the third characteristic is that the methods of
17 assessment of the subjects' response are well
18 defined and reliable.
19 So on to the first characteristic, the
20 comparability of the treatment and control groups.
21 In the 323 and 324 trials, the primary efficacy
22 analysis included only patients who received at

1 least one dose of the study drug. As you'll hear
2 from Dr. Yan, unblinded patients and treating
3 physicians often knew the random treatment
4 assignment before treatment started.
5 What we observed and the point we took away
6 from this is we know that patients were unblinded
7 this caused bias. And in the trial, looking at the
8 data, it's very hard to find situations in which
9 you can distinguish bias from treatment effect,
10 from placebo effect, from differences in the
11 baseline population.
12 What we took away from the dropout rates
13 was -- that occurred before treatment, to us, the
14 only obvious information added or the difference
15 was the information about the treatment group. So
16 the dropout rates before treatment were 3.1 percent
17 in the 323 trial and 5.8 percent in the 324 trial.
18 So knowing the treatment, this dropout, informed as
19 it was by knowledge of treatment, defeats
20 randomization as a method to ensure comparability
21 of the two treatment groups.
22 Not only is there informed dropout, which is

1 a problem by itself that can cause treatment groups
2 to have differences, but dropout was unbalanced in
3 the 324 trial, 12.6 percent in the interferon group
4 and 2.3 percent in the alemtuzumab group. The
5 10 percent difference in dropout rate for 324
6 suggests that for the full analysis and modified
7 intent-to-treat population, the patients in the
8 interferon group may be different on average from
9 the patients in the alemtuzumab group.
10 Using knowledge about treatment assignment,
11 physicians and patients could choose to some extent
12 the patients that were in the analysis population
13 of the trial. Hence, the course of the disease in
14 the two groups may have differed in ways that
15 influence the primary outcomes, especially for the
16 full analysis population in the 324 trial.
17 The conclusion of this review is that
18 neither trial fully demonstrated the first
19 characteristic of adequate and well-controlled
20 trials; namely because of the large number of
21 untreated randomized patients. The method of
22 assigning patients to treatment and control groups

1 did not minimize bias and assure comparability of
2 the groups in the full analysis subsets.
3 As to the second characteristic, we asked
4 the question were adequate measures taken to
5 minimize bias on the part of the subjects,
6 observers, and analysts of the data. It is in the
7 control of bias that the 323 and 324 trials have
8 their most serious weaknesses. I'll be making two
9 major points for each of the major clinical
10 outcomes. First, the primary SAD and relapse
11 events are highly dependent on subjective responses
12 from patients and treating physicians. Second, the
13 applicant's methods for controlling bias inherent
14 in reports from unblinded patients and treating
15 physicians are inadequate.
16 Before defining what an SAD event is, I need
17 to describe the Expanded Disability Data Scale
18 itself for those of you who are not familiar with
19 it. The EDSS is an ordinal clinical scale ranging
20 from zero, normal, to 10, which is death due to MS,
21 in half-point increments.
22 Determination of the EDSS follows a complex

1 algorithm involving seven domains of functional
2 neurological systems and a formal neurological exam
3 with up to 136 separate neurological exam elements.
4 These elements include limb strength, sensation,
5 vision, hearing, reflexes, mood, mentation, walking
6 distance, and bowel or bladder symptoms.
7 Most of these exam items depend directly on
8 the effort exerted by the subject to perform a
9 test, describe a feeling, or recall a symptom.
10 This is what I mean when I say subjective.
11 Conclusion. Although there are hundreds of items
12 recorded, the EDSS is very subjective, relying
13 heavily on the patient's subjective observations.
14 The SAD primary endpoint is entirely based
15 on the EDSS' scores determined every three months
16 by blinded EDSS raters. The occurrence of an SAD
17 event depends on the reference or baseline EDSS
18 score determined before starting treatment in the
19 trial. Sustained accumulation of disability for
20 patients is defined as an increase of two steps in
21 the EDSS score that is sustained over a six-month
22 consecutive period.

1 The bias that the trial protocols permit in
2 the underlying EDSS scores by unblinding the
3 patients, and to some extent the treating
4 physician, is carried forward into the
5 determination of disability events. Hence,
6 blinding EDSS raters does not control bias
7 introduced by patients and treating physicians in
8 the determination of the SAD outcome because the
9 EDSS scores are themselves biased.
10 Now let's look at relapse. Relapse is
11 defined in the protocols as new neurological
12 symptoms or worsening of previous neurological
13 symptoms where the symptoms that are attributable
14 to MS last at least 48 hours, present at normal
15 body temperature, are preceded by at least one
16 month of clinical stability, and are associated
17 with an objective change on neurological
18 examination. Please note that the objective change
19 on neurological examination is not really
20 objective. The electronic case report form uses
21 the EDSS Neurostatus exam as the primary basis for
22 the objective change on neurological examination.

1 And as we have just seen, the EDSS is itself highly
2 subjective.
3 Reporting and classifying events called
4 relapse events is much more complicated than for
5 SAD events, and consequently may be more subject to
6 bias in an open-label trial. Here is a summary of
7 the sequence of events that are described in the
8 protocol that lead to the declaration that a
9 relapse event has occurred. As I go through this,
10 please think about how knowledge of the treatment
11 being received could have affected the patients or
12 the treating physicians making each decision as the
13 relapse event is reported, evaluated, and finally
14 adjudicated.
15 Well, naturally, the patient is out of the
16 clinic. They're living their life at home, at
17 work, their usual daily activities. They must of
18 course experience the symptoms, and then recognize
19 the symptoms as a relapse. And there's a critical
20 event that has to take place. The patient has to
21 decide whether these symptoms are worthy of
22 reporting and whether to report the symptoms.

1 Having decided that they are, they have to go
2 through the effort to actually notify the site
3 theoretically within 48 hours of symptom onset.
4 There were few instructions given to the
5 patients what to do if it got to be 96 hours or two
6 weeks after the symptom onset, what they should do
7 then. But nevertheless, if they notified the site,
8 at that point, the unblinded site staff takes a
9 phone call or asks the patient about the relapse
10 that they had, and has to decide whether or not
11 it's due to, as you heard, a broken ankle or in
12 other ways is possibly related to MS -- is not
13 related to MS or definitely not related to MS.
14 The staff then needs to schedule a visit
15 within seven days of the onset of the event. And
16 at that point, the patient comes to the clinic and
17 is evaluated by a blinded rater who has no
18 reference to previous EDSS scores and with whom
19 conversation is limited to minimum historical
20 information needed to complete the EDSS.
21 The clinical event reporting then continues
22 when the treating neurologist comes into the

1 picture, and either that person or an unblinded
2 designee performs a physical examination, records
3 vital signs, takes a history of recent symptoms,
4 and orders needed laboratory tests. Then the
5 treating neurologist -- and I think this is key to
6 focus on this. That person who is unblinded
7 completes the clinical event case report form
8 source documents, determines whether there is a
9 fever or other disqualifying event, and determines
10 if treatment for a relapse is warranted. The
11 unblinded site staff then enter the data into the
12 electronic case report form. And at that point,
13 the data is prepared and sent to the Relapse
14 Adjudication Panel who reviews the data in their
15 adjudication process.
16 Let's look at the data reported to the
17 Relapse Adjudication Panel. It takes about 16
18 pages. They're relatively dense, maybe 20 lines on
19 each page. The data included the report of the
20 treating physician from the relapse assessment
21 form, including whether the clinical event was
22 attributable to MS. It contains all the 100-plus

1 elements from three -- the baseline and most
2 immediately previous and post-relapse -- EDSS
3 scores, a redacted clinical investigators adverse
4 event report, and a summary of reported prior
5 clinical events.
6 The main point here is that all the data
7 that the Relapse Adjudication Panel looks at
8 originated from an unblinded source, the patient
9 primarily and the treating physician secondarily.
10 Just as the blinded EDSS rater scores could not
11 account for patient biases, neither could the
12 Relapse Adjudication Panel account for the bias in
13 the physician and patient-dependent data reports
14 that they reviewed. The Relapse Adjudication Panel
15 had no untainted source of information and, hence,
16 could not distinguish the effects of alemtuzumab or
17 interferon from those of bias, placebo effects, and
18 baseline differences in the study population.
19 As a reviewer, I had to look at the data,
20 that the Relapse Adjudication Panel rejected the
21 same number of possible events from both treatment
22 groups in two ways: a) there was no bias in the

1 trial, or b) they couldn't detect the bias, so they
2 couldn't reject it; this all in the face of the
3 fact that based on some of the dropout rates and
4 other observations, that there probably was some
5 bias in the trial. So the conclusion about this
6 second characteristic is that the 323 and 324
7 trials did not adequately control bias on the part
8 of the subjects and the treating physicians.
9 Let's look at the third characteristic.
10 Were the methods of assessment of subjects'
11 responses well defined and reliable? Another way I
12 have of thinking of this is did the procedures in
13 the protocol limit the impact of bias on the
14 primary outcomes?
15 We've already discussed the fact that in the
16 323 and 324 trials, the subjects' knowledge of the
17 assigned treatment could influence both the relapse
18 and disability primary outcomes because they are
19 subjective in interrelated patient-report measures.
20 This bias in the EDSS affects the relapse rate as
21 well as the SAD rate because the EDSS testing
22 confirmed the presence of an "objective" change in

1 the neurological exam during an unscheduled visit
2 to assess a possible relapse event.
3 Now the question is, are there other
4 features of the trial design that increase the
5 opportunity for bias to influence the primary
6 clinical outcomes? And there are quite a few, but
7 I wanted to focus on some in particular.
8 We know from the early dropout rate that
9 knowledge of the treatment group influenced patient
10 and treating physician behavior. Given that the
11 patients and treating physicians knew the treatment
12 assignment, what other aspects were there that
13 could add to the bias expressed by the patient
14 during relapse reporting and performance of the
15 EDSS?
16 First of all, the results of the positive
17 interim results of the phase 2 trial were
18 disseminated prior to the start of those trials.
19 This would have increased the patients'
20 anticipation of a positive alemtuzumab benefit.
21 Unequal randomization would have discouraged the
22 participation of patients who were worried about

1 the safety of alemtuzumab and encouraged those who
2 expected to benefit from alemtuzumab.
3 Now, the consent form may have increased the
4 bias in an unusual way by notifying patients that
5 they would be withdrawn from the trial if they
6 became worse. For the alemtuzumab subjects who
7 wanted to stay in the trial to get the benefits
8 they expected from alemtuzumab, this requirement
9 could have reduced the likelihood that they would
10 report clinical events. The opposite would be true
11 of the interferon subjects.
12 I'll talk a little bit more about this
13 later, but I wanted to go on now and point out that
14 other aspects of the protocol allowed unblinded
15 patients and treating physicians to make choices
16 that could influence the trial outcomes. For
17 instance, the order of the events for relapse event
18 reporting is actually in the protocol as a strong
19 recommendation and not a requirement.
20 The 48-hour time limit for reporting relapse
21 and the 7-day limit for scheduling a clinic visit
22 were not really enforced, and the electronic case

1 report form did not document the time or content of
2 the patient calls. So it was hard to determine if
3 the 48-hour criteria was met and to what extent it
4 was. The protocol also didn't set time limits for
5 data in the electronic case report form that EDSS
6 scores and relapse assessment could be entered long
7 after the actual exam. This made it difficult
8 during review to go back and determine how precise
9 the procedure was and how much room there was for
10 individual judgment of physicians and patients to
11 affect the relapse reporting process.
12 I wanted to give some more attention to the
13 issue I brought up with the statement in the
14 consent form that said, "If your disease becomes
15 worse during treatment, you will be told, and the
16 study treatment will be stopped, and alternative
17 medical care will be discussed with you."
18 The consent form is completely reasonable,
19 and the same reason for withdrawal exists in many
20 trials. The point being made here is that
21 unavoidably, when you remove all doubt about
22 treatment assignment by unblinding the patients,

1 the consequences of the reason for withdrawal can
2 be different for the two treatment groups. The
3 problem is not the consent form but the
4 subjectivity of the outcomes and the ambiguities in
5 the protocols. The expectations created by the
6 consent form can affect the ways patients report
7 symptoms and the effort they exert during
8 neurological testing to determine the EDSS.
9 I wanted to add more information about the
10 use of the post-randomization baseline EDSS as a
11 reference for determining the disability rates
12 because the analysis that you'll hear from
13 Dr. Sharon Yan in the next presentation shows that
14 this aspect of the trial design may have introduced
15 bias with significant effects on the interpretation
16 of the trial results.
17 In most trials, baseline refers to the
18 status of the patient before randomization. I have
19 to confess that it was actually later in the review
20 that I tumbled to the fact that the baseline exam
21 was done after randomization because I was so used
22 to the idea that baseline referred to the

1 characteristics of the patient that was randomized
2 by testing them before randomization.
3 The 323 and 324 trials therefore are unusual
4 because baseline EDSS scores were determined after
5 randomization when many patients were unblinded.
6 In fact, we don't really have the times that the
7 baseline exams were done, the treatment, and the
8 randomization were performed. We have the dates.
9 So what we know is that some of the baseline exams
10 were done on the same day as treatment. We don't
11 know exactly the relationship between the time of
12 randomization, baseline, and actually getting
13 treatment.
14 In many subjects, the unbiased screening
15 EDSS determined immediately before randomization is
16 a more appropriate basis for determining subsequent
17 disability events. If for the 324 and 323 trials,
18 the primary SAD outcome is analyzed using the
19 screening EDSS as a basis, then there are
20 approximately 10 percent more SAD events in the
21 alemtuzumab group and 10 percent fewer SAD events
22 in the interferon beta group.

1 I'll go a little bit off script here to say
2 that what's in the back of my mind is that this SAD
3 event depends on two subsequent events, and what
4 bias -- it's really -- the bit of bias that we were
5 able to get a grip on in the trial is only the
6 first of the three, so we can't really say if
7 there's any bias that was introduced later after
8 randomization and treatment in the subsequent SAD
9 outcomes.
10 "Don't go off script." Okay.
11 (Laughter.)
12 DR. MARLER: I think I'm in the right place.
13 Yes.
14 So the statistical significance, if you just
15 change that one baseline, in the 323 trial, p
16 becomes not .21 but .86, and in the 324 trial, not
17 .0084 but .26. This is quite a significant change.
18 The six-month disability primary outcome
19 lacks statistical significance in both trials when
20 the less biased screening EDSS is used instead of
21 the post-randomization month zero baseline EDSS.
22 If the trials were well controlled, this difference

1 between screening and baseline EDSS would likely be
2 much smaller. With regard to the third
3 characteristic of adequate and well-controlled
4 trials, we conclude that the methods of assessment
5 of subjects' responses were not well defined and
6 are not reliable.
7 I was going to kind of back off and --
8 we've looked at the three characteristics of
9 well-controlled trials in 323 and 324 and
10 identified significant problems. I wanted to take
11 a look from the point of view of the subject in the
12 trial. A subject on Rebif in the 324 trial is
13 administering herself a drug that's failed to
14 prevent relapses in the past. She's likely to have
15 entered the trial with positive expectations for
16 alemtuzumab, perhaps having heard of the remarkably
17 positive interim results from the phase 2 trial and
18 knowing that the chances of receiving alemtuzumab
19 were 4 to 1 or 2 to 1.
20 She may be disappointed that she was
21 assigned to interferon and may worry that it will
22 fail her once again. She knows from the consent

1 form that if she gets worse, she'll be withdrawn
2 from interferon. It's quite possible that she
3 would have a lower threshold for reporting possible
4 relapse events and would be more likely to
5 overstate than understate her symptoms, perhaps
6 desiring to stop taking interferon and start
7 another treatment.
8 The patient in the alemtuzumab group of the
9 324 trial is likely to have the same positive
10 expectation of alemtuzumab and is glad to be
11 assigned to the preferred drug. It's likely that
12 fewer relapses are expected by both the patient and
13 the clinical staff, and the patient may be
14 reluctant to report possible relapses, fearing that
15 the study treatment will be stopped as promised in
16 the consent form. Investigators' and patients'
17 vigilance for relapses may be lower than it is for
18 those taking interferon.
19 There is some evidence that knowledge of
20 treatment assignment influences patients' responses
21 for the early dropout rate before patients received
22 any treatment differed in the two treatment groups

1 of the 324 trial. And then there are the different
2 results using blinded screening compared to
3 unblinded EDSS scores in the analysis of the
4 six-month SAD primary outcomes. And I always
5 wondered if the improvement in EDSS for the
6 alemtuzumab group, looked at from a different
7 perspective, couldn't be evidence of bias.
8 Less strong evidence of bias comes from the
9 improvement in the average EDSS score over two
10 years in patients on alemtuzumab. The applicant
11 points out that this is unusual for a degenerative
12 disease like MS, and claims that the unexpected
13 improvement is a direct effect of alemtuzumab.
14 Another explanation could possibly be that the
15 improvement in the alemtuzumab patients was due, at
16 least in part, to placebo effect and bias
17 introduced by the subjects' positive expectations.
18 In summary, the 323 and 324 trials failed to
19 demonstrate three important characteristics of
20 adequate and well-controlled studies needed as
21 evidence of safety and effectiveness.
22 Well, that's one perspective. Let's address

1 another perspective and ask the question, is the
2 apparent treatment effect so large that any bias or
3 placebo effect could be overwhelmed? In other
4 words, are we dealing with penicillin? Are the
5 effects of alemtuzumab so remarkable and specific
6 that any effect of bias is crowded out by the
7 direct effects of the antibody?
8 Well, three zeros in front of the 1 is
9 significant; there's no doubt about that and raises
10 the question, when you're looking for bias, does a
11 p-value less than .01 really overwhelm any
12 reasonable estimate that you could make about what
13 the effect of bias was or placebo effect? This
14 question is most relevant to the difference in the
15 relapse rates, where the p-value is so remarkably
16 small in both trials.
17 I think the best way I could come up with to
18 test the sensitivity of the p-value to over- and
19 under-reporting by patients was to consider, like
20 the primary relapse rate outcome -- to look at the
21 similar outcome, the proportion of patients who
22 were relapse-free, an outcome that had p-values

1 also of .001 for both trials. The statistics were
2 a little simpler, and I could understand it.
3 The 324 trial had the most positive results
4 for relapse-free rate with 147 patients with
5 relapses in the 426-patient alemtuzumab group, and
6 104 patients with relapses in the 202-patient
7 interferon group. Now, this is the full analysis.
8 It doesn't include the patients that dropped out.
9 So you think about the patients on
10 alemtuzumab. There were 279 that didn't report
11 relapses. But what would be the effect of them
12 under-reporting relapses to shift the p-value above
13 .05. And likewise, with 104 patients who had
14 relapses in the Rebif group, what if some of those
15 relapses were over-reported?
16 Well, this table was constructed. Dr. Yan
17 helped me construct the table to my specifications,
18 and I believe it refers to the p-value for the
19 different percentages of over-reporting.
20 Over-reporting in the Rebif group and
21 under-reporting in the alemtuzumab group, you can
22 look up what the p-value would be. This table

1 shows that small changes in under- and
2 over-reporting I think dramatically affect the
3 trial p-value for the results. If 28 patients,
4 10 percent of the alemtuzumab patients and
5 6 percent of interferon patients, under-reported or
6 over-reported relapses, then the p-value goes to
7 .07 for the number of patients free of relapses.
8 Relatively low rates of under- and
9 over-reporting of relapse events could make a
10 treatment effect that was not statistically
11 significant appear to be highly significant. The
12 large effect reported by the applicant could be
13 explained by relatively small differences caused by
14 bias, placebo effect, or baseline variations in the
15 full analysis population.
16 Let's look at the results from a different
17 perspective. Is there consistency between the
18 results for the two trials or among the different
19 domains represented by the primary, secondary, and
20 exploratory outcomes that would suggest a robust
21 treatment effect and a limited role of bias in the
22 two primary outcomes.

1 We've already looked at the primary outcome
2 results. And although there's astounding
3 consistency across the relapse rate, even with the
4 unblinded design, there is some doubt about the
5 consistency in disability in the results as they're
6 reported by the applicant. There are also
7 inconsistencies between the prespecified secondary
8 outcomes. As might be expected from the six-month
9 disability outcomes, the change in EDSS was
10 statistically significant in the 324 trial and not
11 in the 323 trial.
12 But for me, the surprise is that the
13 prespecified MRI outcome, chosen by the applicant
14 before the trial started, a change in T2 lesion
15 volume that was positive in the data supporting
16 approval of the active comparator, failed to
17 achieve statistical significance in both the 323
18 and 324 trials. MRI outcomes are not surrogates
19 for clinical benefit, but we are accustomed to
20 seeing high degrees of correlation between MRI
21 outcomes and clinical outcomes. The correlation is
22 lacking in the 324 trial.

1 Looking here at some of the two-year
2 tertiary clinical and composite clinical MRI
3 outcomes, we see some inconsistent results across
4 trials for several of the outcomes. One surprising
5 finding here is that the three-month disability
6 outcome in the 324 trial does not confirm the low
7 p-value reported in that same trial for the
8 six-month SAD outcome.
9 The exploratory or tertiary MRI findings are
10 not consistent from trial to trial and differ from
11 highly significant and consistent MRI findings we
12 generally see with approved drugs for MS. It's
13 true that you can pick out some very positive
14 results, but there are almost as many negative
15 results to pick from as well.
16 With regard to our search for a consistent
17 pattern of effectiveness that would offset our
18 concerns about the biases, placebo effect,
19 introduced by the unblinded design, there are
20 troubling inconsistencies across the trials and
21 outcome domains. The likely less biased MRI
22 results do not support the positive findings in

1 reduced relapse rates, but they do support the
2 findings of Dr. Sharon Yan in both trials of no
3 evidence for a reduction in the sustained
4 accumulation of disability.
5 The lack of significance for the three-month
6 disability outcome in the 324 trial stands in
7 contrast to the highly significant difference
8 reported in the application for the six-month SAD
9 rates. Those findings are more consistent with
10 Dr. Yan's analysis using the screening EDSS instead
11 of the more biased baseline EDSS used by the
12 applicant.
13 So at last, beware. I have a summary, a
14 little aside, and then the conclusion. But the
15 summary of my efficacy review, looking at each of
16 those three perspectives, is that the two phase 3
17 trials in the application do not have all the
18 characteristics listed in regulations for
19 well-controlled trials. Hence, there is doubt
20 about the adequacy of the data to support the
21 applicant's claim. Two. There are inconsistent
22 results for primary, secondary, and tertiary

1 outcomes. And three, the very low relapse rate
2 p-values are sensitive to relatively small rates of
3 over- or under-reporting.
4 We're not the only reviewers concerned that
5 the studies were not well controlled. I quote from
6 the editorial that accompanied the publication of
7 the trial results. It stated that "both trials
8 confirmed a notable efficacy of alemtuzumab and
9 superiority over interferon. But the magnitude of
10 the effect is difficult to assess." I did the
11 underlining. "The only rater-blinded design might
12 have been a source of bias in assessments of
13 clinical outcomes, especially in the context of the
14 high expectations created with the phase 2
15 studies." Now granted, our review reached a more
16 negative conclusion, perhaps because we had more
17 information about the details about the limitations
18 of the blinding procedures and the trial conduct.
19 Conclusion. The applicant reports the
20 results of the trials as positive, but this claim
21 must be viewed with the knowledge that the design
22 and execution of the trials create uncertainty

1 about the extent of any effectiveness and must be
2 balanced against the certainty that there are many
3 serious and life-changing toxicities that you'll
4 hear about soon from Dr. Mentari in her
5 presentation of the safety findings. Thank you.
6 **FDA Presentation - Sharon Yan**
7 DR. YAN: Good morning. My name is Sharon
8 Yan, and I'm the statistical reviewer of this
9 submission. Dr. John Marler has covered most of
10 our concerns in efficacy. I will add more details
11 about our concerns and the questions with regard to
12 unbalanced dropout rates, validity of baseline EDSS
13 score, changes in SAD events when screening visits
14 is used as baseline, and our conclusion.
15 A large number of patients dropped out in
16 Study 324 before even receiving treatment. The
17 dropout rate before the initial treatment is
18 13 percent in the interferon group and 2 percent in
19 each of the alemtuzumab groups. The dropout rate
20 is so unbalanced that it caused our great concern
21 because these patients are not included in the
22 analysis data set. In other words, selection bias

1 might have kicked in at the very beginning of the
2 study, and the analysis data set may no longer
3 represent a randomized population.
4 Next, I will elaborate why we are concerned
5 about baseline EDSS score, its validity. Sustained
6 accumulation of disability is one of the primary
7 endpoints. It is determined by comparing the EDSS
8 score to the baseline EDSS score. Therefore,
9 baseline EDSS score is a crucial element in
10 establishing SAD. More than half of the patients
11 had their baseline EDSS actually assessed after
12 randomization.
13 I would acknowledge that a protocol does
14 allow a two-week window between randomization and
15 baseline assessment. The important thing here is
16 not when patients were assessed but when patients
17 were notified of their treatment assignment. If
18 the patients were assessed at baseline knowing
19 their treatment assignment, the assessment could be
20 biased and the baseline could be invalid.
21 Therefore, EDSS score at a screening visit may be a
22 more valid measure to serve as baseline.

1 Here is a flow chart. Patients were
2 assessed at a screening visit for eligibility.
3 After meeting the entry criteria, they were
4 randomized and had their baseline assessed at this
5 randomization visit. But there's a two-week window
6 between randomization and a baseline assessment.
7 If patients were assessed after knowing their
8 treatment, the assessment could be biased, while
9 the screening assessment is not biased because it
10 was performed prior to randomization.
11 During the review process, we asked the
12 sponsor, Genzyme, these two questions. Was there
13 any standard procedure regarding how and when a
14 patient was notified of his or her treatment? What
15 was the earliest time a patient became aware of his
16 or her treatment assignment? Here, I extracted two
17 complete sentences from Genzyme's response.
18 "The protocol did not include a standardized
19 procedure for notification of treatment assignment.
20 The earliest point at which patients could be made
21 aware of treatment assignment was after the site
22 completed the randomization process using IVRS,"

1 which stands for interactive voice response system
2 commonly used for randomization.
3 Here are the numbers of patients who had a
4 baseline assessed at randomization, and here are
5 the number of patients who were assessed after
6 randomization. As we can see, more than half of
7 the patients were assessed after randomization and
8 could have known their treatment assignment before
9 they were assessed.
10 Next, let's look at the number of SAD
11 events. These are the number of SAD events
12 originally reported using randomization visit as
13 the baseline in Study 323. This study did not
14 achieve statistical significance in the treatment
15 effect with a p-value of .22. Here are the number
16 of events when screening visit is used as baseline.
17 As we can see, the percentage of patients who had
18 SAD events is virtually the same for the two
19 treatment groups at 9 percent and the original
20 numerical difference disappeared.
21 If we look at the difference, we can see the
22 changes are moving in the opposite direction, three

1 events lower in the interferon group and four
2 events increased in the alemtuzumab, 12-milligram
3 group, representing 15 percent decrease in
4 interferon group and 13 percent increase in the
5 alemtuzumab 12-milligram group.
6 Next, let's look at the data in Study 324.
7 These are the number of SAD events originally
8 reported using randomization visit as baseline.
9 This study did achieve statistical significance
10 between alemtuzumab 12-milligram group and
11 interferon group with a p-value of less than .01.
12 Alemtuzumab 24-milligram group stopped enrollment
13 after Amendment 2, and the data is to be used for
14 exploratory purpose only.
15 Next, let's look at the number of events
16 when a screening visit is used as baseline. As we
17 can see, the percentage of patients who had SAD
18 event in alemtuzumab 24-milligram group is
19 19 percent higher than the 17 percent in the
20 interferon group. And the treatment difference
21 between alemtuzumab 12-milligram group and
22 interferon group is no longer statistically

1 significant with a p-value of .26.
2 If we look at the difference, again the
3 changes move in the opposite direction. There's a
4 six event decrease in the interferon group and a
5 six event increase in each of the alemtuzumab
6 groups, representing a 15 percent decrease in SAD
7 event in the interferon group and a 11 percent
8 increase in the alemtuzumab 12-milligram group, and
9 a 23 percent increase in the alemtuzumab
10 24-milligram group. Such outcome is consistent
11 with what we would see if there's a bias in favor
12 of alemtuzumab. When the bias at baseline is
13 corrected, the treatment difference disappears.
14 The size of these changes are quite
15 substantial, about 10 percent in all treatment
16 groups across both studies. If you recall,
17 Dr. John Marler has presented a table of p-values,
18 assuming up to 10 percent of possible under- or
19 over-reporting of relapses. As we can understand
20 now, such assumption is not from pure speculation.
21 Does bias also affect relapse rates? The
22 efficacy on relapse rate appears relatively

1 consistent. Despite this, an accurate estimate of
2 relapse rate is almost impossible due to various
3 biases, such as the selection bias in analysis data
4 set; bias introduced by patients and the physicians
5 during the study due to knowledge of treatment;
6 possible over-reporting and under-reporting of
7 relapses; and questionable design and execution of
8 the trials. Thus, the accuracy of reported effects
9 on relapse rate is uncertain.
10 In conclusion, bias appears to play a
11 prominent role in these trials. Effectiveness on
12 SAD has not been established based on inconsistent
13 nominal results, only one study showed a treatment
14 difference, which is not confirmed by the other,
15 and the loss of nominal effect when accounting for
16 baseline bias. Bias may also affect the accuracy
17 of relapse rate estimates. Thank you.
18 **FDA Presentation - Evelyn Mentari**
19 DR. MENTARI: Good morning. My name is
20 Evelyn Mentari, and today I will discuss a review
21 of clinical safety for alemtuzumab. The main
22 safety issues of concern that we will discuss today

1 include secondary autoimmunity, pneumonitis,
2 malignancies, infusion reactions, and infections.
3 Diseases caused by alemtuzumab can only be
4 detected after the diseases occur and after their
5 serious or life-threatening potential have already
6 manifested. Unlike a pill that is taken daily,
7 which can be discontinued if a problem arises,
8 alemtuzumab is administered in two treatment cycles
9 separated by one year.
10 In studies of alemtuzumab in multiple
11 sclerosis, life-threatening diseases, including
12 immune thrombocytopenia and anti-glomerular
13 basement membrane disease, occurred years after the
14 last dose of alemtuzumab was administered. In a
15 published study by Anderson, subjects given
16 alemtuzumab for rheumatoid arthritis had changes in
17 lymphocyte number and changes in the proportions of
18 naive and memory CD4 positive lymphocytes 12 years
19 after the last dose of alemtuzumab was
20 administered. Alemtuzumab causes rare autoimmune
21 diseases at rates up to hundreds of times greater
22 than the general population. Given the known

1 alterations in the immune system caused by
2 alemtuzumab, we are certain that these events are
3 drug related.
4 Alemtuzumab is a monoclonal antibody that
5 depletes cells carrying CD52, including T and B
6 lymphocytes. It leads to profound and prolonged
7 lymphopenia. Depletion of T and B lymphocytes
8 leads to immunosuppression, and post-treatment
9 changes in lymphocyte populations likely lead to
10 autoimmunity with alemtuzumab. Alemtuzumab has
11 been described as causing a resetting of the immune
12 system, and this process starts with an almost
13 complete depletion of certain lymphocyte subgroups.
14 In a published study of four subjects from the
15 extension trial, CD4 positive and CD8 positive
16 lymphocytes were decreased by 99.8 percent and
17 98.5 percent, respectively at day 7.
18 This figure displays the median total
19 lymphocytes counts over time. This line indicates
20 the upper limit of normal for lymphocyte count, and
21 this line indicate the lower limit of normal for
22 lymphocyte count. After the initial drop in

1 lymphocyte count, lymphocytes gradually repopulate
2 with different lymphocyte subsets repopulating at
3 different rates. Lymphocyte depletion can be
4 prolonged, especially in certain cell subgroups.
5 Fifty-seven percent of subjects had unresolved
6 decreases in CD4 positive lymphocyte count after a
7 median of two years of follow-up in Genzyme
8 studies.
9 A wide range of autoimmune diseases have
10 been reported after alemtuzumab therapy. These
11 include thyroid disorders, endocrine
12 ophthalmopathy, immune cytopenias, acquired
13 hemophilia A, autoimmune kidney diseases, type 1
14 diabetes, acute epitheliopathy of the retina,
15 autoimmune skin disease, and undifferentiated
16 connective tissue disorders.
17 The most common category of autoimmune
18 adverse event was thyroid disorders. In
19 alemtuzumab treated subjects receiving all doses,
20 18.5 percent of subjects had a thyroid adverse
21 event compared to 5.4 percent of interferon treated
22 subjects. Of note, an increased risk of thyroid

1 disorders with interferon in MS has been described
2 in the literature. In all studies, which include
3 the controlled trials and the extension study,
4 29.3 percent of alemtuzumab treated subjects had a
5 thyroid adverse event.
6 In controlled trials, most subjects with
7 thyroid disorders did not receive a specific
8 diagnosis. Events were described most frequently
9 as hypothyroidism or hyperthyroidism, and Basedow's
10 disease, also known as Graves' disease, was the
11 most common specific diagnosis. In a published
12 report by Daniels, thyroid dysfunction episodes
13 from the phase 2 study were categorized post hoc by
14 an endocrinologist. In this study, 22 percent of
15 all alemtuzumab subjects had Graves' hypothyroidism
16 compared to 1 percent of interferon treated
17 subjects.
18 Next, I will discuss the thyroid serious
19 adverse events reported in the applicant's studies.
20 A serious adverse event as defined by the Code of
21 Federal Regulations is any adverse drug experience
22 occurring at any dose that results in death,

1 life-threatening adverse drug experience, an
2 inpatient hospitalization or prolongation of
3 hospitalization, persistent or significant
4 disability or incapacity, or a congenital anomaly
5 or birth defect.
6 Thyroid adverse events were reported at a
7 higher frequency in alemtuzumab subjects compared
8 to interferon subjects, and there was a higher
9 proportion of subjects with Graves' disease. In
10 addition to the differences in thyroid diagnoses
11 and frequency between treatment groups, we also see
12 a difference in thyroid event severity between the
13 two treatment groups.
14 In controlled trials, 12 of 1,188
15 alemtuzumab treated subjects had a thyroid serious
16 adverse event, whereas none of the interferon
17 treated subjects had a thyroid serious adverse
18 event in controlled trials. In all follow-up that
19 included the extension study, 2.3 percent of
20 alemtuzumab subjects had a thyroid serious adverse
21 event, and 19 subjects required thyroidectomy.
22 There was a case of thyroid storm in a

1 neonate born to an alemtuzumab treated mother with
2 Graves' disease. This was a case of neonatal
3 Graves' disease, which also occurs in the general
4 population as a result of transfer of
5 anti-thyrotropin-receptor antibodies from mother to
6 fetus. This was a life-threatening event with
7 intermittent apnea and decreases in heart rate.
8 This event raises a general concern for
9 transplacental transfer of autoantibodies with
10 alemtuzumab.
11 We also saw cases of Graves' ophthalmopathy.
12 Graves' ophthalmopathy is a disease in which
13 anti-thyrotropin-receptor antibodies trigger the
14 proliferation of orbital fibroblasts. And this
15 condition can result in facial disfigurement with
16 important psychosocial consequences.
17 As we have previously discussed, 22 percent
18 of all alemtuzumab treated subjects in the phase 2
19 trial had Graves' disease according to a published
20 study. Ophthalmopathy is clinically apparent in 30
21 to 50 percent of patients with Graves' disease, and
22 this disease can be sight threatening in 3 to

1 5 percent of patients.
2 In the controlled trials in the extension
3 study, 1.3 percent of alemtuzumab treated subjects
4 had documented Graves' ophthalmopathy. Graves'
5 ophthalmopathy is likely under-reported in clinical
6 trials because its symptoms can be nonspecific, and
7 there were no formal procedures in place to detect
8 this disease. Signs and symptoms included
9 decreased vision, diplopia, eye pain, eyelid
10 retraction, and exophthalmos. Two subjects
11 required surgical decompression, which often
12 involves removal of part of the bony orbit in order
13 to allow for expansion of orbital contents.
14 Immune cytopenias are another category of
15 autoimmune disease seen after alemtuzumab, and
16 these included immune thrombocytopenia, autoimmune
17 hemolytic anemia, and autoimmune pancytopenia. In
18 Genzyme studies, including controlled trials and
19 the extension study, 2 percent of alemtuzumab
20 treated subjects had confirmed immune
21 thrombocytopenia. There was one death, which was
22 the fatal index case in which the subject had a

1 cerebral hemorrhage, and there are 18 subjects with
2 nadir platelet counts less than 20,000 cells per
3 microliter, which is a level below which
4 spontaneous and potentially fatal bleeding can
5 occur. Antiplatelet antibodies did not precede ITP
6 onset but appeared simultaneously with a drop in
7 platelet count. There are no cases of confirmed
8 ITP in controlled trials. Confirmed immune
9 thrombocytopenia was diagnosed from 4 to 51 months
10 after the first alemtuzumab dose and 1 to 39 months
11 after the last alemtuzumab dose.
12 On this slide, we have the treatment
13 response, which was already discussed by the
14 applicant.
15 The incidence of immune thrombocytopenia in
16 alemtuzumab treated subjects in Genzyme studies was
17 487 cases per 100,000 person-years. In European
18 population-based studies, the estimated incidence
19 of immune thrombocytopenia in adults is
20 approximately 2 cases per 100,000 person-years.
21 Thus, the risk of immune thrombocytopenia with
22 alemtuzumab is approximately 243 times the

1 reference rates.
2 We also saw cases of autoimmune hemolytic
3 anemia, which occurred in 3 of 1,486 alemtuzumab
4 subjects in MS studies. All three subjects tested
5 positive for direct antiglobulin antibodies, and
6 the nadir hemoglobin levels for these subjects
7 range from 2.9 to 8.6 grams per deciliter, which
8 represents a decrease in hemoglobin, ranging from
9 39 to 76 percent from reference range.
10 There was a fatal case of autoimmune
11 hemolytic anemia in a published case series of
12 seven patients treated with alemtuzumab for chronic
13 inflammatory demyelinating polyneuropathy. In this
14 published case, the patient's hemoglobin reached
15 2 grams per deciliter, and the patient died.
16 The incidence of autoimmune hemolytic anemia
17 in alemtuzumab treated subjects in Genzyme studies
18 was 51 cases per 100,000 person-years. This is a
19 rare disease with an estimated incidence of 0.8
20 cases per 100,000 person-years in a U.S.
21 population-based study. Thus, the risk of
22 autoimmune hemolytic anemia with alemtuzumab is

1 over 60 times the reference rates. There are also
2 three cases of autoimmune pancytopenia reported in
3 Genzyme studies, and this included one subject who
4 died from sepsis.
5 In addition to immune cytopenias, we also
6 saw immune coagulopathies with alemtuzumab. There
7 were cases of acquired hemophilia A in which
8 antibodies developed to Factor VIII, which is a
9 pro-coagulant factor. In the CAMMS324 study, one
10 subject developed acquired hemophilia A during
11 hospitalization after his hematocrit level acutely
12 dropped, and an acquired Factor VIII inhibitor was
13 identified after extensive evaluation.
14 There are two additional cases of patients
15 treated with alemtuzumab who were diagnosed with
16 acquired hemophilia A in other indications. There
17 is one patient who was treated for B-cell
18 lymphocytic leukemia who presented with multiple
19 sites of subcutaneous bleeding, psoas muscle
20 hematoma, arterial bleeding, and a nadir hemoglobin
21 of 4.4 grams per deciliter. A patient who was
22 treated for vasculitis died after sustaining a

1 hemoglobin of 6.1 grams per deciliter.
2 In Genzyme clinical studies, including the
3 extension study, there were 6 cases of nephropathy,
4 and these included two cases of anti-glomerular
5 basement membrane disease, 3 cases of membranous
6 glomerulonephritis, 1 case of tubulointerstitial
7 nephritis, and 1 unspecified nephropathy.
8 In clinical studies of alemtuzumab and MS,
9 the incidence of anti-glomerular basement membrane
10 disease was 340 cases per million person-years.
11 The general population incidence is reported to be
12 0.5 to 1 case per million person-years, and thus
13 the risk of anti-glomerular basement membrane
14 disease with alemtuzumab is at least 340 times the
15 reference rates.
16 Anti-glomerular basement membrane disease is
17 a rapidly progressive glomerular nephritis with a
18 high risk of progressing to end-stage renal
19 disease. There are no cases of end-stage renal
20 disease in Genzyme studies, however, there was one
21 published case and two spontaneous MedWatch reports
22 of patients treated with alemtuzumab for MS who had

1 end-stage renal disease or required chronic
2 hemodialysis. In the one published case, this
3 patient required renal transplantation despite
4 treatment for anti-glomerular basement membrane
5 disease. This subject did receive monitoring, and
6 there was no indication of disease one month prior
7 to onset of disease -- there was no indication of
8 anti-glomerular basement membrane antibodies one
9 month prior to onset of disease.
10 There were also two spontaneous MedWatch
11 reports. For one of these reports, we do not have
12 information regarding monitoring, and that subject
13 required renal transplantation. In the other
14 MedWatch report case, we do have evidence that this
15 patient received monitoring, and this patient is
16 currently receiving chronic hemodialysis.
17 Other autoimmune conditions reported after
18 alemtuzumab treatment include type 1 diabetes
19 mellitus; autoimmune acute epitheliopathy of the
20 retina; undifferentiated connective tissue
21 disorders; and autoimmune skin disease. And in
22 summary, naive T and B cells are depleted by

1 alemtuzumab to a relatively greater extent than
2 memory T and B cells, and an altered immune
3 reconstitution is a likely underlying mechanism of
4 autoimmunity with alemtuzumab.
5 Many of the autoimmune diseases seen after
6 alemtuzumab treatment are accompanied by measurable
7 pathogenic antibodies. This illustrates the broad
8 nature of the disease process that we are seeing
9 after alemtuzumab treatment. And because of this
10 broad process, many of the symptoms of autoimmune
11 disease can be nonspecific. So it is likely that
12 not all autoimmune manifestations with alemtuzumab
13 have been identified. In addition, in the
14 applicant's presentation, it was discussed that
15 many ITP events were identified by patients.
16 However, with a wide range of disease that we are
17 seeing with alemtuzumab, this is a challenging
18 prospect.
19 In addition to autoimmune diseases,
20 pulmonary diseases have also been reported after
21 alemtuzumab. Eight of 1,486 alemtuzumab treated
22 subjects had findings consistent with pneumonitis.

1 Seven were diagnosed with pneumonitis, including
2 one that had a specific diagnosis of
3 hypersensitivity pneumonitis, and one subject who
4 had progressive pulmonary fibrosis. One of the 8
5 had hemoptysis and bilateral ground glass opacities
6 on CT scan. There are no cases with evidence of
7 pneumonitis in interferon subjects in controlled
8 trials.
9 Published reports also described pulmonary
10 disease after alemtuzumab treatment. There are two
11 cases of hypersensitivity pneumonitis in
12 alemtuzumab treated multiple sclerosis patients
13 reported in the literature. There is a published
14 case report of fatal interstitial pneumonitis in a
15 chronic lymphocytic leukemia patient. And there is
16 one case of diffuse alveolar hemorrhage in a
17 patient treated with alemtuzumab for
18 immunosuppression post-kidney transplant.
19 Increased risks of some malignancies are
20 also of concern with alemtuzumab. On this slide,
21 we have a summary of information regarding six
22 cases of thyroid cancer that were seen in

1 alemtuzumab treated subjects in Genzyme studies.
2 Four of these cases occurred in controlled trials
3 compared to zero in the interferon group, and two
4 additional cases occurred in the extension trial.
5 There were two cases in which patients had evidence
6 of locally advanced disease. In one patient, there
7 is evidence of thyroid cancer in the lymph nodes,
8 and another patient had a PET scan concerning for
9 activity in the lower neck.
10 It is important to note that while the
11 applicant describes that four of these cases had
12 thyroid cancer described as microcarcinoma, the
13 other two had disease advanced beyond the thyroid,
14 so there was no middle ground between these two
15 categories. In addition, the applicant describes
16 that these cases of thyroid cancer may have been
17 discovered because of increased ascertainment.
18 However, increased ascertainment of thyroid disease
19 with alemtuzumab treatment is a direct effect of an
20 adverse event of alemtuzumab, namely thyroid
21 disease, which was observed in 30 percent of
22 patients. And in addition, the rates of thyroid

1 cancer have been reported to be increased in
2 patients with Graves' disease in published reports
3 and literature.
4 The worldwide incidence rate for thyroid
5 cancer in female alemtuzumab treated subjects was
6 130 cases per 100,000 person-years. The U.S.
7 incidence for thyroid cancer in female alemtuzumab
8 treated subjects was 298 cases per 100,000 person-
9 years.
10 The incidence of reported adverse events
11 with alemtuzumab was consistently lower in the
12 sponsor-defined non-EU, Europe, and Israel
13 geographic region, which comprised 31 percent of
14 the overall subject population. For this reason,
15 we are concerned about regional differences in
16 adverse event reporting and think that the rate
17 reported for U.S. patients may be more indicative
18 of the rate that we can expect in the postmarketing
19 period in the U.S. population.
20 The SEER thyroid cancer incidence for
21 females of all races and all ages is 18 cases per
22 100,000 person-years. Thus, the worldwide

1 incidence rate for thyroid cancer in female
2 alemtuzumab treated subjects in Genzyme trials is 7
3 times the SEER rate, and the U.S. incidence rate
4 for thyroid cancer in female alemtuzumab treated
5 subjects in Genzyme trials is over 16 times the
6 SEER rate.
7 The Worldwide incidence rate for thyroid
8 cancer in male patients in Genzyme studies was 50
9 cases per 100,000 person-years, and the SEER
10 reference rate for males of all races and all ages
11 is 6 cases per 100,000 person-years. Thus, the
12 worldwide incidence rate for thyroid cancer in male
13 alemtuzumab treated subjects in Genzyme trials is 8
14 times the SEER rate.
15 There were also three cases of melanoma
16 diagnosed in the extension study. And in addition,
17 there was one case of atypical melanocytic tumor.
18 Based on pathology, a Mayo clinic physician who was
19 consulted on this case said that the atypical
20 melanocytic tumor case should be treated like a
21 malignant melanoma.
22 The worldwide incidence rate for melanoma in

1 Genzyme MS trials, using the three melanoma cases
2 and not including the atypical melanocytic tumor
3 case, is 51 cases per 100,000 person-years. The
4 U.S. incidence rate for melanoma in Genzyme MS
5 trials was 88 cases per 100,000 person-years. In a
6 population-based study in Denmark, the incidence of
7 melanoma in MS patients from 1968 to 1997 was 18.8
8 per 100,000 person-years.
9 The SEER age-adjusted incidence rates of
10 melanoma in the U.S. are listed on this slide. The
11 median age for Genzyme subjects in MS studies was
12 33, and the interquartile range was 28 to 41.
13 Thus, the incidence rates for age groups most
14 represented in Genzyme trials ranged from 6.99 to
15 17.84 cases of melanoma per 100,000 person-years.
16 Using a conservative estimate calculated
17 from rates reported in the Danish study of MS
18 patients, the worldwide incidence rate for melanoma
19 in Genzyme MS trials is approximately 3 times the
20 reference rates, and the U.S. incidence for
21 melanoma in Genzyme MS trials is approximately 5
22 times the reference rate given in the Danish trial.

1 And just to put this in perspective, in a recent
2 meta-analysis, the risk of melanoma with the use of
3 tanning beds is actually 1.7 times reference rates.
4 Another category of safety concerns seen
5 with alemtuzumab is infusion reactions. Infusion
6 of alemtuzumab is associated with a cytokine
7 release syndrome. Prior to infusion, subjects
8 received prophylactic methylprednisolone and other
9 pretreatment medications at the investigator's
10 discretion, including antihistamines or
11 antipyretics. Ninety-two percent of subjects
12 reported an infusion reaction, and common infusion
13 reaction adverse events included fever, nausea,
14 headache, rash, flushing, hypotension, and
15 tachycardia.
16 2.5 percent of subjects in controlled trials
17 and the extension study had a serious
18 infusion-related adverse event. These included
19 life-threatening events such as anaphylaxis,
20 including one case of anaphylactic shock, cardiac
21 arrhythmias, including atrial fibrillation,
22 bradycardia, with rates in the 30's and 40's, and

1 tachycardia, chest pain, hypotension, angioedema,
2 brain stem syndrome, and headache.
3 Vital sign adverse events were frequent
4 during and after infusion. As you can see, there
5 are hundreds of adverse events indicating abnormal
6 vital signs. However, vital sign measurements
7 during and after infusion were not available.
8 Thus, the overall severity of vital sign
9 abnormalities during and after infusion could be
10 assessed. And this is an important piece of
11 information needed to assess the risk of infusion
12 as we are evaluating the possibility of bringing
13 this drug to the postmarketing setting.
14 Some subjects were routinely hospitalized
15 prior to alemtuzumab infusion, although this was
16 not described in the study protocol. The number of
17 routinely hospitalized subjects is not known.
18 Also, the optimal period of observation
19 post-infusion is unclear. Genzyme recommends the
20 observation for two hours after infusion. However,
21 serious adverse events that occurred more than two
22 hours after the end of alemtuzumab infusion

1 included bradycardia and atrial fibrillation.
2 Also, a quarter of patients who had a serious
3 adverse event had no time recorded, so we are
4 unable to assess the relationship between the onset
5 of adverse event and association of infusion in
6 those patients.
7 Postmarketing cases of serious and fatal
8 infusion reactions have been reported with the use
9 of alemtuzumab for B-cell lymphocytic leukemia.
10 Fatal infusion reactions included cardiac arrest
11 and anaphylactic shock.
12 Next, I will briefly discuss infections with
13 alemtuzumab. For the 12-milligram per day
14 alemtuzumab dose, the incidence of infection,
15 adverse events in controlled trials was
16 71.8 percent in alemtuzumab treated subjects
17 compared with 54.2 percent of interferon treated
18 subjects. Serious infections were reported in
19 approximately 3 percent of subjects compared to
20 1 percent of interferon treated subjects. And in
21 all alemtuzumab study subjects, including the
22 extension study, serious infections were reported

1 in approximately 5 percent of subjects.
2 For alemtuzumab treated subjects receiving
3 the 12-milligram per day dose in controlled trials,
4 the overall incidence of herpes viral infection was
5 higher than those receiving interferon.
6 Alemtuzumab treated subjects had a 15 percent rate
7 of herpes infection compared to 3 percent in
8 interferon patients. In all studies, including the
9 extension study, 9 percent had oral herpes, 7.6
10 percent had herpes zoster. There were 5 cases of
11 ophthalmic herpes, and 1 case of herpes meningitis.
12 A protocol for a prophylaxis for herpes was
13 instituted while the phase 3 trials were underway,
14 and this included administration of acyclovir
15 beginning on the first day of any alemtuzumab
16 treatment cycle and continuing for 28 days after
17 the last infusion day. Phase 2 study subjects did
18 not receive acyclovir prophylaxis.
19 This slide displays the incidence of herpes
20 viral infections by month and by acyclovir
21 prophylaxis in the alemtuzumab 12-milligram per day
22 group in controlled studies. And as you can see,

1 the blue bar, representing people who did not
2 receive acyclovir prophylaxis, had a higher
3 incidence of herpes events in month 1 during which
4 acyclovir was actually administered. However, in
5 later months, people who received acyclovir
6 prophylaxis actually had higher rates of herpes
7 infections.
8 This slide summarizes the data seen on the
9 previous slide. In cycle 1, subjects who received
10 acyclovir had a 21 percent incidence of herpes
11 infections, compared to a 14.3 percent incidence of
12 herpes infections in those who did not receive
13 acyclovir. And in cycle 2, in subjects who
14 received acyclovir, the rate of herpes infections
15 was 11.5 compared to 8.9, in subjects who did not
16 receive acyclovir. Thus, there is an overall
17 increase rate of herpes virus infections in those
18 who received acyclovir prophylaxis.
19 This slide summarizes the major safety
20 concerns and includes data from controlled trials
21 and the extension study. Alemtuzumab treated
22 subjects had a markedly higher risk of events in

1 all of the categories listed. On this slide, we
2 have a shorter list of events, but these events
3 were seen exclusively in alemtuzumab treated
4 subjects in Genzyme studies. And when we add up
5 the numbers for these events, the sum of subjects
6 with these adverse events is more than 8 percent.
7 In conclusion, the safety concerns seen with
8 alemtuzumab cannot be prevented by monitoring or
9 prophylactic measures, and the adverse effects of
10 alemtuzumab occur years after the last alemtuzumab
11 dose has been administered. Because the
12 postmarketing setting involves a broader range of
13 patients and less structured monitoring, there may
14 be an increased risk of serious and fatal outcomes.
15 Thank you.
16 **FDA Presentation - Nyedra Booker**
17 DR. BOOKER: Good morning. My name is
18 Nyedra Booker, and I will be discussing risk
19 management considerations for alemtuzumab. I will
20 begin with an introduction to the REMS, which is
21 also the risk evaluation and mitigation strategies.
22 I will then review the serious risks and the

1 applicant's proposed REMS, then proceed with a
2 discussion of the impact of a REMS, and conclude
3 with a summary and closing remarks.
4 The Food and Drug Administration Act of
5 2007, or FDAAA, authorizes the FDA to require a
6 REMS. A REMS is a risk management plan that
7 utilizes strategies beyond labeling to ensure that
8 the benefits of a drug outweighs its risk, and it
9 is designed to achieve specific goals to mitigate
10 the serious risks associated with the use of a
11 drug.
12 A REMS may include one or more of the
13 following. It may include a medication guide or
14 patient package insert, a communication plan,
15 elements to assure safe use, which I will discuss
16 in an additional slide, and an implementation plan.
17 This implementation plan addresses how the drug
18 will be implemented safely. And then finally, a
19 REMS must include a timetable for submission of
20 assessments.
21 FDAAA defines the following six types of
22 elements to assure safe use, which may result in

1 restricted distribution of a drug. For example,
2 prescribers may be required to have particular
3 training or be specially certified in order to
4 prescribe the drug, or the drug may be dispensed
5 only to patients with evidence of safe-use
6 conditions. For example, a patient could be
7 required to be counseled about the risks associated
8 with the drug, and then sign an acknowledgment that
9 they understand both the risks and benefits of the
10 drug. In summary, a REMS may be required if the
11 FDA determines that there are risks that may
12 outweigh the benefits of a drug.
13 As Dr. Mentari just discussed, there are
14 several major safety concerns with the use of
15 alemtuzumab, and this slide outlines the
16 applicant's proposal for addressing many of the
17 major safety concerns through a REMS. Prescribers
18 must be informed of the risks of alemtuzumab by
19 completing an education component and enrolling in
20 the REMS program. Patients must also be enrolled
21 in the alemtuzumab REMS program and be informed of
22 the risks as well as the periodic monitoring

1 requirements.

2 There's a restricted distribution in which
3 alemtuzumab would be distributed only through
4 certified healthcare facilities, and dispensing
5 facilities must be enrolled in the REMS program and
6 must verify prescriber and patient enrollment prior
7 to infusing alemtuzumab, as well as complete an
8 infusion confirmation form. This is just a form
9 that confirms that the patient has received the
10 alemtuzumab dose.

11 So a REMS can provide several tools and
12 strategies to address the serious risks with the
13 drug. In the next few slides, I will discuss what
14 a REMS for alemtuzumab will and may do. I will
15 also discuss what any REMS for alemtuzumab is
16 unlikely to do.

17 The applicant's proposed REMS will inform
18 prescribers and patients about the serious risks of
19 alemtuzumab by requiring that prescribers undergo
20 the training as part of a certification process,
21 and that they attest to understanding the serious
22 risk of the drug. The REMS will also facilitate

1 patient counseling as a part of the enrollment
2 process and require patients to acknowledge that
3 they understand the risks.
4 The applicant's proposed REMS may support
5 patient monitoring by educating patients about the
6 importance of monitoring and having them agree to
7 the monitoring requirements. However,
8 documentation of the monitoring is not required
9 under the REMS proposal that is currently under
10 review within the agency. Also, while infusion
11 centers will be educated about the program
12 requirements, documentation that patients were
13 observed for infusion reactions for the time frame
14 proposed by the applicant is not a requirement
15 under the current REMS proposal.
16 Now, we've thought about how the applicant's
17 proposed REMS might be modified to ensure
18 documentation of patient monitoring. We've even
19 considered strategies internally such as a REMS
20 requirement for enhanced tracking of laboratory
21 values and documentation of patient monitoring both
22 during and following the infusion. However, after

1 further consideration, we have determined that even
2 with these types of modifications to the REMS, the
3 following limitations still remain.
4 First, the time frame for the dosing and
5 administration of alemtuzumab does not support
6 close and frequent follow-up with the prescriber
7 without potentially creating undue burden. Also,
8 patients who discontinued alemtuzumab prior to
9 receiving the second course of therapy have little
10 incentive to continue monitoring. And as
11 Dr. Mentari has discussed, while the applicant
12 recommends observation for two hours after
13 infusion, the optimal period of observation
14 post-infusion is uncertain.
15 Also, while monitoring can support prompt
16 identification of adverse events, a REMS will not
17 mitigate most of these events observed with
18 alemtuzumab. Even if patients are fully compliant
19 with the monitoring requirements, the following
20 concerns still remain.
21 First, there is no specific strategies that
22 have been identified that will prevent or lessen

1 the frequency of the serious adverse events.
2 Second, serious adverse events can occur years
3 after alemtuzumab dosing. And then also, there is
4 a 12-month waiting period before decisions around
5 drug discontinuation can be applied, and that's due
6 to the way the drug is dosed. An importantly, many
7 of these serious events are lifelong and can be
8 debilitating or even fatal.
9 So in summary, there are many serious risks
10 with the use of alemtuzumab, and a REMS will not
11 mitigate most of these risks. At most, a REMS will
12 ensure the prescribers and patients are informed
13 about these risks, and a REMS may help mitigate
14 some of the serious outcomes associated with the
15 infusions, such as, for example, infusion
16 reactions.
17 So in closing, several REMS strategies have
18 been considered, both those proposed by the
19 applicant, as well as additional strategies that we
20 have discussed internally. However, when we
21 consider the nature of the serious risks with
22 alemtuzumab, we do not believe that any of the

1 strategies that both we and the applicant have
2 considered will ensure that the benefits of
3 alemtuzumab outweigh the risks. Thank you.
4 **Clarifying Questions**
5 DR. FOUNTAIN: Thank you.
6 Are there any clarifying questions for the
7 FDA? Dr. Bagiella?
8 DR. BAGIELLA: I wanted to ask whether or
9 not you conducted an analysis stratifying by
10 patients who were assessed at baseline on the day
11 of randomization and those who were assessed at
12 baseline two weeks after randomization, and whether
13 or not there was a difference in the response
14 between those two?
15 DR. YAN: Yes, I did analysis separate with
16 the patients in those two groups, those assessed at
17 randomization and those assessed after
18 randomization. And particularly in Study 324,
19 generally all patients -- all treatment groups have
20 lower EDSS scores at baseline at randomization
21 instead of at screening visits. But the interferon
22 group relatively has lower EDSS score for those

1 patients who were assessed after randomization.
2 DR. FOUNTAIN: Dr. Clancy?
3 DR. CLANCY: The FDA's presentation started
4 off with a discussion regarding the fact that there
5 is bias, and how do we measure, and how do we
6 define the bias. I'm often involved in recruiting
7 children into seizure trials, and we always do
8 double-blind, so that's not the issue. But I've
9 always noticed that some centers are capable of
10 bringing in 50 kids, and we struggle to get two or
11 three kids. And I'd like to be a fly on the wall
12 and know how do they bring in 50 kids, and after
13 four months, we bring in only a few, which leads to
14 the question of maybe these are the groups of
15 people who are so enthusiastic, will provide so
16 much information about how wonderful the new study
17 drug is and how pathetic their condition is now,
18 that the patients don't just have their own bias,
19 but the testing center has set them up for this
20 enthusiasm. How else could they get so many
21 patients in?
22 That leads to the question of if we were to

1 do an analysis on this patient population and
2 separate it out by those who were enrolled in these
3 large collectors of patients, the hypothesis being
4 that they were overly biased at the
5 beginning -- that's how they got so many
6 patients -- versus the other centers that had one
7 or two and gave a pretty straightforward, plain
8 description of what's involved in the study, I
9 think that actually could -- it would be
10 interesting to see whether or not the response
11 rates were significantly different between those
12 two groups because, again, the patients were
13 biased, and the examiners were biased.
14 DR. FOUNTAIN: So is the question to the
15 FDA -- are you asking do they do analysis by site?
16 Is that what you --
17 DR. CLANCY: You could collect the three
18 big-time collectors and compare it to maybe the
19 same number of patients that all came from little
20 areas, and see if that affects the outcome. And if
21 it does, I think that's further evidence that there
22 was bias because something -- someone had to be

1 magnetic enough to get that many patients.
2 DR. FOUNTAIN: Right. I guess that would go
3 to Dr. Marler maybe.
4 DR. MARLER: I guess I can say that there
5 were sites that recruited significantly more than
6 other sites, but we didn't do the particular
7 analysis that you're talking about.
8 DR. FOUNTAIN: Dr. Bastings?
9 DR. BASTINGS: The sponsor may have that
10 information, maybe.
11 DR. PANZARA: Yes, we do actually. I'll
12 turn that over to Dr. Lake.
13 DR. LAKE: Hi. So we did what is called a
14 leverage analysis. And so what we do with that is
15 we take out each site, and then recalculate the
16 treatment effect estimate and plot that on a forest
17 plot.
18 If I could have slide 1 up, please? So this
19 is showing -- slide 1 up, please?
20 DR. FOUNTAIN: It might take a moment to
21 switch.
22 DR. LAKE: Okay. All right. Sorry.

1 So what we've done here is ranked each site
2 by the number of patients that they've enrolled.
3 And then we've taken out this site -- each site and
4 then re-performed the analysis. And you can see
5 that over the course of the study -- or,
6 sorry -- over all of these sites, the treatment
7 effect estimate remains the same.
8 If we did the same as well for SAD -- I can
9 pull up slide 2, please -- we also see that a
10 specific site does not seem to be driving the
11 results. And when we take the highest enrolling
12 site out, then we see consistent effects across all
13 of these sites.
14 DR. CLANCY: Thank you. That exactly
15 answered my question. Appreciate it.
16 DR. FOUNTAIN: Dr. Unger?
17 DR. UNGER: Thanks. That's an excellent
18 suggestion. And I think maybe a more important
19 analysis that we'll do is basically just to look at
20 the results by site. It's important that we look
21 at the treatment effect by site and also the
22 variance by site because if you think there's some

1 kind of hanky-panky at a given site, and you find
2 that results at a given site are too good to be
3 true, based on the treatment effect and the
4 variance, you need to figure that out. And we've
5 seen that before, another development program. So
6 we'll take your advice. Thanks.
7 DR. FOUNTAIN: Do you have a comment as
8 well?
9 DR. YAN: Yes. We did analysis about the
10 treatment effects by sites, and we didn't find
11 large discrepancies in relapse rate. But there was
12 discrepancy in the SAD events, particularly in
13 Study 324, the relapse rate in the Eastern European
14 sites, it's higher in alemtuzumab than the
15 interferon group.
16 DR. FOUNTAIN: Thank you. And I'm sorry. I
17 should have asked everyone to please state your
18 name when you begin to speak since we're being
19 recorded.
20 I have a question that I think goes maybe to
21 Dr. Mentari. And that is, there seems to be a
22 difference in interpretation of the effect of

1 acyclovir. In the sponsor's analysis, they
2 compared the patients who had acyclovir compared to
3 those who didn't overall. And I think in your
4 analysis, it was by time. So their result found a
5 difference in incidence of herpetic infections, and
6 by your analysis, I gather you didn't. Is that
7 right?
8 DR. MENTARI: Both analyses were displayed
9 so they can be compared within the documents that
10 were distributed. I believe the analyses were the
11 same, however, the sponsor accounted for month 1
12 out of each year, and during that time, there was
13 an improvement with acyclovir. But accounting for
14 the entire year, there was no improvement overall.
15 The sponsor can comment if I have anything that
16 I've misstated.
17 DR. FOUNTAIN: I understand. Thank you.
18 Next, Dr. Zivin.
19 DR. ZIVIN: I understand that the FDA said
20 at their last statement that the risks outweigh the
21 benefits. To put that in better perspective for
22 me, I would like to know -- and I'm not sure who

1 should answer this question -- what is the
2 therapeutic index.
3 DR. MARLER: Would you like that in
4 absolute -- in disability or in relapse?
5 DR. ZIVIN: Both.
6 DR. MARLER: Well, I was afraid you might
7 say that. Why did I ask?
8 (Laughter.)
9 DR. MARLER: Perhaps the sponsor would like
10 to offer an opinion as well. I could only
11 think -- and I didn't ask for a formal analysis or
12 not -- but to look for the absolute difference
13 between those patients who were without SAD event
14 in the two groups, and using of course what I have
15 to assume might be a little bit optimistic
16 estimates. But those that were given in the
17 on-phase analysis by the sponsor showed about an
18 8 percent absolute difference in the number of
19 patients who essentially didn't have a relapse
20 because of alemtuzumab, using their analysis. I
21 guess you could look at the number of patients who
22 had no relapses over two years, but I don't

1 remember accurately what those percentages are.
2 Then the other thing that you have to
3 compute is some estimate of what the other half of
4 the equation is, the risk part of the equation.
5 And Dr. Mentari estimated that when you take the
6 really serious, add up all those little half
7 percents for melanoma and the different autoimmune
8 disorders and so on, that she got a total -- and
9 again, this is subject to however the applicant
10 wants to estimate the same thing -- was a similar
11 number, close to 8 percent, as is for disability.
12 I don't know if that's helpful at all.
13 DR. ZIVIN: Well, it gives me a general
14 feel.
15 DR. MARLER: I think that's all it should.
16 And I think it points out the dilemma that we face
17 trying to estimate the risk-benefit in this.
18 DR. ZIVIN: Should we wait until later this
19 afternoon to --
20 DR. FOUNTAIN: Yes. If there's more
21 discussion about that, that seems like a topic that
22 probably might occupy quite a bit of our time.

1 DR. ZIVIN: Okay.
2 DR. FOUNTAIN: Unless you have a specific
3 question about the data or presentation or things
4 like that.
5 DR. ZIVIN: Okay.
6 DR. FOUNTAIN: Okay. We're going to stop at
7 12:15, which is in two minutes. Dr. Hoffmann, do
8 you have a brief question?
9 DR. HOFFMANN: Yes. Richard Hoffmann. One
10 of the things I liked about Dr. Mentari's review
11 was the use of using incident rates of potential
12 adverse drug reactions compared to reference rates.
13 I think they were a more meaningful number,
14 especially for patients to consider when they're
15 making a decision whether they want to use this
16 drug or not.
17 So my question is, if this drug were
18 approved, could or would the FDA include the
19 reference rate comparison to the incident rates of
20 potential adverse drug reactions in the patient
21 medication guide so that they could actually use
22 this in their decision-making process before they

1 are administered the drug? Thank you.
2 DR. BASTINGS: I think that's something
3 that's typically handled once we have made the
4 decision to approve the product. And then we have
5 discussions with the applicant as to what has to be
6 discussed in the medication guide. So it's a
7 possibility, but that's up for discussion once
8 we've made the decision to approve the product.
9 DR. HOFFMANN: I just think it's a good
10 idea.
11 DR. BASTINGS: Right. Thank you for the
12 feedback.
13 DR. FOUNTAIN: Thank you. It's now 12:15,
14 so we'll now break for lunch. We have noted the
15 questions. And if anyone else would like to ask a
16 question, let us know. We'll keep track of that
17 because we have more time to ask questions later.
18 We'll reconvene in this room in 45 minutes
19 from now, so at 1:00, at which time we'll begin the
20 open public hearing session. Please take any
21 personal belongings you may want with you at this
22 time. Panel members, please remember that there

1 should be no discussion of the meeting topic during
2 lunch amongst yourselves or with any other members
3 of the audience. Thank you.
4 (Whereupon, at 12:13 p.m., a luncheon recess
5 was taken.)
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1 A F T E R N O O N S E S S I O N

2 (1:02 p.m.)

3 **Open Public Hearing**

4 DR. FOUNTAIN: Welcome back, everyone, after
5 lunch. There will be a few people joining us here
6 in just a few minutes.
7 Both the Food and Drug Administration and
8 the public believe in a transparent process for
9 information gathering and decision making. To
10 ensure such transparency of the open public hearing
11 session of the advocacy committee meeting, FDA
12 believes it is important to understand the context
13 of an individual's presentation.
14 For this reason, FDA encourages you, the
15 open public hearing speaker, at the beginning of
16 your written or oral statement, to advise the
17 committee of any financial relationship that you
18 may have with a sponsor, its products, and if
19 known, its direct competitors. For example, this
20 financial information may include the sponsor's
21 payment of your travel, lodging, or other expenses
22 in connection with your attendance at the meeting

1 today. Likewise, FDA encourages you, at the
2 beginning of your statement, to advise the
3 committee if you do not have such financial
4 relationships.
5 If you choose not to address this issue of
6 financial relationships at the beginning of your
7 statement, it will not preclude you from speaking.
8 The FDA and this committee place great importance
9 in the open public hearing process. The insights
10 and comments provided can help the agency and this
11 committee in their consideration of the issues
12 before us.
13 That said, in many instances and for many
14 topics, there will be a variety of opinions. One
15 of our goals today is for this open public hearing
16 to be conducted in a fair and open way, where every
17 participant is listened to carefully, and treated
18 with dignity, courtesy, and respect. Therefore,
19 please speak only when recognized by the
20 chairperson, by me. So thank you for your
21 cooperation. Each open public hearing speaker will
22 have five minutes.

1 There's a light that will blink yellow, that
2 will turn yellow when you have 30 seconds left, and
3 the red light will go off when you get to five
4 minutes. And because we have so many speakers,
5 right at five minutes, I'll ask you to conclude
6 your remarks if you haven't already. And I'm
7 afraid we won't have much discretion to go beyond
8 five minutes.
9 Will speaker number 1 step up to the podium
10 and introduce yourself? Please state your name and
11 any organization you're representing for the
12 record.
13 MR. FRANKLIN: Good afternoon. I'm Douglas
14 Franklin, and I have had the privilege of being the
15 president and chief executive officer of the
16 Multiple Sclerosis Association of America, MSAA,
17 for the past 15 years.
18 MSAA is a national non-profit charitable
19 organization that is, as our mission states, a
20 leading resource for the entire MS community,
21 improving lives today through our vital services
22 and support. Last year alone, MSAA provided direct

1 service to more than 60,000 individuals affected by
2 multiple sclerosis, and our website attracts over
3 1 million visitors each year.
4 I want to thank the members of the FDA's
5 Peripheral and Central Nervous System Drugs
6 Advisory Committee for the opportunity to briefly
7 speak to you about the new drug, Lemtrada,
8 currently under review for treating relapsing forms
9 of multiple sclerosis.
10 Before beginning, I would disclose that MSAA
11 has received grant support for our patient programs
12 from Genzyme, a Sanofi company, and a number of
13 other pharmaceutical companies. Nobody paid for me
14 to be here today.
15 As advocates for people affected by multiple
16 sclerosis, we continue to support the development
17 of safe and effective medications to treat the
18 disease. Recently, several new drugs that have
19 demonstrated improved efficacy in clinical trials
20 have reached the marketplace.
21 Based on his review of the data available,
22 MSAA's chief medical officer, Dr. Jack Burks,

1 believes Lemtrada, with its ability to reduce
2 relapses, and possibly improve disability, and
3 prevent disease progression, has the potential to
4 be a major contributor in the fight to manage MS.
5 Dr. Burks is a neurologist with more than
6 35 years of experience in this field, and he was
7 one of the co-founders in the early '80s of the
8 first medical center dedicated to MS, the Rocky
9 Mountain MS Center in Denver, Colorado. He
10 unfortunately is out of the country today.
11 As a major patient advocacy organization,
12 MSAA believes there continues to be a need for
13 additional, effective, and safe medications for MS
14 patients. These more powerful agents, however,
15 also bring the potential risk of increased safety
16 concerns. We've seen this with some other MS
17 drugs, that risk can be lessened with the
18 institution of robust risk mitigation plans, plans
19 that inform patients and physicians of possible
20 adverse effects, and he closely monitors patients
21 through clinical visits and testing.
22 The issue of risk versus benefit is one that

1 is being vigorously debated within the MS
2 community. The determination of which MS
3 medication is the most appropriate for which MS
4 patient remains elusive.
5 One size does not fit all. This is why MSAA
6 strongly believes that treatment decisions must be
7 made by knowledgeable physicians and informed
8 patients, where risks and effectiveness can be
9 weighed in the context of the patient's individual
10 and personal situations. In fact, this is one of
11 the primary reasons MSAA's SEARCH program was
12 developed, to help patients consider important
13 factors when choosing appropriate MS therapy.
14 MSAA's SEARCH program encourages patients to
15 discuss the following with their physicians, the
16 acronym SEARCH, S, safety, effectiveness,
17 affordability, risks, convenience, and health
18 outcomes. These questions help focus the
19 discussion for patients and their physicians when
20 weighing risk versus benefit. MSAA has been and
21 will continue to be very active in this arena,
22 providing education, developing tools that assist

1 both physicians and patients.
2 We are aware of the concerns that have been
3 expressed about the design of Lemtrada's clinical
4 trial and possible safety factors. These are
5 important issues for the FDA to evaluate and
6 adjudicate.
7 In summary, MSAA believes more choice and
8 additional effective treatment options are
9 beneficial for MS patients. Lemtrada has the
10 potential to be a highly effective MS treatment.
11 The risk of adverse events often increases with an
12 increase in a medication's efficacy. The
13 determination of risk versus benefit is best to be
14 considered between the treating physician and the
15 informed patient. Robust monitoring programs with
16 other treatments has proven effective in mitigating
17 some adverse effects.
18 MSAA is committed to supporting both the MS
19 patient and healthcare communities in their
20 understanding of all MS medications. I appreciate
21 the opportunity to address you today. Thank you.
22 DR. FOUNTAIN: Thank you.

1 Will speaker number 2 step up to the podium
2 and please introduce yourself? Please state your
3 name and any organization you're representing for
4 the record.
5 MR. COETZEE: Thank you, Mr. Chairman. My
6 name is Timothy Coetzee, and I am speaking on
7 behalf of the National Multiple Sclerosis Society.
8 Thank you for the opportunity to speak today. I'd
9 like to note that this statement reflects a few
10 updates from what we originally submitted.
11 I represent the largest advocacy
12 organization for people with MS in the United
13 States. The membership of our organization
14 includes more than 370,000 people self-identified
15 as having MS, as well as the families and care
16 partners of these individuals.
17 As the society's chief advocacy services and
18 research officer, I lead our comprehensive research
19 efforts aimed at stopping at mass progression,
20 restoring function, and ending the disease forever.
21 Since its founding in 1946, the National Multiple
22 Sclerosis Society has invested over $820 million to

1 advance understanding of MS and to develop new and
2 better treatments for the disease.
3 I am here today to attest to the unmet need
4 that people with MS have for additional treatment
5 options. MS is a chronic, often disabling disease
6 that attacks the central nervous system. The
7 progress, severity, and symptoms of MS are
8 unpredictable and may vary from person to person.
9 MS can have profound effects on the quality
10 of life, both for patients and their families. The
11 disease can make it difficult for individuals to
12 run, walk, maintain a productive career, pick up
13 their child, tend to everyday needs or activities,
14 and even store and retrieve memories.
15 Likewise, the family and care partners are
16 also profoundly affected by the disease. We do not
17 know the cause of MS and there is no cure. While
18 there are 10 FDA-approved medications that modify
19 the disease course for relapsing forms of MS, these
20 therapies are only partially effective.
21 We also know that some people do not respond
22 or are unable to tolerate the side effects of the

1 currently available therapies. And yet, over 20
2 years of clinical experience with currently
3 available disease-modifying therapies has convinced
4 us that the most effective means at reducing
5 disease activity and slowing the damage that
6 contributes to the future loss of neurological
7 function is early and continued treatment. Having
8 new, effective therapies with novel modes of
9 actions would provide greater options for more
10 people and especially those with active disease.
11 Some may question whether people with MS
12 would be willing to consider taking a treatment
13 option with a high risk-benefit profile in light of
14 the availability of other therapies for relapsing
15 MS. I can assure the committee that people with MS
16 are aware that some therapies will have higher risk
17 profiles, and they want to be able to make their
18 own treatment decisions in consultation with their
19 healthcare providers and care partners.
20 We know this from a variety of sources, such
21 as results of a survey that we conducted with our
22 MS constituency, at a time that another MS therapy

1 with high potential risk-benefit profile was under
2 review by the FDA. We also know this from our
3 interactions with a broad network of MS clinicians.
4 The FDA and the advisory committee play a
5 crucial role in the review of investigational
6 therapies. In this meeting, the committee is being
7 asked to consider issues related to clinical trial
8 designs as well as the risk-benefit profile of
9 alemtuzumab.
10 We recognize that the agency and the sponsor
11 have different viewpoints with regard to clinical
12 trial designs for alemtuzumab. However, we are
13 concerned that debating trial design at this late
14 stage could be perceived as minimizing the personal
15 sacrifices that hundreds of people with MS made by
16 participating in these trials. This late debate
17 could also create uncertainty and stifle innovation
18 and hope for development of new treatment options
19 for people with MS.
20 We ask the committee to carefully weigh the
21 potential benefits and risks of alemtuzumab in
22 light of the challenges of living with MS. As you

1 will hear from other speakers who live with the
2 disease, there is an urgent need for new and
3 improved treatment options to enable people with MS
4 to live their best lives.
5 The kinds of decisions being faced today
6 with alemtuzumab will likely be faced again and
7 again as new and stronger medications are
8 developed. The risks of the medications will need
9 to be weighed against the risk of doing nothing.
10 Thank you.
11 DR. FOUNTAIN: Thank you.
12 Will speaker number 3 step to the podium and
13 introduce yourself? And please state your name and
14 any organization you're representing for the
15 record.
16 MS. SCOTT: Hi. My name is Carrie Scott. I
17 have relapsing remitting MS. I was not in the
18 clinical trial for Lemtrada. I have had MS for
19 seven years. During that seven years, my life has
20 drastically changed.
21 I used to work for a large insurance
22 company. I ran a marathon and was an avid

1 exerciser. I taught step aerobics, was a huge
2 multitasker. And during the past seven years, I
3 have tried five -- six disease-modifying therapies.
4 When I was first diagnosed, there were only five,
5 so now that there are 10, it's absolutely
6 wonderful. But even with 10, MS is so different
7 for every person that it touches, that the therapy
8 has to be different for everybody.
9 My first symptom was hearing loss when I
10 exercised. So I would go deaf in my right ear.
11 And some of the symptoms that I have now include my
12 last relapse. I was unable to swallow and I lost
13 15 pounds in about four weeks.
14 I have severe nausea daily, like I'm
15 pregnant. I run fevers. I have numbness and
16 buzzing, weakness. I have electric shocks. I'm
17 weather intolerant. I have problems with balance.
18 And my worst symptom, which is invisible, is the
19 cognitive one.
20 Most of you may have a hard time remembering
21 somebody's name when you meet them. I have trouble
22 with that, but I also have trouble just remembering

1 what the conversation is about, the last word out
2 of my mouth, just in general at times where I am.
3 So those are the most frustrating because, to you,
4 I probably look okay. But I'm not.
5 I've been extremely involved with research
6 and gratitude for the people that have been trying
7 to find a cure for MS. I visit congressmen and
8 senators, and other advocates for MS. So I was
9 honored to be asked to come and speak here.
10 Because Lemtrada has been approved in
11 Europe, I'm hoping that it will make it easier for
12 it to be approved in the United States. There's
13 always the fear that someone might travel to Europe
14 to obtain something that might help them. If
15 you're desperate, and there aren't any options that
16 are working for you, you might actually make that
17 trip, and then come back and have side effects
18 here.
19 In summary, I'd just like to say that we
20 need Lemtrada. We need more disease-modifying
21 therapies that have to be safe and effective, but
22 also for the person with MS, it's their ultimate

1 choice to decide what they're willing to risk. If
2 I could not swallow food for six months, I would
3 take a lot of risks. Thank you very much.
4 DR. FOUNTAIN: Thank you.
5 Will speaker number 4 step up to the podium
6 and introduce yourself? And please state your name
7 and any organization you're representing for the
8 record.
9 MS. BURDICK: My name is Melissa Burdick,
10 and I am not here with anybody. I'm here by
11 myself. My side starts, alemtuzumab, the eagle has
12 landed, in Europe anyway.
13 Alemtuzumab was compared against the most
14 widely used class of medications in the world. It
15 as not compared against a placebo as most other
16 studies. At the end of the day, a reasonable
17 person would conclude that alemtuzumab is better
18 than the medications used in first-line therapy for
19 reducing relapses and reducing the rate of
20 worsening disability.
21 Can the FDA justify the rejection of a
22 transformational medication such as alemtuzumab

1 based on safety considerations?
2 Withdrawal from therapy due to adverse
3 events, alemtuzumab, 3.25 percent, Rebif, 12.1
4 percent. The proof is in the pudding. Autoimmune
5 thyroid diseases, alemtuzumab, 30 percent, Rebif, 4
6 percent.
7 There is a concern about a lifelong risk of
8 hypothyroidism resulting from alemtuzumab. An
9 estimated 20 million Americans have some form of
10 thyroid disease. One woman in 8 will develop a
11 thyroid disorder during her lifetime. Most thyroid
12 diseases are lifelong conditions that can be
13 managed with medication. In fact, both of my
14 sisters and my mother have hypothyroidism and will
15 be on Synthroid for the rest of their lives.
16 Generic Synthroid was prescribed over
17 70 million times last year in the United States.
18 It would be absurd to reject Lemtrada based on
19 concerns of thyroid disease. I would gladly trade
20 my lifelong MS for lifelong hypothyroidism.
21 The symptoms of MS include paralysis,
22 blindness, and incontinence versus one Synthroid

1 tablet per day. Which would you choose? You can
2 replace thyroid, but you cannot replace neurons.
3 There is a concern for increased incidence
4 of thyroid cancer, alemtuzumab, 6, Rebif, zero.
5 Most patients with thyroid cancer normally do not
6 die of their disease. You guys already went over
7 all three actions. The five-year follow-up data,
8 ITPA, alemtuzumab, 2.8 percent, Rebif, zero
9 percent. ITPA is treatable and curable. There is
10 no cure for MS.
11 The risk of PML for a patient on Tysabri,
12 from the perspective of an MS patient and why the
13 MS population needs alternative therapies -- as of
14 July 2nd, 2013, 88 patients have died from PML.
15 PML-reported cases while on disease-modifying
16 therapy as of October 2013, alemtuzumab, zero,
17 Tysabri, 401. How can you justify a rejection of
18 Lemtrada due to potentially lethal complications
19 when Tysabri has already resulted in 88 lethal
20 complications and hundreds of patients with severe
21 disability due to PML?
22 Death is a complication of disease-modifying

1 therapy, alemtuzumab, 1, an unrecognized ITPA in
2 phase 2 trial, Tysabri, 88. After adopting a risk
3 management strategy for Lemtrada and comparing it
4 to the risk of Tysabri, a reasonable person would
5 conclude that Lemtrada is safer than Tysabri.
6 The risk of PML for a patient who is
7 JCV positive and has been on the drug for more than
8 48 months is 1 in 164. If your risk of PML was 1
9 in 164, would you choose to stay in Tysabri?
10 Patients like me were started on Tysabri after we
11 failed or could not tolerate the other available
12 therapies.
13 Seventy percent of patients who start on
14 Tysabri withdraw from therapy by 48 months due to
15 fear of PML. The patients who fail the
16 injectables, who then switch to Tysabri, who now
17 fear PML, can choose to go on oral therapy. What
18 happens if these patients can't tolerate the oral
19 therapies or relapse? An alternative therapy such
20 as Lemtrada is needed for these people.
21 A new treatment paradigm, zero tolerance, no
22 disease activity, escalate therapy slowly as

1 disease worsens, treat the disease at the earliest
2 presentation with the most effective therapy,
3 maintenance therapy versus induction therapy.
4 Who should make these choices? In the new
5 era of personalized medicine, the regulators should
6 enable the patients and neurologists to make these
7 choices. Alemtuzumab durable remission, cure for
8 some patients, both outcomes are beneficial.
9 Do we need to wait 20 years to find out, or
10 can we manage the risks and offer this option now?
11 Alemtuzumab offers the MS patients a 50 or
12 60 percent chance of durable remission or cure in
13 exchange for a 30 percent chance of thyroid disease
14 and 3 percent chance of ITP. I call that a
15 no-brainer. Time is brain. If you or one of your
16 family members had MS, wouldn't you want them to
17 have a choice? We as patients deserve the right to
18 have a choice.
19 I also wanted to comment on the double-dummy
20 placebo. If you gave patients a placebo, we as
21 patients who have been on the infusions, whether
22 it's subcutaneous or intramuscular, would know the

1 difference as soon as we were on it for one or two
2 treatments, as well as the infusion. You would get
3 a rash, so you would know.
4 I'm going on Tecfidera. If that does not
5 work for me, I have no other options available if
6 Lemtrada is not passed. Thank you.
7 DR. FOUNTAIN: Thank you.
8 Next is speaker number 5. Please step up to
9 the podium and introduce yourself. Please state
10 your name and any organization you're representing
11 for the record.
12 MS. GUESS: Good afternoon. I'm Teresa
13 Guess, and I would like to disclose that my travel
14 has been supported by Genzyme. I have been a
15 registered nurse for 21 years and an MS patient for
16 13 years. I became a board-certified MS nurse in
17 2008.
18 I'm very, very pleased to be here today to
19 share my story with you all; and more than ever and
20 I'm blessed to be able to make my way through this
21 hotel, into this meeting room, and up to this
22 podium without the use of my cane or my scooter.

1 I began my fight against MS with Avonex many
2 years ago, suffered many side effects. Moved on to
3 Betaseron, and then Betaseron with methotrexate,
4 and in double-dose Betaseron. As my MS worsened,
5 my EDSS was 6.5, and I was in the 79th percentile
6 of MS disease severity. I had great difficulty
7 with my mobility. I was weak. My cognition had
8 greatly decreased. I had lost brain volume. I
9 could hear you, but I couldn't comprehend what you
10 were saying. And when I wanted to reply, the words
11 were garbled. You couldn't understand what I was
12 saying. I lost my job.
13 My neurologist, Dr. Sam Hunter, presented me
14 with two options, Tysabri or Campath. He said my
15 window of opportunity was quickly closing, and that
16 we needed to make a decision, and we needed to make
17 it and follow through with it quickly.
18 I asked him, "If I were your sister and that
19 was your sister's chart that you're holding in your
20 hands, what would you say to her?" To which he
21 replied, "Campath hands down." So I looked at him
22 and I said, "Okay. Let's do it." I had been given

1 sufficient information on both drugs. I'd been
2 well educated about the protocol, and I knew what
3 risks were involved. I knew what the side effects
4 may be headed my way, but I was ready to take that
5 risk.
6 My first round of alemtuzumab was in April
7 of 2008. As I said, I had been well educated on
8 what might happen, so when I broke out in the
9 lovely pink rash, I wasn't too awfully terrified.
10 But I do want to share with you, if you're ever
11 having a round of alemtuzumab and you start to
12 cough just to clear your throat, beware, they will
13 bring the crash cart and they will yell for the
14 neurologist. I learned that very, very quickly.
15 They are on top of things at those infusion
16 centers.
17 Upon recovering from the first round of
18 alemtuzumab, I felt so good, I had forgotten what
19 feeling good felt like. It was absolutely amazing.
20 My second treatment was in 2009, and my third
21 treatment in January of 2013.
22 Alemtuzumab has given me back my quality of

1 life. It has allowed me to return to things that I
2 have not been able to do for many years because of
3 MS. I can run, I can play with my four
4 grandchildren, and I can ride a bike with my niece
5 and my nephew. I don't have to simply sit on the
6 sidelines and watch life go by anymore.
7 MS doesn't just affect the patient. It
8 affects the entire family. When my oldest
9 grandchild was five -- she's 10 now. When she was
10 in kindergarten at age five, I went to her school
11 to have lunch with her, and I was walking with my
12 cane. And this little boy looked at her and he
13 said, "Hailey, how come your grandma is walking
14 with that stick?" To which my little granddaughter
15 replied with her hands on her hips, "My mammy has
16 multiple ferocious and that's not a stick. It's a
17 cane."
18 It affects the entire family. That's why I
19 fight so hard to be mobile. That's why I wanted to
20 take the risk. We need to please allow other
21 people who are suffering the devastating effects of
22 multiple sclerosis to have an option, to have the

1 option of alemtuzumab to fight their disease so
2 that they can continue to live the good life, so
3 that they can continue to reach their goals, and do
4 the things that are important to them and to their
5 families.
6 Sometimes we don't realize what we have
7 until we lose it, and we take so much for granted.
8 Were you able to get up out of the bed this
9 morning, walk to the bathroom, get dressed without
10 asking for help? A lot of MS patients were not
11 able to. Please give these patients another chance
12 at life.
13 Sometimes, I get so excited I just want to
14 jump up and down, just because I can. Thank you.
15 DR. FOUNTAIN: Thank you.
16 Next is speaker number 6. Can you please
17 step up to the podium and introduce yourself? And
18 please state your name and any organization, if
19 you're representing one, for the record.
20 DR. GOLDBLATT: My name is David Goldblatt.
21 I am a neuroradiologist from Austin, Texas. I'm
22 married and I have two grown children. My wife and

1 I are empty-nesters. I've been in practice in
2 Austin for 25 years, and a lot of my work has
3 involved diagnosis and follow-up of patients with
4 MS.
5 So it was ironic when I woke up one
6 morning -- I think it was in 2000 -- and I couldn't
7 feel anything from my waist down. And I kind of
8 knew what was going on, I thought, because I didn't
9 think I'd had a stroke in my spinal cord, so I was
10 pretty sure that I had MS. And that was verified
11 shortly. I went on the interferon treatment in the
12 beginning, and that was fine. I tolerated it well.
13 I know there's a lot of people that don't.
14 I had a large flare when I was on Rebif. I
15 put my phone to my ear one morning, and I couldn't
16 feel my ear. And then my whole face got numb, and
17 my shoulder, and arm. And when it got to my hand,
18 I started really worrying about was I going to be
19 able to do my job, because at that time, I was
20 still doing arteriograms, and I needed to feel
21 somebody's pulse with my left hand if I wanted to
22 stick the artery. It was a real big concern at

1 that point. I had not really dealt with the issue
2 of was I going to be able to work or not.
3 At that time, I was offered the opportunity
4 to take alemtuzumab, Campath at the time, and I
5 decided to. I felt like I had really good
6 information about what my risks were. I felt like
7 it was eyes wide open. I knew that I was taking a
8 risk, and I know that I continue to take a risk at
9 this time. I am now 10 years following my first
10 treatment, and I have not had any clinical anything
11 in that time. I have had no imaging evidence of
12 disease activity. And I am not sure at what point
13 you saw that somebody is cured. I really don't
14 know about that. I know for a lot of cancers, it's
15 five years.
16 So I feel really, really fortunate that I
17 was allowed the opportunity to take this therapy.
18 I believe that it was, for my life, a miracle. I
19 was -- my original disease involved my spinal cord,
20 and I still have trouble walking a little bit.
21 It's hard. If you're a neurologist, you'll know
22 that I'm not walking well. But when I'm at a party

1 and I get up from sitting -- I've been sitting for
2 a little while, I get up, and I kind of lurch
3 around a little bit because I'm just not that
4 steady. And people ironically think that I've had
5 too much to drink, and that's really not usually
6 the case.
7 But I would say that I feel incredibly
8 fortunate that I was able to walk here today, that
9 I was able to walk into this meeting to talk to
10 you. And I really think it's critical that people
11 who have significant disease, and stand to lose
12 function, and stand to become disabled have the
13 opportunity to have access to this drug.
14 I understand your issues with safety, and I
15 think that, nowadays, patients are taking more
16 responsibility, should be involved in decision
17 making, and should be allowed to make the decision
18 that they may decide that the risk-benefit ratio is
19 adequate for them, that they would like to take
20 this medication.
21 So I urge you to approve this drug. I think
22 it's a really, really important advance. And I

1 thank you very much for your attention.
2 DR. FOUNTAIN: Thank you.
3 Would speaker number 6 step up to the podium
4 and introduce yourself? And please state your name
5 and any organization you're representing for the
6 record. Sorry. Speaker number 7.
7 MR. JOHNSON: My name is Harold C. Johnson,
8 and this is my MS journey. First of all, Genzyme
9 compensated for my travel here. I am happy to be
10 here. I am grateful for this opportunity.
11 It started when I was driving down Fulton
12 Avenue in Swansea, Illinois. I received a phone
13 call, and I was told I have multiple -- that I have
14 MS. Soon after, my doctor, Dr. Barry Singer from
15 Missouri Baptist, started me on Rebif. I did
16 injections three times a week. Eventually, the
17 lesions grew to over 100 plus with 16 black holes,
18 and 23 remain active on the MRIs, with a gadolinium
19 enhancement.
20 Then he mentioned a trial for Lemtrada, and
21 I did some research along with asking about a
22 thousand questions, and he reviewed with me all the

1 possible side effects. And since Rebif wasn't
2 cutting it, I decided to go with Lemtrada.
3 After a little while, the dark clouds in my
4 life parted and the sun shined through brightly.
5 Soon after, I married my beautiful wife, Jessica,
6 who supports me through anything and everything. I
7 obtained a full-time job as a computer technician
8 at Southwestern Illinois College, which is the
9 second largest community college in Illinois.
10 Every MRI since the beginning of my
11 Lemtrada, no additional active lesions whatsoever.
12 It is absolutely amazing. Besides my wife,
13 Lemtrada has been the best thing that has ever
14 happened to me. It is my goal to continue to help
15 not only myself, but others living with MS.
16 I want to thank Genzyme for all their
17 research and everybody else in the clinical trials.
18 I feel like I have my life back. I feel like
19 Superman. If anybody wants to see me do 20
20 push-ups, I can do it right now. I ride my bike on
21 the weekends. I ride up to 20 miles at a time. On
22 the Rebif, I could barely walk.

1 Genzyme has had me do monthly online surveys
2 with pictures that give me a reminder of what to
3 watch for. I have none of these side effects. I
4 have monthly blood draws. They check my blood, and
5 nothing has come up. If it does, I always ask that
6 they'll let me know, and they're on it. Every
7 three months, I go to my neurologist and I get an
8 EDSS test and a bunch of other questions. And I
9 pass all of them with flying colors.
10 So I ask the FDA, please approve this
11 medicine for myself and others living with MS.
12 Thank you very much.
13 DR. FOUNTAIN: Thank you.
14 Will speaker number 8 step to the podium,
15 and please state your name and any organization you
16 might be affiliated with?
17 Is speaker number 8 here?
18 (No response.)
19 DR. FOUNTAIN: All right. We'll move on to
20 speaker number 9.
21 MS. MUNLEY: Good afternoon. My name is
22 Karen Munley. I am a person who has lived with

1 very active MS for 20 years. Before I get started,
2 I have a little bit of my background in disclosure
3 for you.
4 I have been a pharmaceutical representative
5 for 27 years. The last eight of those have been
6 with Bayer Healthcare Pharmaceuticals, representing
7 the drug Betaseron for relapsing forms of multiple
8 sclerosis. Bayer and Genzyme will co-promote
9 alemtuzumab if and/or when I gets approval, hoping
10 for that. And I am here today at my own
11 initiative. I'm actually on vacation. I, at my
12 own expense, flew down here because as a patient, I
13 want you to hear my story and how excited I am
14 about this drug. I am not receiving any
15 compensation from Genzyme or Bayer to be here
16 today.
17 So my MS history. I was diagnosed with MS
18 in 1993, which coincidentally was the year that
19 Betaseron got approved. At that time, I did not go
20 on therapy. If I had known what we know now about
21 early therapy being so crucial, I definitely would
22 have rethought that decision. However, I would go

1 on to do several other clinical trials, like my
2 first DMT with Avonex. And as you can see, I would
3 actually also then -- I would actually do Avonex
4 and Solu-Medrol treatment because Avonex alone was
5 not strong enough for eight years.
6 When that looked like I was continuing to
7 progress, I decided to do the double-dose Copaxone
8 trial, which did not go very well for me. And I
9 ended up, I wasn't double dose. Moved on to
10 Tysabri. Couldn't use that because I had an
11 allergy.
12 So then I initiated Betaseron, which really
13 did help me for a while. I could get rid of all
14 those steroids I had been taking. But my MS has
15 always been very, very active, and my MRI scans go
16 to prove it. And I continue to have disease
17 activity with one to two exacerbations per year and
18 disease progression as well.
19 So in 2009, I got very concerned that I was
20 trending towards a secondary progressive MS course
21 and thought, "I've done everything else I can
22 possibly do with all the DMTs that are approved

1 right now." Having worked for Bayer, I knew that
2 Tysabri was on the horizon. And I fortunately
3 found a clinic that would take me as a patient
4 because my MS was too old to qualify for the CARE
5 trials.
6 In discussion with the neurologist that was
7 able to treat me, we had this very conversation
8 about risk-reward so that I could weigh it all out.
9 The risks from my perspective were 20 to 30 percent
10 thyroid abnormalities, ITP, Goodpasture syndrome,
11 maybe some opportunistic infections.
12 The ones that was of concern to me was
13 cancer because my mother is a two-time survivor of
14 breast cancer, and I myself have had some LCIS
15 issues.
16 Versus the reward, it's such a huge
17 reduction in relapses. I can't tell you how
18 frightening it is every time an MS patient has a
19 relapse. What lurks around the corner? Was this
20 going to be the big one? Am I going to be able to
21 walk tomorrow? Will I be able to play with my kids
22 tomorrow? That fear is always there. And a

1 71 percent reduction in sustained accumulation of
2 disability, that is huge; huge for an MS patient.
3 It was a no-brainer decision, like I heard somebody
4 else say over here, not hard at all.
5 I put this slide up because this is actually
6 the form that my physician uses to monitor my
7 blood, which is all that is really required as far
8 as monitoring goes, monthly blood draws. And going
9 into a lab is not terribly difficult, although I'm
10 hearing that it is even possible that maybe nurses
11 would come to the patient's home, which would make
12 sure that each and every month, the patient would
13 actually be tested.
14 My life with alemtuzumab is amazingly
15 different, but let me first start off by saying
16 that I had no infusion reactions. I've had no
17 opportunistic pathogen problems. I've had no
18 problems at all whatsoever with alemtuzumab.
19 The really, really, really exciting thing
20 about alemtuzumab is I've had no exacerbations
21 since my first infusion in 2010. In three years,
22 I've had not one single exacerbation. For somebody

1 that had one to two a year, that's pretty darn
2 good.
3 My EDSS score improved from a 3 to a 2. It
4 may not sound like much to you, but from an MS
5 patient standpoint, it means a lot because it could
6 be the difference between my walking 40 feet,
7 50 feet, or however long it is, and not being as
8 tired as I often get.
9 My MS severity score improved from the 26th
10 percentile to the 11th percentile. Huge. Huge
11 improvement. My MRI metrics improved, too many to
12 talk about. And the downside would be that I did
13 develop Graves' disease, and that's easily
14 mitigated by taking a pill one time a day. And I
15 don't view that as any trade-off that I wouldn't do
16 again at all.
17 So in summary, I have lived with very active
18 MS for over 20 years, and alemtuzumab is the only
19 therapy that I have ever used that worked to stop
20 the exacerbations and to improve disability.
21 Hypothyroidism is a very small trade-off to feel
22 this good. In fact, many days, I forget that I

1 have MS.
2 How many patients who have MS for 20 years
3 or more, how many patients that have lived with MS
4 for 20 years can say, "I forget I have MS"? I
5 can't tell you how liberating that is. And I know,
6 when we were having lunch in our breakout room over
7 here, it was the one thing we talked about.
8 Everybody feels the same way. This is such an
9 amazing drug. And I implore you, I beg you, to
10 please let other MS patients have the same
11 opportunities that we have had had. Thank you.
12 DR. FOUNTAIN: Thank you for your comments.
13 Next is speaker number 10.
14 MS. LOVE: Hello. My name is Amy, and in
15 the light of full disclosure, Genzyme helped me
16 with my travel and my lodging to be here today.
17 I was diagnosed with MS almost 11 years ago,
18 and like many MS patients, I had no idea that
19 anything was wrong until December of 2002, when I
20 started having pain in my right eye. I dismissed
21 it as bad sinus pressure, and then two days before
22 Christmas, I woke up, and I had totally lost vision

1 in my eye.
2 A trip to the ER and then the next day to an
3 ophthalmologist, who looked at my eye and calmly
4 said, "You have what I think is an optic neuritis.
5 And I bet you have MS, but we'll need an MRI to be
6 sure."
7 It was Christmas Eve, and I was left
8 speechless. He said Merry Christmas, and waved,
9 and walked out the door. I sat stunned. I
10 couldn't believe it. I thought my life was over.
11 But it turns out that nothing could have been
12 farther from the truth.
13 I was referred to a neurologist and was
14 asked to join the new drug trial for alemtuzumab.
15 My doctor explained the preliminary results for the
16 drug were good, and I was a candidate to join the
17 trial and receive treatment.
18 Since my diagnosis, I've been infused four
19 different times with the drug over the last
20 10 years, and I haven't needed retreatment since my
21 last infusion in '08. My first treatment in '03
22 was the hardest. Back then, I experienced the

1 flu-like symptoms of slight fever and hives, all
2 that were side effects that were manageable.
3 My neuritis went away, and my vision came
4 back as good as ever. In the weeks following each
5 treatment, I continue to feel better still. My
6 balance returned along with my focus and my overall
7 energy, and to me, I felt like my old self again,
8 the person I was before MS entered my life.
9 I am not an activist. I am far from it.
10 Beyond my immediate family and my doctors and
11 nurses, no one else really knows that I have been
12 living with this disease. I made a conscious
13 decision not to tell anyone outside of my family,
14 yet I'm here today speaking out because I think
15 this meeting and this treatment is that important.
16 I want you all to know that this drug works
17 and that, for me, it has changed my life in the
18 best possible way. It slowed and all but stopped
19 the progression of my MS. While I may look like a
20 normal person, more importantly, I feel like a
21 normal person, and I know that I'm one of the lucky
22 ones.

1 I believe in what this drug can do because
2 it has worked so well for me. It does have side
3 effects, but they were easily managed before and
4 after infusion. What to watch for was clearly and
5 repeatedly told to me by my doctor and her staff.
6 I watched, as did my neurologist, to make sure that
7 none of the side effects were extreme or a danger
8 to my overall health.
9 Being a part of the drug study, not all of
10 the potential side effects were known when I
11 joined. In the past 10 years, my neurologist and
12 others have worked hard and have been able to crack
13 that code. I was made aware of the potential for
14 ITP and also for thyroid issues. And given a
15 choice between a permanent disability and possible
16 thyroid problems or even cancer, I still chose to
17 receive alemtuzumab.
18 MS has no cure, and not knowing what MS can
19 do to your body in the long term is what is so
20 nerve-wracking about it. Any hope to stop the
21 unknown, I jumped at the chance. As it turns out,
22 I did not get cancer, but my thyroid did become

1 overactive, and a simple daily pill fixed my
2 problem.
3 In little over a year after it stated, I no
4 longer required the pill, and my thyroid function
5 is normal. For me, taking a daily pill for a year
6 was a very small price to pay for not having any
7 long-term disability due to my MS.
8 I find it troubling that there are many
9 other people out there who need this treatment, who
10 could benefit greatly from receiving it, and yet
11 they aren't allowed to receive it at this time. I
12 get to talk to other patients who have MS at my
13 neurologist's office. We have the same disease,
14 yet the course of MS has taken very different turns
15 for others.
16 I met a woman my age, and we were diagnosed
17 within months of each other. I know I can easily
18 walk the three miles at our MS walk each year. I
19 haven't been admitted to a hospital in the last
20 10 years, and I haven't woke up in the morning,
21 unable to move or get out of bed. She couldn't say
22 that. And now I know that many people with MS

1 cannot say that, either. This story rocked me to
2 my core, and, again, I know that I'm the lucky one
3 because I was given this drug.
4 Side effects, of course, are a possibility,
5 but side effects are a part of taking an over-the-
6 counter aspirin or a decongestant, too. I firmly
7 believe that as long as patients are counseled and
8 reminded to watch and listen to what their bodies
9 are telling them, I don't think that the worst of
10 the side effects can come true.
11 For MS patients taking this or any other
12 drug, though, it is imperative that we stay in tune
13 with our bodies and what our bodies are telling us.
14 MS patients like me can't ignore what our bodies
15 are saying. And as much as we don't want to think
16 that our disease may be acting up, we have to watch
17 for signals. This is true for anyone who is given
18 any drug to fight MS, not just this one.
19 I believe in what this drug can do, and it
20 has worked so well for me. I've been all too aware
21 that I was given an opportunity to receive a
22 treatment that many other people were not.

1 I have no cumulative disability. I have had
2 nothing new on my annual MRIs for the last five
3 years. This medicine works. As a patient who took
4 the drug and has had very good results, the
5 benefits have far outweighed any of the risks. I
6 believe that this medicine and all that it has done
7 for me for my diagnosis in 2003 until today.
8 I encourage you to approve alemtuzumab as a
9 medicine for MS patients and make it available to
10 others. I am blessed beyond belief and I am
11 grateful for it every day. And again, I'm one of
12 the lucky ones, and I know it. Thank you for your
13 time and consideration today.
14 DR. FOUNTAIN: Thank you. And I thank all
15 of you, particularly for telling your personal
16 stories.
17 I'm sorry. Is there speaker number 11? My
18 list is a little different. Please step to the
19 microphone.
20 MS. RUSSELL: Good afternoon. My name is
21 Maureen Russell. I'm 30 years old, and I am not at
22 all sponsored by Genzyme or anyone who would

1 benefit from the approval of this drug.
2 Good afternoon. As I said, my name is
3 Maureen, and I would like to thank, first of all,
4 the members of this panel, this committee, for
5 allowing me a few minutes this afternoon to share
6 my story with my journey with MS. And then also,
7 thank you again for your continued work and support
8 for new therapeutic options as we all try to find a
9 cure for MS.
10 Like many people in this room today living
11 with MS, the journey to find the best treatment
12 plan for me has been long and complicated, much
13 like my commute this morning. In fact, when I was
14 first diagnosed at the age of 18 in the year 2000,
15 my neurologist dismissed prescribing one of the
16 three then-approved treatment plans because he
17 thought I was young enough. I'd be healthy. It's
18 fine. Let's just say that my mother did not agree
19 with that statement.
20 So then I went two years without treatment.
21 As we've heard today, that early treatment is
22 usually the best idea for MS patients. I lost two

1 years of that, unfortunately. So since then, I
2 have seen three different doctors and have been on
3 four treatments to control my MS, switching from
4 one to another when that one doesn't work anymore.
5 My entire adulthood has been shaped by my
6 fight against MS. Interferon treatments during
7 college left me fatigued and feverish. In fact, I
8 learned that when you're 19 and you live with a
9 bunch of skinny girls in south Indiana in December,
10 it's not okay to sleep with the window open. In
11 fact, I had to sleep with ice packs on me instead.
12 Subsequent relapses during graduate school at the
13 University of Syracuse and then here down in D.C.
14 left me admitted to the George Washington Hospital
15 Center at least twice in one year.
16 From 2007 to 2010, I benefited from another
17 daily injection treatment, but ended up relapsing
18 in 2010, unable to feel my left arm. With each
19 relapse, rounds of steroid infusions took their
20 toll. It was not until being prescribed a monthly
21 IV treatment in July of 2011 that my treatments
22 finally began to affect the progression of my MS.

1 Unfortunately, that medicine's side effects
2 left me feeling weak and helpless. Every day, I
3 fought back tears at the thought of having to walk
4 from the Metro to my current office in the
5 Pentagon. While the medicine was working,
6 according to my doctor, I was overwhelmed by the
7 side effects.
8 Recently, I informed my neurologist that I
9 needed another treatment option. And, fortunately,
10 thanks to everyone in this room, the FDA, there was
11 one, an oral therapy, that I just started in
12 January.
13 For me, this new therapeutic option has made
14 a tremendous difference in my life. My MRI scans
15 show no new or enhancing lesions in the last year.
16 As well, my energy levels have returned, and I
17 finally did something I never thought I would be
18 able to do, train for a long-distance race.
19 On October 20th of this year, I completed
20 the Army 10-miler, and I plan on training for a
21 new, longer race next year. See, running while
22 crying is also very hard.

1 So finally, I'm here to advocate on behalf
2 of all those people with MS who have not yet been
3 able to find their ideal training protocol. And
4 I'm also doing this for myself because I don't
5 know, at this time next year, in two years, if my
6 current treatment will actually still be helping.
7 Cross your fingers it does. And hopefully if that
8 day does come, another treatment like this one that
9 you're discussing today or any ones that are in the
10 pipeline will be there for me to take in the
11 future.
12 So for my fellow MS warriors, continued FDA
13 support for research leading to new MS treatments
14 will hopefully help match the right person to the
15 right drug. And because of all of you, the FDA,
16 the treatment and the approved treatments, as well
17 as those that are in the future, an MS diagnosis
18 does not preclude you from leading an amazing life.
19 I obviously talked way too fast because I
20 have lots more time to go, but thank you again for
21 this opportunity. And if you have any questions,
22 please let me know. Thank you.

1 **Clarifying Questions (continued)**

2 DR. FOUNTAIN: Thank you. And I thank
3 everyone for your comments. They are appreciated
4 by the panel.
5 The open public hearing portion of this
6 meeting has now concluded, and we'll no longer take
7 comments from the audience. The committee will now
8 turn its attention to address the task at hand, the
9 careful consideration of the data before the
10 committee as well as the public comments. But
11 before we begin any open discussion, I'd like us to
12 revisit any specific questions that are clarifying
13 for either the sponsor or the FDA. So if there are
14 questions remaining. Okay.
15 DR. KLASSEN: I have a question, I think.
16 This would be for the side effects. With respect
17 to the autoimmune issues, do they tend to cluster
18 in one patient more than once, or are they all
19 individual events? I mean, are there patients that
20 had thyroiditis and ITP, or how does that sort out?
21 DR. MENTARI: I don't know if we did a
22 specific analysis for overlap, but there didn't

1 seem to be a significant overlap in where patients
2 would have numerous autoimmune diseases in a single
3 patient. Thyroid disease is common enough that
4 there were patients who had thyroid disease as well
5 as another autoimmune disease.
6 There were three cases of autoimmune
7 pancytopenia, two of which to my knowledge were
8 cases in which the effects on multiple cell lines
9 were diagnosed simultaneously, but there was one
10 patient in which ITP and autoimmune hemolytic
11 anemia were diagnosed separately. And he later had
12 the diagnosis of autoimmune pancytopenia. But
13 generally I don't know, other than with the thyroid
14 disease, that there is any clustering per se.
15 Does the sponsor have any additions to those
16 comments?
17 DR. FOUNTAIN: So does that go back to your
18 comment that 8 percent of people had one of those
19 serious complications? That's 8 percent of
20 subjects, not 8 percent of anything else.
21 DR. MENTARI: That's right. That was the
22 head count, so it was subjects.

1 DR. FOUNTAIN: All right. Dr. Ascensao?
2 DR. ASCENSAO: In follow-up for that, was
3 there any difference in the incidence of autoimmune
4 phenomenon occurring in patients who had previously
5 received one of the interferon components as
6 opposed to patients who were naive to the therapy
7 with alemtuzumab?
8 DR. MENTARI: My understanding of the data
9 is that those incidences were generally similar.
10 Is that similar to your assessment?
11 DR. PANZARA: Yes. The incidence of thyroid
12 disorders were similar between treatment naive and
13 the treatment-experienced population with about 5
14 to 6 percent of Rebif patients in each study also
15 having those numbers.
16 DR. FOUNTAIN: Following up on questions
17 from earlier, Dr. Lu, do you still have a question?
18 DR. LU: Yes. So in this, we are asked to
19 evaluate the treatment efficacy for MS overall, but
20 this study design specifically has active control
21 arm. So should we consider that in to the picture
22 when we think about whether it's treatment for the

1 disease itself, comparing to active and effective
2 treatments, in your consideration?
3 DR. BASTINGS: I can answer that. Yes.
4 Certainly, you have to take into consideration the
5 fact that the study is using an active control,
6 absolutely.
7 DR. LU: So just imagining if they choose
8 originally, I mean, that's after the fact. They
9 have a placebo control. And so if you look for the
10 MRI picture, that there is consistent decreasing
11 over time. So it's really that the picture shows
12 the one year that you compare to a very active
13 treatment, in other words, the main reason there
14 was no effect for the lesion difference.
15 DR. PANZARA: That is correct.
16 DR. LU: Right. Well -- you
17 can't -- hypothetical in the case, but you have to
18 put the totality of the picture about efficacy.
19 Right?
20 DR. BASTINGS: Yes. You have to integrate,
21 as you said, the totality of the picture and find
22 that it was an active control, the study design,

1 the open-label design, and so on.
2 DR. PANZARA: Rebif patients tend to have a
3 70 to 80 percent reduction in gadolinium-enhancing
4 lesions. And this would be, then, therefore put in
5 that context.
6 DR. MARLER: There's one slight thing that
7 you have to consider as well, in that the active
8 control in the larger 324 trial included patients
9 who had failed the active control or a drug similar
10 to it, so that I don't think it's well known how
11 well Rebif does treating patients who have
12 previously failed Rebif.
13 DR. PANZARA: Just one clarification on
14 that, actually, is that we did that analysis. We
15 looked at patients who had come into the study,
16 having tried Rebif before and other interferons
17 versus drugs they hadn't received before, and the
18 effect size was consistent, whether they had tried
19 and had disease activity on relapse versus the
20 other therapeutic.
21 So we thought about that. That's an
22 important question. Also, the threshold for

1 inclusion of the patients in the study was one that
2 we selected, so that it was viewed by our experts
3 that they were not treatment failures, but rather
4 had a level of disease activity that would at least
5 start a discussion of changing therapy.
6 So we thought about that, so when we did
7 that specific comparison, it does not appear that
8 that was a factor in the efficacy.
9 DR. FOUNTAIN: Dr. Mielke?
10 DR. MIELKE: I want to get back to some of
11 the presentation on bias. And one of the things
12 that was brought up was a consent form and the fact
13 of saying in here where if the disease became
14 worse, your treatment may be stopped.
15 But this doesn't necessarily mean a relapse.
16 So if individuals relapse, then they were still
17 allowed to continue on the treatment if they chose.
18 Correct?
19 DR. PANZARA: Yes, that's correct. That
20 statement in the consent form is one of a pretty
21 standardized statement --.
22 DR. MIELKE: Right.

1 DR. PANZARA: -- where you would just tell
2 people we are obligated to inform people that if
3 they have disease activity in the study, because
4 they may be receiving a less effective therapy, we
5 can't force them to stay in the study.
6 So we gave them the option as just a warning
7 that they should talk to their doctor about it, but
8 they were required to stay in the study until the
9 end. Otherwise, they couldn't be entered into the
10 open-label extension study. That is correct.
11 DR. MIELKE: So it's not really likely to
12 bias reporting of relapse or symptoms in that
13 regard.
14 DR. PANZARA: There was no benefit to them
15 to not tell people they were getting worse in terms
16 of providing them with alemtuzumab for sure.
17 DR. FOUNTAIN: Ms. Sitcov?
18 MS. SITCOV: Yes. Thank you. As a patient
19 representative, I feel as though it's my duty to
20 point out this observation. And that is, I sort of
21 think to myself, I've been in three different -- I
22 think this is my fourth FDA hearing. I was at the

1 Tysabri hearing, and we had numerous people
2 testifying. And some of it was quite negative
3 coming from patients or family members.
4 I'm so struck by the fact that FDA doctors
5 are saying the sponsor has not submitted
6 well-controlled studies to support safety and
7 effectiveness and dealt with the bias issue. And
8 the sponsor, of course, has the sort of polar
9 opposite view.
10 But what I have to take into consideration
11 is the incredibly moving testimony on the part of
12 the patient population. I think I read something
13 like 25 letters that were sent to the FDA from
14 patients and advocacy groups that are really
15 remarkable. And every single one describes this
16 drug as life-changing.
17 I don't know if there's a question in my
18 explanation, but I just wonder if there's any
19 comment the agency or the sponsor has to this
20 observation of mine.
21 DR. BASTINGS: We certainly welcome patient
22 testimonies about their experience, but we also

1 have to take into consideration of course the
2 results of the clinical studies and the evidence
3 that is presented to us. And that is the primary
4 basis for the decision that the agency has to make
5 at the end of the review cycle. But testimonies
6 are certainly very important to hear.
7 DR. FOUNTAIN: Dr. Alexander?
8 DR. ALEXANDER: I wanted to follow up on the
9 question about bias and the consent form. In the
10 agency's presentation, there were a number of
11 different examples of potential avenues whereby
12 bias might be introduced beyond the absence of
13 double-blinding. So there was a comment about
14 unequal randomization. The consent form was a
15 second. The third were the absence of the
16 institution of strict time limits for the reporting
17 and in the case report forms. And so I'm just
18 trying to understand more about the communication
19 between the agency and the sponsor at the time that
20 the protocol was being developed.
21 Were each of those subject to negotiation,
22 and comment, and urging or recommendations on the

1 part of the agency that the trial be otherwise
2 designed? And if so, could you just speak to that
3 a little bit?
4 DR. DUNN: Yes. So there were a variety of
5 interactions with the sponsor throughout their
6 clinical development program at different stages of
7 their protocols. And so our comments took
8 different forms, but had a consistent theme. We
9 consistently discouraged the sponsor from pursuing
10 the clinical development program using the
11 open-label design.
12 Later in development, when more formal
13 development of the phase 3 trials or when they were
14 considering submitting the application to us for
15 approval, we gave them very specific information
16 that had to do with what types of information they
17 could include in order to help increase a
18 demonstration of the rigor of the trial, help us in
19 our analysis of assessing the effects of potential
20 bias in the trial.
21 So while there is a spectrum throughout
22 clinical development over many years in terms of

1 how much detail is provided at what time, there's a
2 very consistent message delivered throughout, up to
3 and including the meeting immediately prior to the
4 application being submitted, where we indicated our
5 discomfort with the clinical trials as designed.
6 DR. ALEXANDER: So for example, did the
7 agency encourage a 1 to 1 randomization as just one
8 example, or did the agency encourage a strict
9 institution of a requirement for the case report
10 forms being completed within seven days of a
11 relapse event, as just two examples?
12 DR. DUNN: Right. So I might ask Dr. Marler
13 to comment on some of these specifics, but in a
14 general sense, a number of these specific issues,
15 we would have to go back into the records to see
16 how much we commented on any one particular issue.
17 I would say, though, that I believe I'm
18 fairly on target here, and I'm sure that
19 Dr. Panzara will jump in if I'm not. A lot of the
20 specifics that we've presented today are a result
21 of our review of the application itself. And those
22 come about in concert with the work of the sponsor

1 presenting the application to us, in terms of
2 issues that we have discovered, and considered, and
3 attempted to comment on.
4 It's doubtful in my mind that each and every
5 thing that we've described today as a potential
6 weakness was discussed in a specific sense, even if
7 we went back and checked the records. I think that
8 philosophically we discussed types of issues and
9 concepts that could be used to support and buttress
10 the trials.
11 DR. PANZARA: Yeah. So there were many
12 interactions, as Dr. Dunn said. But to your
13 specific questions, no, on those specific points,
14 no. And if you really want to hear more details,
15 Jennifer Panagoulias should probably come.
16 DR. DUNN: I guess I would just follow up
17 with one additional thing, which is that
18 there's -- I don't know how familiar everybody here
19 is with the special protocol assessment process
20 that's been alluded to or discussed a little bit
21 here. But one of the most particular places that
22 we lay out before trials are conducted, that are

1 designed to be a primary study supporting approval,
2 one of the primary places we lay out our thoughts
3 about the design of a trial and its ability to
4 support approval is through that process called the
5 special protocol assessment.
6 So in most situations, and I think probably
7 in this situation also, the greatest detail would
8 have been provided during that process of special
9 protocol assessment, which typically occurs prior
10 to the trial being conducted.
11 Another interaction is the pre-application,
12 meeting and that's where we provided an enormous
13 amount of very, very specific guidance, which
14 summed up years and years of concerns about the
15 design of the trials and suggested many techniques
16 in great detail about how to address that to the
17 best degree possible.
18 DR. FOUNTAIN: That's fine.
19 MS. PANAGOULIAS: I'd just like to add,
20 though, that the submission meeting takes place
21 when the clinical studies are completed.
22 DR. FOUNTAIN: Dr. Zivin?

1 DR. ZIVIN: I have one and a half questions
2 for the sponsor. The FDA already came up with
3 their idea of what the therapeutic index is for
4 this drug, and they said it was essentially zero
5 unless I'm misquoting them.
6 DR. DUNN: Yes. May I?
7 DR. ZIVIN: Please do.
8 DR. DUNN: Yes. I want to clarify very,
9 very clearly, to be redundant. The FDA has not
10 come up with a final opinion. What you've heard
11 here is the typical presentation of our initial
12 review of the data that we're bringing to the
13 committee because we seek the committee's
14 assistance in considering this.
15 Final decisions in no way have been reached,
16 and I would not want the committee to labor under
17 the misassumption that we have reached the
18 conclusion that you've stated.
19 DR. FOUNTAIN: Would it be fair to go so far
20 as to say that that's one of the major questions
21 you're going to address?
22 DR. DUNN: I think that's eminently fair.

1 DR. FOUNTAIN: What is the therapeutic index
2 that's acceptable or --
3 DR. DUNN: Well, that question specifically,
4 we may come back to later. The question doesn't
5 have to do with therapeutic index, per se. I
6 realize Dr. Zivin brought that up earlier, and we
7 can talk about that a little bit. Perhaps he
8 should continue those questions.
9 But I just wanted to clarify any questions
10 about what conclusions the agency, in terms of what
11 our action would be, has reached about this. It is
12 most definitely an open decision at this point.
13 DR. ZIVIN: Okay. Then what does the
14 sponsor think the therapeutic index is?
15 DR. PANZARA: When considering the benefit
16 of alemtuzumab, we wanted to really look at all the
17 facets of efficacy, namely the imaging, disability
18 progression, and relapses.
19 There is an evolving paradigm looking for
20 the presence of how much disease activity there
21 would be, namely how much can you prevent? How
22 many numbers of patients can you treat to prevent

1 an episode of lack of relapses, lack of disability
2 progression, and lack of imaging abnormalities, so
3 lack of disease activity.
4 So we put that against the risk in the
5 study -- I'd like to see slide 2 up, please -- and
6 we've done a number needed to treat versus number
7 needed to harm.
8 What you see here is, looking at the
9 efficacy outcomes, the number needed to treat to
10 prevent one disease activity episode, MS disease
11 activity, as compared to the key events, serious
12 thyroid abnormalities, ITP, and nephropathy.
13 So this gives you a bit of an idea in terms
14 of the balance, if you will, or the index of
15 efficacy. And you can see it's quite favorable.
16 DR. ZIVIN: Okay. Then the next question
17 that I have is, you published your primary article
18 about this trial in the Lancet in 2012, I believe.
19 DR. PANZARA: Yes.
20 DR. ZIVIN: And there was an adverse
21 editorial that came along with that. What do you
22 have to say about that editorial?

1 DR. PANZARA: I think the piece of the
2 editorial that was quoted here does mention the
3 question that this is a rater-blinded study; that
4 we have to consider bias. But the efficacy itself
5 actually was -- that editorial acknowledged the
6 efficacy of the product.
7 So I don't think we would characterize it as
8 an adverse editorial. I think it was putting the
9 efficacy into the context. And I think what we've,
10 though, shown today is that when you put that
11 efficacy into context with all of the analyses and
12 the procedures that we've put in place, that
13 warrants the effect size that we see, and I think
14 supports that this is a meaningful effect and
15 interpretable.
16 DR. FOUNTAIN: Dr. Clancy?
17 DR. CLANCY: So several years ago, the FDA
18 had a discussion about a new anti-seizure
19 medication called Sabril, vigabatrin. And it was
20 directed against one of the most devastating forms
21 of pediatric epilepsy that you could ever imagine.
22 The substance would be dispensed from a

1 specialized pharmacy by specialized physicians who
2 knew what the deal was. And they had a risk
3 management mitigation strategy in order to protect
4 the health of the children who were receiving this
5 drug to try to suppress these seizures, and their
6 encephalopathy, and so forth.
7 But over the years, I think that's softened
8 quite a bit. It was done religiously, every three
9 months punctually. Patients showed up. And now I
10 notice that there's a little bit of a warm and
11 fuzzy feeling about it. It's not that bad. And my
12 sense is that it's sort of fading out a bit.
13 Now, these kids have -- their treatment,
14 within a short period of time, six months. This
15 study is going to linger on for year after year
16 after year. So do we know how effective other
17 mitigation strategies have been? Do they sustain
18 their vigor over year after year after year? And
19 are we going to be able to continue that in this
20 population, where years after their two infusions,
21 they're still going to be running the risk of skin
22 disease, thyroid disease, and so forth.

1 So how are we going to guarantee that what
2 on paper sounds good, sounds good to have a safe
3 blanket around them, but is that just going to fade
4 with the passage of time? Or how are we going to
5 commit to that and actually make it work?
6 DR. PANZARA: Right. I think that this is
7 an important question that we've had to consider
8 because the efficacy, as you point out, with annual
9 dosing is sustained in many patients. So the best
10 data we have is from the trials themselves, which I
11 acknowledge is not the postmarketing experience.
12 But within the trials themselves, we had
13 north of 98, 99 percent compliance with all of our
14 blood draws. So that's encouraging. And I think,
15 as we've heard today, the blood draws can be
16 arranged in very different settings. And I'm going
17 to ask Jennifer Panagoulias to talk about the
18 procedures of how we are going to do this.
19 Then I want to actually then turn to
20 Dr. Fox, who's been doing it, to give you a sense
21 of how it is to manage.
22 Jennifer?

1 MS. PANAGOULIAS: Actually, I'd like to
2 begin by directly addressing your question about
3 effectiveness. And as with all REMS that have
4 elements to assure safe use, one is required to
5 include a timetable for assessment that provides
6 reports on the performance of the programs.
7 So what we've proposed to FDA are specific
8 effectiveness checks on an annual basis, and we
9 would be providing that in reports to the agency
10 for some time. So it'd be looking directly at if
11 the educational messages were effective,
12 specifically through surveys to patients and
13 physicians, as well as other measures to ensure
14 that program conditions are met.
15 In particular, we've designed this program
16 to be somewhat similar to the existing program for
17 Tysabri called the TOUCH program, with which many
18 neurologists are familiar working with. And I'd
19 ask Dr. Fox to comment on compliance.
20 DR. FOX: I agree that REMS programs are
21 fluid. They do change over time. In the case of
22 Tysabri, if anything, it has become more intense.

1 We have better information, better knowledge about
2 it now, and so testing has become more rigorous.
3 Our understanding it and our communication with the
4 patients has become much improved compared to at
5 the time of its launch.
6 I see the REMS program here also potentially
7 changing over time, but I don't see it necessarily
8 becoming more lax because, as somebody in clinical
9 trials for this period of time, I have not had
10 difficulty in maintaining the REMS program as it
11 was designed for the phase 3 trials. And the
12 reason is because they knew the responsibilities.
13 I don't see from the standpoint of a
14 neurologist, who is used to following blood levels
15 and anti-convulsants or the anticoagulant profiles
16 on patients -- it really slacking off any more than
17 we've seen in clinical practice. It is up to the
18 doctor and the patient themselves to continue that.
19 DR. FOUNTAIN: Is there any information from
20 Europe about that or is it too early to tell?
21 DR. PANZARA: The European risk management
22 program is very different. There is no controlled

1 distribution in Europe. It is not something that
2 you can do in Europe, but the program in place has
3 the same educational elements. And it's only in
4 its beginning stages, but it is for first-line use
5 in Europe for active patients, and we are
6 continuing to evaluate.
7 DR. FOUNTAIN: So the answer's no?
8 DR. PANZARA: No. We don't have anything.
9 DR. FOUNTAIN: Dr. Kramer?
10 DR. DUNN: Actually, can I just quickly
11 follow up on some of these REMS issues? I think we
12 have a couple points to make. In a general sense,
13 if there's a question about whether or not the
14 agency would be intimately involved in the conduct
15 and monitoring of any REMS, we most certainly would
16 be.
17 So I think both the sponsor and the agency
18 would be equally committed to close monitoring and
19 assessment of any REMS program, were it to be put
20 in place.
21 But I would return you to Dr. Booker's
22 conclusion, which was a summary of the primary

1 review aspects of the proposed REMS and our
2 considerations of it, which is that the issue to do
3 with the REMS is not so much can it be monitored
4 closely, but whether or not the REMS in total can
5 ensure that the benefits outweigh the risks. And
6 that is really the primary issue with the REMS here
7 for our consideration.
8 But please rest assured that if a REMS is
9 put in place, it will be looked at very closely.
10 This particular REMS, in conjunction with the
11 clinical profile of the drug, would have some
12 unusual features that cause concern for our ability
13 to effectively monitor and mitigate the risks
14 associated with its use.
15 DR. PANZARA: Yes. As Jennifer Panagoulias
16 said, it's very similar to the TOUCH program, where
17 it's not about mitigation, but early intervention.
18 DR. FOUNTAIN: Do you have something else to
19 add to that, Dr. Unger?
20 DR. UNGER: Yes. Can I just add one thing?
21 I mean, the thing that differentiates this, I
22 believe, would be that most of the programs we're

1 familiar with are you get the monitoring in order
2 to enable a subsequent dose of a drug.
3 So if this drug is given twice and you want
4 to monitor the patient for years, it's very
5 different than an iPLEDGE program or something,
6 where you have to have a pregnancy test in order to
7 actually get the drug. So that's what makes this
8 different.
9 DR. DUNN: Again, keep in mind the goal of
10 the REMS is to ensure that the benefits outweigh
11 the risks.
12 DR. FOUNTAIN: Dr. Kramer?
13 DR. KRAMER: Thank you. I have a question.
14 I thought Dr. Marler laid out the bias issues
15 around open trials very nicely. And his first
16 point was around raising the issues of the timing
17 of the randomization versus potential unblinding.
18 And Amelia asked a question. It was the same
19 question that I was thinking about just prior to
20 the lunch break. And that was about a comparison
21 of those patients who had already been randomized
22 versus those patients who hadn't been randomized

1 yet and were randomized after the potential
2 unblinding.
3 I couldn't really understand the answer very
4 clearly. And I was wondering if anybody actually
5 had a slide showing those analyses.
6 DR. FOUNTAIN: Does the sponsor have a
7 slide?
8 DR. PANZARA: Yes. We do, actually. I'll
9 turn it to Dr. Lake.
10 DR. LAKE: Thanks. Slide 3 up, please.
11 This is from the core presentation. And actually,
12 in the second gray -- or first gray box up from the
13 bottom, you can see that we've stratified the SAD
14 analysis by whether or not the baseline EDSS was
15 performed on the day of or after randomization.
16 And you can see the treatment effect estimates are
17 relatively constant or consistent between those
18 two.
19 I'd also like to mention that while we're
20 looking at SAD, which are usually low event rates,
21 and when you do this screen to baseline switch, we
22 do see that the time to SAD significance is lost in

1 actually two approved MS therapies to date.
2 When we look at the EDSS change, we see
3 statistical significance whether we use the
4 screening value or the baseline value. So when we
5 look at all of the patients, we do see a
6 significant shift between the distributions of
7 alemtuzumab and Rebif-treated patients, whether we
8 use screening or baseline.
9 DR. PANZARA: Just for clarity, also, on the
10 screening versus baseline, it's been suggested that
11 this was a 14-day period. Actually, the median
12 time, even though there was the difference between
13 screening and baseline for a proportion of the
14 patients, was three days. That was the mean time
15 with a median of 1.
16 DR. FOUNTAIN: Next, I think we'll take a
17 few more questions that are clarifying, and then
18 maybe we'll turn our attention. And we can have
19 more questions, but sort of focus them around the
20 specific questions that were asked so that we can
21 kind of approach some of these things.
22 So we have Dr. Bagiella, then Blumenthal,

1 Smith, Alexander. Then maybe we'll turn our
2 attention and we'll continue with everyone else
3 who's asked questions, framing it around the
4 questions the FDA has asked us to address.
5 DR. BAGIELLA: So I'm going back to the
6 question of the screening at the baseline. So the
7 three days is the median time between the screening
8 and the randomization, or is the median time
9 between randomization at baseline.
10 DR. PANZARA: So this is a complicated
11 issue. I'm going to have Steve walk you through
12 it.
13 DR. LAKE: So the mean time is actually
14 addressing that difference between the time of
15 randomization and the baseline EDSS. So that was
16 three days. The median was 1, reflecting that
17 50 percent of the patients had their baseline EDSS
18 on the day of randomization.
19 DR. BAGIELLA: So my follow-up question is,
20 it is very, very unusual in randomized clinical
21 trials to have a baseline after randomization.
22 What was the rationale for you to have this very

1 unusual design?
2 DR. LAKE: So this was a blinded-rater
3 study, so we were depending on that blinded rater,
4 as well as, I think some of these were logistic
5 complications. There was the randomization,
6 assignment of treatment, and then some logistic
7 complications of bringing patients in for their
8 infusion on their baseline.
9 DR. FOUNTAIN: Next, Dr. Blumenthal?
10 DR. BLUMENTHAL: A question for the FDA.
11 We've discussed already the disagreements between
12 the FDA and the sponsor about study design. And
13 one of the things that I'm having trouble resolving
14 is how the sponsor could have addressed some of the
15 concerns that have been raised.
16 Dr. Mentari's data tells us that 92 percent
17 of the patients who received alemtuzumab had
18 infusion reactions. So if you have a study
19 protocol where everyone gets IV infusions and
20 everyone gets subcutaneous injections, I think the
21 research subjects are going to know whether they
22 got active monoclonal antibody, or whether they got

1 interferon, or in the case of a comparator that is
2 placebo and not active drug, whether they got
3 placebo.
4 Is there a study design that you propose to
5 the sponsor that would have gotten around that
6 issue?
7 DR. BASTINGS: Yes. We think there are two
8 ways around the issue. One way is the double-dummy
9 design that we proposed. The issue, as you
10 mentioned, is that there will be unblinding of some
11 patients by adverse events, but the unblinding is
12 certainly not 100 percent.
13 A number of patients would not have any
14 adverse reaction, let's say, during the infusion
15 and would not be unblinded. Other patients may
16 have symptoms and may guess that maybe they're
17 getting the treatment, maybe not, but there still
18 will be a level of uncertainty in these patients.
19 The same is true for the patients who would
20 be assigned to the interferon. Some people may
21 experience adverse events. A substantial fraction
22 of patients will not. So again, it's not going to

1 be 100 percent. In both situations, there will be
2 a substantial proportion of patients who will not
3 have adverse events causing unblinding.
4 On the other hand, it's very useful not to
5 unblind other site participants and to maintain a
6 blind not only of the patients, but all of the
7 study personnel at the site level, because the more
8 people are unblinded, the more opportunities you
9 have to introduce bias.
10 So what we recommended to the sponsor was a
11 double-dummy design. At some point, another
12 proposal we made, and that may be the best way to
13 address the adverse event potential of unblinding
14 is to use two different dose levels of drug.
15 If you have a higher dose and a lower dose
16 that both give the same adverse event, but at
17 different proportions, that can be a good way to
18 show dose response and show that the higher dose
19 beats the low dose, with both groups getting the
20 same kind of adverse event.
21 That's certainly an option that has been
22 successful in other programs.

1 DR. PANZARA: To comment on that, just to
2 add one point, the suggestion was made to use lower
3 subtherapeutic doses of some of these medications,
4 and we were uncomfortable with that. And I think
5 that we have to consider that also and our ability
6 to execute that also.
7 But I think one point about the
8 double-blinding study in the MS therapeutic space
9 in general, Dr. Rudick has been involved in every
10 MS program to date. I think it'd be helpful to
11 have him address that question about unblinding
12 side effect profiles.
13 DR. RUDICK: First of all, I think that the
14 issues that the FDA is raising about study design
15 and about the outcome measures we're using are very
16 good ones. And we're all concerned about these
17 issues. But I want to just make a couple of points
18 about this topic in general.
19 In the late '80s, when we designed the
20 Avonex trial, we designed it as a double-blind
21 study, double-masked. But we were pretty sure the
22 patients were going to know -- to Dr. Blumenthal's

1 point, they were going to know whether they were
2 getting interferon because we had done some dose-
3 finding studies and the side effects were so clear
4 cut that it was not going to be possible to be sure
5 that there was 100 percent effective double
6 masking.
7 So we actually invented, in the late 80s,
8 this concept of the blinded rater. I think we did
9 that for the first time. And we went to all kinds
10 of extremes to isolate the EDSS examiner from not
11 only knowing the treatment assignment, but from
12 discussing it with anyone at all in the study sites
13 who had anything to do with the patients.
14 So that's where the rated blinder came from.
15 It was designed to be part of a double-masked
16 study. And of course, the practical issues and
17 other issues making it almost impossible to do a
18 100 percent effective double-masked study make that
19 blinded rater even more important.
20 But in just about every study I've been
21 involved with, we have not been able to effectively
22 double mask the study completely because of these

1 side effect issues.
2 The second thing that's been brought up is
3 this issue of patient expectation of benefit or
4 what some people call therapeutic misconception.
5 In my experience, every patient in a clinical trial
6 has an opinion about which is the better arm to be
7 on. For placebo-controlled trials, it's obvious,
8 but for the active-arm comparisons, they always
9 want the stronger drug or the newer drug. So this
10 issue that was brought up, which is an important
11 one, is really pretty generic.
12 So this is why we do two things. We do the
13 best we can with rater blinding. And then we add
14 things that are a little less subjective so that we
15 can reassure ourselves that the bias wasn't the
16 main cause of the efficacy if we see it. One is to
17 use clinical measures that are a little more
18 objective like MSFC and MRI measures. And that was
19 done in this study. So I'm happy with that.
20 The last thing is an editorial comment. It
21 certainly doesn't represent the sponsor view. This
22 is my own view. And that is that the requirement

1 to have double-masked studies not only really
2 precludes testing a lot of things that really can't
3 be done for reasons that Dr. Blumenthal raised, but
4 if that had been applied to -- if the issue of bias
5 had been applied in the same way it's being applied
6 here to the original Avonex, Betaseron, Rebif, and
7 Copaxone studies, we wouldn't have any drugs at all
8 because it would have been impossible to know how
9 much of those effects were biased.
10 The last point is, the difference between
11 placebo and active arm in those studies is actually
12 smaller than what's being reported in the CARE MS
13 studies between the active arms.
14 DR. FOUNTAIN: All right. Dr. Smith?
15 DR. SMITH: Thank you. My question has to
16 do with your cases of ITP. As you know, ITP in an
17 adult is a chronic disease that can last many, many
18 years. And the definition you're using for ITP is
19 a platelet count of less than 100,000 with no other
20 cause, which is a consensus definition.
21 Unfortunately, ITP for most patients remains
22 an incurable disease. About 30 percent of people

1 in their first episode require a splenectomy, and
2 on relapse -- on medication, about 70 percent of
3 people require a splenectomy. The other thing is,
4 the disease can last a very, very long time.
5 So the question I have for you is really
6 two. One is, how many people in your study
7 actually had true thrombocytopenia? That is, they
8 did not meet the definition that you used for ITP,
9 but their platelet count was less than 150,000.
10 The second question I have for you is a bit
11 more theoretical. And that is, you describe a
12 defect in T-cell regulation that may be a side
13 effect of Campath therapy. I mean, there's years
14 and years of experience with Campath in other
15 areas, in other parts of the world.
16 T-cell dysregulation has been associated
17 with bone marrow aplasia and aplastic anemia. And
18 my experience, at least I think in my experience,
19 I've seen people treated with Campath that have
20 developed aplasia many years after receiving a
21 dose.
22 Do you have any information about that and

1 how that would impact the consequences of therapy,
2 would impact for these patients with MS?
3 DR. PANZARA: So I'll begin with the second
4 part about the dysregulation of T-cell function. I
5 think that, given the depletion of repopulation
6 that we see, it wasn't my intent to suggest that
7 what's happening with the changes and the
8 proportions is a defect.
9 What we are seeing is that the populations
10 are definitely changing. The single doses that we
11 are giving are different from some -- the single
12 lower doses are different. So what we're seeing
13 with the repopulation and the cell types is
14 different from some of the other indications.
15 So I can't really speculate about the effect
16 you've mentioned, but I can tell you this is not a
17 defect in T-cells that we're seeing. It really is
18 a different pattern that has been seen in other
19 diseases.
20 Regarding ITP, there are two questions
21 you've asked there, first of all about true
22 thrombocytopenia that we've seen. And actually, I

1 can show you the mean platelet counts throughout
2 the studies that have demonstrated that, actually,
3 overall, there's a lower platelet count in the
4 comparator group overall than the alemtuzumab
5 population, with the cases of thrombocytopenia that
6 we have seen really specifically to ITP.
7 The cases of ITP have all been reviewed by
8 Dr. Cuker, who is our hematologist here, and I'll
9 have him comment because the cases that we're
10 seeing in alemtuzumab are actually quite different
11 than the adult form that you're describing there.
12 And I think it'd be helpful to have him talk to you
13 about that.
14 DR. CUKER: Hello. My name is Adam Cuker.
15 I'm a hematologist at the University of
16 Pennsylvania. May I please have slide 3 up?
17 So Dr. Smith, as you well know, we separate
18 ITP in adults between primary and secondary ITP;
19 primary, where we can identify an underlying
20 etiology. In secondary ITP, there is an associated
21 predisposing condition.
22 As you point out, primary ITP in adults

1 tends to be a chronic disease. Patients often
2 respond well to therapy, but when the therapy is
3 tapered, the patients relapse, and many of them do
4 require maintenance therapies such as splenectomy
5 to maintain a hemostatic platelet count.
6 It's very interesting to note that the
7 behavior of alemtuzumab-associated ITP appears to
8 be quite different from typical primary ITP in
9 adults. And I think here, a picture is worth a
10 thousand words.
11 So I want to show you the platelet count
12 profile that is up on the screen. On the Y axis,
13 we have the platelet count. And this is one
14 individual subject who developed ITP during the
15 clinical development program. And month on study
16 is shown on the X axis.
17 The green vertical lines represent the
18 patient's treatment with alemtuzumab. You can see
19 this particular subject received three courses of
20 therapy. The last course of therapy was at about
21 24 months. And if you see the platelet count,
22 you'll notice that it remains within the normal

1 range until about month 36. And then there's a
2 precipitous drop.
3 So this highlights two important points
4 about alemtuzumab-associated ITP. First, the delay
5 in onset. This particular subject developed ITP
6 36 months after the initial treatment and about
7 12 months after the last treatment.
8 A second important point to note is the
9 precipitous drop in platelet count. If you look
10 down in the left lower corner of the slide, you'll
11 see that this patient was treated with a
12 methylprednisolone taper that was fairly rapid.
13 And you'll notice that the platelet count rose
14 quite quickly in response to this treatment. So
15 that highlights a third important point that we
16 have seen again and again in these cases, and that
17 is response to standard ITP therapy.
18 Then the fourth point I want to make is what
19 really seems to differentiate this condition from
20 typical and primary ITP in adults. And that is
21 that after this patient responded to the
22 methylprednisolone taper, they were off therapy,

1 and the platelet count remained in the normal range
2 to the point of last follow-up.
3 So we're talking about from month 36 to
4 month 120. And I'll just point out again that
5 that's very different than what we usually see in
6 primary ITP in adults. And it suggests that this
7 disorder, this particular disorder of alemtuzumab-
8 associated ITP, while serious, tends not to
9 be -- it does not appear to be a chronic
10 complication.
11 DR. FOUNTAIN: Did you want to say
12 something, Dr. Mentari?
13 DR. MENTARI: I did want to comment on
14 Dr. Cuker's description of the course of ITP with
15 alemtuzumab. While that graph represented the
16 experience of that one patient, there were patients
17 with multiple episodes. Is that correct? Do you
18 have any additional detail about the number of
19 episodes that occurred in a wider range of
20 patients?
21 DR. CUKER: Make I ask for slide SA-84 up on
22 the screen, please? Yes.

1 So we used I think a slightly different
2 definition of ITP than you, and so we identified 28
3 medically confirmed cases of ITP.
4 I'm sorry. Let me ask for the right slide
5 so I can get this information to you. And so the
6 index case was, as you know, a fatal case of
7 intracranial hemorrhage. So that individual did
8 not receive treatment.
9 So this slide summarizes how the individual
10 patients were treated who did receive treatment.
11 And so, if you see here, we start with 28 medically
12 confirmed cases of ITP. There were three patients
13 who did not receive treatment, one of whom was the
14 fatal index case. Two other patients were judged
15 by their treating team not to require therapy.
16 Twenty patients out of the 25 who received
17 treatment received only corticosteroids and IVIG.
18 And those patients all responded and had lasting
19 responses at the time of the last data analysis,
20 which I believe for this was June 30th, 2013.
21 There were four patients who went on to
22 receive therapy in addition to corticosteroids with

1 Danazol and/or rituximab. And there was one
2 patient who underwent splenectomy.
3 I did a medical review of the cases, the
4 patients who received second-line therapies, things
5 like splenectomy and rituximab. And it's my
6 opinion that, in some of those cases, the treatment
7 may have been given sooner than we would typically
8 have recommended. But at least we see here that 20
9 out of the 25 patients that receive treatment
10 responded and had durable responses with
11 corticosteroids and/or IVIG first-line treatments.
12 And that would be highly atypical for primary adult
13 ITP.
14 DR. SMITH: Mr. Chairman, can I just ask
15 another question?
16 DR. FOUNTAIN: Yes.
17 DR. SMITH: Just a follow-up question. How
18 many people develop thrombocytopenia that was
19 prolonged, that did not meet the criteria for ITP?
20 You didn't really answer that question. Any idea?
21 DR. PANZARA: Yes. So we actually did an
22 analysis two ways. First, why don't we start with

1 the mean platelets over time to show the overall
2 population, and then I'll show the shifts table
3 that will show you the shifting to
4 thrombocytopenia, which I believe is what you're
5 most interested in.
6 Can we have slide 1 up, please. First,
7 beginning with the overall population, this is the
8 platelet counts for the overall population for the
9 12- and 24-milligram dose groups as well as
10 alemtuzumab. There is the platelet counts on the
11 Y axis and time on the X axis. And as you can see,
12 platelet counts remain relatively stable throughout
13 as a mean.
14 Now may I have the shift table, please from
15 CTC grade, please? It will be one moment.
16 DR. FOUNTAIN: So can I just clarify your
17 answer to the previous question? There were no
18 patients who had more than one episode of ITP?
19 That is, those that were treated with a second-line
20 therapy had persistent ITP, but not more than one
21 episode, individual episode of ITP.
22 DR. CUKER: That's right. And so there were

1 some patients who may have been given initial
2 course of corticosteroids or IVIG, for example; had
3 a response. Then as the treatment was tapered,
4 their platelet count may have fallen, and they were
5 given more first-line therapy and then responded.
6 I hope I'm answering your question now, but
7 there were no patients as of the cutoff that
8 received treatment and were continuing to require
9 therapy for months after their initial
10 presentation.
11 DR. FOUNTAIN: And no recurrent episodes. I
12 think that was the original issue. No one had more
13 than one episode. It was cured, and then it came
14 back.
15 DR. CUKER: That's right. I think where the
16 confusion is, is in what did we define as an
17 episode. So if the patient, for example, presents
18 with a low platelet count, gets IVIG, responds, and
19 then two weeks later their platelet count falls, I
20 would consider that to be a single episode, not a
21 separate episode. So I think it gets a bit
22 confusing about how we define episodes. But as of

1 the June 30th cutoff date of this year --
2 DR. FOUNTAIN: Yes. I think we understand
3 the answer to your question. Thank you.
4 DR. CUKER: Okay. Thank you.
5 DR. PANZARA: So now, slide 2 up, please, to
6 answer the other question. I don't have the
7 individual patient numbers here, but this again
8 shows you can see the numbers across the bottom of
9 the screen for people who shift, starting a
10 baseline at month 33 and 36, CTC grade in terms of
11 platelet abnormalities.
12 So you can see that, overall, the counts
13 were quite balanced between the groups. And when
14 you look at the zero- to two-year analysis, the
15 cases that are identified are the ones that fall
16 into the ITP categories that we've already
17 discussed.
18 DR. MENTARI: I'd like to comment on that
19 slide. I don't know what the total numbers are,
20 and I think, Dr. Panzara, you said you don't have
21 them. I know in the shift tables that we received,
22 they included platelet numbers that were derived

1 from clinical visits, but not necessarily from
2 visits that occurred because of visits to outside
3 hospitals or emergency rooms.
4 Do you have any comment on what type of data
5 this is that you're describing?
6 DR. PANZARA: These are the scheduled
7 assessments that we're showing here, again, the
8 overall testing throughout the clinical lab
9 testing.
10 DR. MENTARI: So this slide might not
11 reflect all cases of ITP and might not reflect all
12 cases of thrombocytopenia to my knowledge.
13 DR. PANZARA: So all cases of
14 thrombocytopenia -- all cases of ITP were the cases
15 that I've presented earlier. Whether there is an
16 individual case that dropped below 150 is the
17 threshold that was given. This slide may not
18 reflect that, but remember, patients are having a
19 CBC every month.
20 DR. FOUNTAIN: Dr. Bastings?
21 DR. BASTINGS: Yes. To go back to the issue
22 of what study design FDA would have liked, I

1 mentioned a design that uses a low dose and a high
2 dose. And there was a suggestion that the low dose
3 would be -- operating, but that was not the intent
4 at all. We did not intend to have a pseudo-placebo
5 or a low dose of alemtuzumab that would not be
6 effective.
7 What we expect with the design is two
8 effective doses, just the high dose being more
9 effective than the low dose.
10 DR. FOUNTAIN: Thank you.
11 Dr. Alexander, do you still have a question?
12 DR. ALEXANDER: Yes. First, just a comment
13 about the REMS and ETASUs. I mean, I'm reassured
14 that there would be an ETASU if this product were
15 approved. I think that's appropriate. I don't
16 think we should look to the evidence of the
17 experience that we've gleaned from the clinical
18 trials in any means to try to assess or estimate
19 what the likely adherence or impact of the ETASU
20 would be. And I guess just a historical note,
21 which is that, unfortunately, it's terribly
22 difficult to know what the impact of these types of

1 risk mitigations are on clinical practice.
2 We know in many settings, regulatory
3 interventions have had little or no impact, and in
4 others, they've had a substantial impact. But I
5 think it's anybody's guess what the likely impact
6 of the ETASU would be or how closely it would be
7 adhered to.
8 There was a question about why the screening
9 EDSS measures weren't used in the original
10 protocol. And I had the same question, but I don't
11 think I really understood the answers. I mean, the
12 two explanations that were given was, one, that
13 this was a rater-blinded study, but that's not
14 really a scientific rationale not to use the
15 screening measures. And the other was logistical
16 problems getting patients in, but I would think
17 that they would need to be screened and that
18 evaluation would be performed regardless. So I'd
19 like for the sponsor to address that
20 Then just a second question for the sponsor,
21 what's the specific frequency and nature of testing
22 or other interventions, such as the use of an

1 antiviral, that are recommended to accompany this
2 product? That is, am I correct in understanding
3 that patients would be expected to have a CBC, a
4 comprehensive metabolic panel, a TSH, a free T-4,
5 and are there others? And would those be monthly?
6 And what other clinical interventions are proposed
7 to accompany this product if it's approved?
8 DR. PANZARA: So I'll begin with the first
9 question, which is to address your earlier comment
10 about the screening versus baseline. Again, I
11 think it's important to describe the limitations of
12 screening versus baseline, and this applies not
13 just here, but to others. So I'm going to talk to
14 other studies. I'm going to pass this to you for
15 now.
16 DR. LAKE: Sorry. I might have been
17 introducing some confusion. So the screening value
18 was used to qualify patients for the study. They
19 had to meet certain EDSS criterion to be included
20 in the study. The baseline EDSS was used for the
21 primary analysis, and that was prespecified in the
22 statistical analysis plan.

1 DR. ALEXANDER: What would be the scientific
2 detriment of using the screening-derived EDSS as
3 the baseline measure?
4 DR. LAKE: To answer that, I'd like to turn
5 it over to Dr. Gary Cutter.
6 DR. CUTTER: By convention, most studies use
7 the baseline value. The screening values are often
8 higher than baseline because patients when they're
9 getting screened, they're closer to a relapse.
10 They're concerned about it, and the idea is to get
11 the best measure of the usual behavior of the
12 patient at baseline.
13 What has complicated this is the question of
14 whether or not the baseline -- my understanding is
15 the centers in general. And I must say, I was not
16 involved in the design or the operation of the
17 trial. But my understanding is that this was an
18 opportunity for the staff to get their act
19 together; in essence to be prepared for the patient
20 when they came in. But I'll leave that for someone
21 with the company to discuss.
22 Slide 2, please. Just to give you an idea,

1 this is what I presented at ECTRIMS, and it shows
2 the general nature of what happens in terms of
3 screening and baseline data. The yellow
4 portion -- and this is again in the Combi trial, a
5 double-blind study. The yellow area is the
6 proportion of people who actually have lower values
7 than their screening values, which is about
8 35 percent. There's another 24 percent that go up,
9 and we hit about 42 percent in the center.
10 If you think about what's going on, it could
11 be that either patients or even the staff are
12 trying to recruit. It's always pressure to
13 recruit. So oftentimes, people use that as an
14 entry level, but then revert to the formal baseline
15 and write that in the protocol. That's extremely
16 common in every study I know.
17 I actually can't think of studies that use
18 the screening. I know this was raised in the FDA's
19 review, and they found the same thing when they
20 reviewed the natalizumab Sentinel trial. And if
21 you have a higher baseline value, it's going to
22 diminish the number of events.

1 Let me have slide 3, please. This is the
2 current 324 trial on the right side, and on the
3 left side is the survival curve for those same
4 groups. The yellow group is the group whose
5 screening was higher than baseline. The blue group
6 is on the left, blue graph up at the top. Those
7 are the individuals whose screening was greater
8 than baseline.
9 So what you can see is, by changing
10 individuals, and whether you use their screen or
11 their baseline, you actually change their time to
12 failure. So if you move somebody from a lower
13 baseline value to a higher baseline value, the
14 disease has to overcome with more time to have the
15 disease evolve to be able to fail.
16 When you do that in a study where there are
17 people who drop out, they can no longer be
18 observed. They get in a mortal time bias. So if
19 you move individuals who indeed fail under the
20 baseline definition and they drop out of the study,
21 if you go to a higher value at screening, then they
22 can't drop out, they can't fail.

1 I think a lot of this argument about
2 screening and baseline really comes from this
3 randomness that I think you can see here. These
4 curves look similar. I think also what happens,
5 this is seen in other studies, and the EDSS has a
6 lot of variability with it. It was described as
7 subjective. I think it's a little more objective
8 than that because these are actually fairly serious
9 symptoms, certainly severe relapses, I think, as
10 some of the patients pointed out.
11 DR. FOUNTAIN: Thank you. Is it also
12 possible that the intention was for the baseline to
13 occur at the same date as randomization? I think,
14 if I were reading that protocol, I'd think they
15 occurred at the same time. And then for logistical
16 reasons, it was separate and that wasn't recognized
17 until later?
18 DR. LAKE: Yes. I think that is probably
19 most likely the case.
20 DR. FOUNTAIN: So the answer to the question
21 about scientific rationale would be that,
22 beforehand, that wasn't a consideration.

1 DR. LAKE: No. That wasn't a consideration.
2 Screening is do you get the patient to do the
3 study. Baseline EDSS is to assess their SAD.
4 Again, if I could have slide 2 up, please?
5 DR. KRYSCIO: Can we ask a question? Now,
6 this is Dick Kryscio.
7 Dr. Cutter, on all those studies that you
8 showed up there, when did the patient know they
9 were randomized to whatever treatment?
10 DR. CUTTER: Those are the two studies that
11 I've talked about. The one on the right, I can't
12 say when the patient knew. This is the 324 study.
13 I can't say when the patient knew. I think what
14 has been done, on 324, they're using a separate
15 system for randomization, the IVRS systems. And
16 those systems record the date that the staff
17 randomizes a patient, and that's compared to the
18 date when the form is filled out for the baseline
19 exam. And that's where that baseline and
20 randomization difference seem to be coming from.
21 In the system on the left, that is a system
22 that I use that's an integrated system. We don't

1 use an IVRS system, so the time stamps are the
2 same. And we were able just to provide drug.
3 DR. PANZARA: I just want to make sure we
4 answered your question.
5 DR. MARLER: But the patients were blinded.
6 Correct?
7 DR. PANZARA: Excuse me. I didn't hear the
8 question.
9 DR. MARLER: The patients were blinded after
10 randomization?
11 DR. PANZARA: No. These are graphs that
12 were done for this trial.
13 DR. CUTTER: On the right side, it's the 324
14 trial.
15 DR. MARLER: On the Combi trial.
16 DR. CUTTER: In Combi, the patients were
17 double-blind.
18 DR. MARLER: Right. Thank you.
19 DR. CUTTER: Sorry. I may be the first in a
20 line of several comments. I'm not sure. A
21 discussion of the baseline versus the screening
22 loses the focus of what the issue is. The issue

1 here is not about the relative merits of baseline
2 and screening values.
3 Studies routinely have those and we
4 understand there's some variability. And we
5 understand why those are done. The issue here is
6 patients' awareness and not just patients, but the
7 study as a whole, their awareness of their
8 treatment allocation.
9 The issue here is, which value do you use as
10 it relates to an awareness of what group you're
11 randomized to? Any discussion about the relative
12 merits of using a screening value or a baseline
13 value, particularly when using comparisons to other
14 double-blind trials done more conventionally seems
15 to completely miss the point.
16 So I don't know if you all want to amplify
17 on that or not, but that really is the issue. And
18 keep in mind that I want to return to something
19 Dr. Marler said during his presentation.
20 This issue of the screening and baseline
21 value, which in this particular trial where it was
22 done open label, is only taking on a certain degree

1 of importance in occupying some discussion because
2 it reflects an effort that we made in one area
3 only, that we had the opportunity to try to
4 address, however imperfectly -- but to try to avail
5 ourselves with information that we had to account
6 for the bias that we think is pervasive in these
7 trials.
8 By definition, we think it's pervasive.
9 What we don't know is its effect. And that's what
10 we're charged with sorting out. We think these
11 trials by definition don't have one of the primary
12 features of typical clinical trial design.
13 This is basic principles. And so what we do
14 is try to correct for that. Dr. Marler pointed out
15 in his discussion that we don't have the ability to
16 conduct some post hoc maneuver to approximate a
17 correction for that bias at all the other various
18 times that it was measured.
19 DR. DUNN: Excuse me
20 DR. LAKE: Could I just make one comment,
21 please? It's that, in terms of trying to assess
22 these differences between screening and baseline, I

1 think one thing that I tried to make clear in my
2 core presentation was that the logic doesn't really
3 hold up between the two studies, 323 and 324.
4 In the 324 study, we see potentially Rebif
5 patients, knowing that they received Rebif,
6 artificially improving their baseline EDSS, and we
7 don't see that in the -- sorry, that's the 324
8 study. We see the opposite thing in the 323.
9 So this is, I think, still indicative. And
10 as Dr. Cutter talked about, just the random
11 variability in the EDSS between two different time
12 points, these mean changes are expected.
13 DR. FOUNTAIN: I think we've
14 discussed -- there are many issues to discuss, and
15 this might be a good time to turn our attention to
16 the question so we can frame it, put it in that
17 framework. So unless there's a specific question
18 with regard to this, that will help us answer the
19 question. So if someone has a particular question
20 or comment in regard to this or if you need more
21 information, we'll be glad to discuss it more. But
22 if you feel like we can move on to the questions,

1 then we'll do that.
2 DR. ALEXANDER: I was wondering about the
3 second part of my question, which was, what does
4 the sponsor propose that clinicians do each month
5 or how frequently and what interventions?
6 MS. PANAGOULIAS: So the labeling will
7 recommend a monthly CBC, monthly serum creatinine
8 for nephropathy, also a monthly urinalysis, and a
9 quarterly TSH. That would be the lab monitoring.
10 In addition, you mentioned in your question
11 what other treatments, and we are recommending
12 acyclovir prophylaxis at the time of infusion and
13 for a month thereafter and also administration of
14 methylprednisolone to manage infusion-associated
15 reactions concurrent with treatment.
16 DR. FOUNTAIN: Dr. Zivin, do you have a
17 relevant question?
18 DR. ZIVIN: The FDA, in their briefing
19 documents, unless I misunderstood them, seemed to
20 indicate that your blinded raters were not blinded
21 entirely, and I'd like to know what your response
22 is to that.

1 DR. PANZARA: That's not correct. We had
2 blinded raters. We had procedures in place to
3 assess, through monitoring, et cetera, the blinding
4 of the raters. We had a monthly attestation to
5 confirm that they were blinded. They had to attest
6 to that.
7 If they were unblinded, they were removed
8 from being a blinded rater for that patient. And
9 in all of these things, once an unblinded rater was
10 identified, all of those unblinded evaluations were
11 put in sensitivity analyses where those events of
12 unblinding were removed.
13 So blinded raters were an important part of
14 this, and the examinations that they performed were
15 done with a Neurostatus exam, which -- the
16 neurological exam. One could argue a neurological
17 exam is subjective, but the Neurostatus scale that
18 we used attempts to add a level of objectivity to
19 the exam.
20 There was less than 1 percent of patients
21 that we've identified -- raters, excuse me -- that
22 we had identified were unblinded at any point

1 during this study. And in addition, we did
2 analyses where we would remove sites where a single
3 rater was unblinded, just assuming the whole site
4 now is unblinded, and even that didn't have an
5 effect on the primary outcome.
6 DR. FOUNTAIN: Comments, Dr. Dunn?
7 DR. DUNN: Yes. So we don't contest in any
8 way that the sponsor attempted to blind the raters
9 in the conventional way to the assessments. We
10 encouraged and request rater blinding in
11 double-blind trials due to the increased
12 reliability of those assessments, particularly in
13 situations where a patient may suspect, due to side
14 effects as we've discussed, what treatment
15 assignment they may have.
16 That's a very different scenario than a
17 patient knowing. And that really comes back to the
18 heart of what this is all about. Here, we have an
19 absolute ascertainment. It's not a side effect
20 where you suspect you may be on a certain treatment
21 and that might influence certain things. And in
22 those situations, we still think rater blinding is

1 very important.
2 Here, we have an ostensibly blinded rater
3 who is interacting with a patient, who knows what
4 they have. And that patient has been participating
5 in the trial with multiple interactions with
6 various people and endeavors who also know what
7 that patient has.
8 So what we have is a potential, but the
9 devil is in what you don't know. We're trying to
10 talk about the screening baseline thing. With
11 bias, it could reach everywhere, and we're
12 concerned about the tendrils on bias and their
13 impacts throughout the trial.
14 So we don't contend in any way that the
15 sponsor didn't use rater blinding in the
16 conventional way that we think of it. Our question
17 is about the impact of the biases of the trial and
18 the reliability of that assessment.
19 DR. FOUNTAIN: Is it relevant to this
20 particular point?
21 DR. ALEXANDER: I'm a little confused about
22 the trial design and about some of the comments

1 that Dr. Bastings made, the comment about the
2 preferred strategy that FDA would have recommended,
3 would it be a double-dummy trial.
4 That said, it would still have included that
5 80 percent of patients who in this particular trial
6 had interferon before and were still being treated
7 with interferon, it's a strategy that -- at least
8 for those of us who are not neurologists, it's a
9 little bit unusual that you would treat the
10 patients. And even if you had a double-dummy
11 design trial, you would still run into the same
12 potential statistical problem.
13 So I'm not sure how we're going to resolve
14 this issue because when you're comparing the trial
15 using a medication to which the patients in the
16 past seem to have either failed, or become
17 resistant, or in the opinion of the treating
18 physician not being helped by it -- and we're still
19 going back to the same drug, comparing with the new
20 drug. I'm not sure I see how we're going to
21 resolve this issue about the validity of the trial.
22 DR. BASTINGS: No. We think the situation

1 would be vastly different with a double-dummy
2 design because, again, all of the site personnel
3 and the people surrounding the patient would be
4 blinded, and the patient themselves would -- I
5 believe a substantial proportion of patients would
6 remain blinded. Even if they had a side effect,
7 they still would have a substantial doubt about
8 what treatment has been assigned to them.
9 So we believe that it's a much better
10 situation to be in than to go into the trial
11 knowing the treatment assignment. We think it's a
12 very different situation.
13 DR. FOUNTAIN: Dr. Unger?
14 DR. UNGER: I would take the fact that
15 92 percent of patients on alemtuzumab had an
16 infusion reaction as pretty good evidence that if
17 you know what treatment you're on, you have an
18 infusion reaction. We've dealt with plenty of
19 biologics over the years that cause infusion
20 reactions. It's very unusual that 92 percent have
21 an infusion reaction.
22 The patients here who are on interferon, of

1 course, didn't get a placebo. But had you taken
2 patients, and given them a placebo infusion, and
3 told them they could have an infusion reaction,
4 you'd have a substantial percentage of patients who
5 had something, and that would have been interpreted
6 as a reaction to a drug.
7 So the bias is very difficult. It's
8 like -- I think Dr. Bastings said, it's very
9 difficult to know what the effect is. The fact
10 that you have differential dropout before
11 treatment, a huge difference, means that people did
12 have an expectation. They wanted to be on the
13 experimental drug. They have a terrible disease.
14 They want to feel better. And it's that bias of
15 wanting to be better and knowing that you're on the
16 drug, that affects something like EDSS, that's
17 susceptible to bias.
18 DR. PANZARA: So just one clarification
19 about the infusion-associated reactions. Both
20 groups received methylprednisolone. So all
21 patients had infusions. And that gave us the
22 opportunity to get at the question that Dr. Unger

1 is talking about, is with his broad definition of
2 what's an infusion-associated reaction, if you give
3 him an infusion and it matches the timing and the
4 infusion of alemtuzumab, do you see infusion-
5 associated reactions associated with that?
6 I'd like to show slide 1, we do. About half
7 of the Rebif patients do see something, but 90
8 percent of patients have infusion-associated
9 reactions on alemtuzumab. There's a dose effect
10 where you get -- this is a dose-blinded study, so
11 patients were not aware that they were getting 12
12 or 24.
13 You see a dose effect and infusion-
14 associated reactions, where there is higher numbers
15 of grade 3 and 4 infusion-associated reactions. So
16 we have an infusion comparator here and we have a
17 dose effect with dose blinding, again to
18 suggest -- and these are very obvious side effects
19 in terms of the types of side effects, so these
20 aren't a subtle difference
21 DR. DUNN: Dr. Panzara, why did you blind
22 patients to their dose?

1 DR. PANZARA: Because originally, as you
2 recall, the 324 study had a 24-milligram arm. And
3 when that study was designed, the 12- and the 24-
4 milligram dose groups were blinded with a central
5 pharmacist mixing. And so patients themselves were
6 not aware of their dose level. And the people that
7 got 24 stayed on 24 for two years, and the people
8 who got 12 stayed on 12, even though the arm was
9 discontinued.
10 DR. DUNN: But why was it important to blind
11 them?
12 DR. PANZARA: I think it was important for
13 this particular case is they understand a little
14 bit more about the safety profile to get at the
15 issues that Dr. Unger -- but really, there was no
16 statistical significance in phase 2. I think what
17 we were trying to understand is a little more about
18 the profile of the drug.
19 DR. MENTARI: Could I just get a
20 clarification on the previous slide? When you're
21 referring to the Rebif group, the infusion reaction
22 is upon administration of Rebif. Is that correct?

1 DR. PANZARA: It's upon the administration
2 of methylprednisolone with a time frame similar to
3 that. What we did was use a -- as with the
4 infusion-associated reaction for alemtuzumab,
5 anything occurring within 24 hours of an infusion
6 of alemtuzumab over the first six days of the first
7 course, four days of the second course, were
8 counted as an infusion-associated reaction. We
9 applied the same definition to the
10 methylprednisolone infusions that the Rebif
11 patients received to allow an infusion control, if
12 you will.
13 DR. MENTARI: Could you show that slide
14 again?
15 DR. PANZARA: Sure, absolutely.
16 DR. MENTARI: Is that data just for
17 methylprednisolone infusion?
18 DR. PANZARA: This is any event occurring in
19 time of the methylprednisolone infusion.
20 DR. MENTARI: So the infusions that the
21 Rebif patients were under different circumstances
22 because --

1 DR. PANZARA: That's correct.
2 DR. MENTARI: -- it was with the
3 understanding that it was methylprednisolone.
4 DR. PANZARA: That's correct. They knew it
5 was methylprednisolone, but they, again, did not
6 know whether it was 12 or 24.
7 DR. FOUNTAIN: I think we've made the point
8 clear that you did blinding between 12 and
9 24 milligrams to find a difference and didn't do
10 blinding with Rebif, as we've talked about. And
11 the patients had lots of side effects, and could
12 very well be because they were unblinded.
13 DR. BASTINGS: I think that slide -- can
14 you bring up the slide?
15 DR. PANZARA: The one we just showed?
16 DR. BASTINGS: Yes, the one that you just
17 showed.
18 DR. PANZARA: Can I have the
19 infusion-associated reaction slide again, the
20 overall summary? Slide 2 up, please.
21 DR. BASTINGS: I think that slide is
22 actually the best argument for a double-dummy

1 study. It shows that people in the Rebif group had
2 a fairly high rate of events at the time of
3 infusion, even though they knew they were not
4 getting alemtuzumab.
5 So if they were in a situation where they
6 were being blinded, that rate probably would have
7 been even higher.
8 DR. PANZARA: Yes.
9 DR. FOUNTAIN: All right. So this would be
10 a good time --
11 DR. PANZARA: -- to address -- there's also,
12 remember, you have another thing going on here.
13 These people are injecting themselves three times a
14 week, so it's not just the infusion that we're
15 addressing here.
16 DR. FOUNTAIN: So I think this would be a
17 good time to take a break. We're behind just a
18 little bit in terms of our break, so let's take a
19 15-minute break. It's 3:10 now, so let's reconvene
20 in 15 minutes at 3:25. And I'll remind the members
21 of the committee not to discuss the meeting topic
22 outside of the committee meeting.

1 (Whereupon, a recess was taken.)

2 **Questions to the Committee and Discussion**

3 DR. FOUNTAIN: If everyone would take their
4 seat, please, we'll get back to work.
5 This is a complicated topic, so I'm glad
6 that everyone is being vigilant in helping us stay
7 on task about as best we can. Now, we'll shift to
8 the specific discussions of the questions. We'll
9 now proceed with the questions to the committee and
10 panel discussions. I would like to remind public
11 observers that while this meeting is open for
12 public observation, public attendees may not
13 participate except at the specific request of the
14 panel.
15 We will be using an electronic voting system
16 for this meeting. Once we begin the vote, the
17 buttons will start flashing and will continue to
18 flash even after you've entered your vote. So you
19 push the button, but it keeps flashing. It's okay.
20 It's already registered your vote.
21 If you're unsure of your vote or you wish to
22 change your vote, you may press the corresponding

1 button until the vote is closed. After everyone
2 has completed their vote, the vote will be locked
3 in. The vote will then be displayed on the screen.
4 The DFO will read the vote from the screen into the
5 record. Next, we will go around the room, and each
6 individual who voted will state their name and vote
7 into the record.
8 You can also state the reason why you voted
9 as you did, if you want to. We'll continue in the
10 same manner until all questions have been answered
11 or discussed.
12 All right. So question number 1 has quite a
13 preface and then the specific question. Adequate
14 and well-controlled studies include the following
15 characteristics: a design that permits a valid
16 comparison with a control to provide a quantitative
17 assessment of drug effect; adequate measures are
18 taken to minimize bias on the part of the subjects,
19 observers and analysis of the data; methods of
20 assessment of subjects' response are well defined
21 and reliable; an analysis of the results of the
22 study adequate to assess the effects of the drug.

1 An adequate and well-controlled study is
2 capable of distinguishing the effect of a drug from
3 other influences such as spontaneous change in the
4 course of the disease, placebo effect, or biased
5 observation.
6 So here's the specific question upon which
7 we will vote and then discuss: Are Trials 323 and
8 324 adequate and well controlled?
9 Vote now. Remember, it'll continue blinking
10 after you've registered your vote. You can change
11 it till they stop blinking when all the votes have
12 been registered. You can vote yes, no or abstain.
13 So everyone, please vote. All the voting
14 members, vote either yes, no or abstain.
15 Okay. Everyone's voted.
16 (Vote taken.)
17 LCDR JOHNSON: I will now read the vote into
18 the record. We have six yes, 11 no, one abstain,
19 and zero no vote.
20 DR. FOUNTAIN: The vote is displayed on the
21 table, and why don't we go around the room. You
22 can suggest how you voted, and if you'd like to

1 make a comment, you can.
2 We'll start with Dr. Woods.
3 DR. WOODS: Mark Woods, I voted no. I think
4 the FDA built a very nice case for where this trial
5 did not measure up, and so I was compelled to vote
6 no.
7 DR. FOUNTAIN: Ms. Sitcov, please. You can
8 just go from person to person. Just state your
9 name and then you vote.
10 MS. SITCOV: Cynthia Sitcov. I abstained.
11 I felt that was the right thing for me to do at the
12 moment. I felt that the sponsor and the FDA both
13 made reasonable arguments.
14 DR. HOFFMANN: Richard Hoffmann, I voted
15 yes. I thought that although the trials were not
16 ideal in design, in hindsight, that's really all we
17 have right now to work with. And I think the
18 studies do get some support by having the European
19 Medicines Agency also feel that they were designed
20 okay and also some support from the Lancet journal,
21 which is a very reputable journal that published
22 the results in spite of one editorial that kind of

1 contradicted the study designs.
2 So I think this is where we go from here,
3 and hopefully, that will provide a new treatment
4 for some MS patients.
5 DR. WALLIN: Mitch Wallin. I voted yes.
6 Though there's problems with the trial, I thought
7 that at least from the relapsing standpoint and
8 comparing it to a platform therapy was reasonable.
9 There's other safety issues I have concern about,
10 but I think for this particular question, I voted
11 yes.
12 DR. LU: Ying Lu. I vote no. I think the
13 problem is not only active control, but also the
14 process that the patient being revealed before we
15 collect the baseline information, and also the
16 potential bias that is really hard to evaluate the
17 impact.
18 DR. KRYSCIO: Dick Kryscio. I voted no for
19 similar reasons. I felt that the FDA made a more
20 compelling case as to why there's potential bias
21 associated with the randomization in the study.
22 DR. BAGIELLA: Emilia Bagiella. I voted no

1 for exactly the same reasons.
2 DR. KLASSEN: David Klassen. I voted no.
3 And I recognize the study is very difficult to do,
4 and it's complicated. And we're not sure that you
5 can do a truly blinded study, but I thought there
6 were other avenues for potential bias that were
7 pretty well laid out. And so I thought the
8 potential for bias was real.
9 DR. SMITH: Roy Smith. I voted no because
10 of the potential bias in the studies.
11 DR. ASCENSAO: Joao Ascensao. I voted yes.
12 I believe that the studies could have perhaps been
13 better designed, but I think the evidence presented
14 today suggested that the drug may have some
15 efficacy beyond the issues associated with a
16 potential bias.
17 DR. BLUMENTHAL: David Blumenthal. I voted
18 yes. Very tough call because the decision to not
19 have adequate controls is going to be unsettling to
20 many members of the committee, but at the end of
21 the day, I thought that even with appropriate
22 precautions subjects would have known if they were

1 getting active drug or if they were not. And the
2 dropout prior to the first dose of drug perhaps
3 would not have occurred with adequate controls, but
4 dropout during -- or the patient being aware of
5 their treatment during the study perhaps -- was
6 very difficult to address even if all the FDA
7 recommendations had been followed.
8 DR. FOUNTAIN: Nathan Fountain. I voted no,
9 but I actually thought it was an adequate but not
10 well-controlled study; that is, that there were
11 many issues we've talked about. I thought in the
12 aggregate, those issues were many small things
13 rather than one large thing. I was less concerned
14 about the blinding.
15 But the question is, is it adequate and well
16 controlled? And in the aggregate for this whole
17 population as it was studied, I did not think it
18 was entirely well controlled.
19 DR. ROSENBERG: I'm Paul Rosenberg. I voted
20 yes because I think had the double dummy study been
21 performed, that a very substantial number of
22 patients would have been unblinded, and we would be

1 having virtually the same discussion.
2 DR. ALEXANDER: Caleb Alexander. I voted no
3 for the reasons that have been stated. And also, I
4 wasn't totally clear on some of the scientific
5 rationale for some of the decisions that were made
6 within the protocol.
7 DR. CLANCY: Robert Clancy. I voted no.
8 I'm actually very concerned about the unblinding.
9 This means that one of the fundamental principles
10 of a fair trial has been violated. And because the
11 symptoms of MS are sometimes very sensory, I have
12 numbness, I have loss of vision, I feel dizzy, I
13 feel woozy and so forth, those can be suppressed if
14 a patient has an agenda or the center has an
15 agenda. Those symptoms can be suppressed and blown
16 off to the extra cup of tea they had, and I can't
17 trust the results.
18 DR. ZIVIN: Justin Zivin. I voted yes. I
19 was torn in this vote between yes and abstain. A
20 study like this can't be blinded, but as long as
21 the raters are adequately blinded, then that's an
22 adequate study design as far as I'm concerned. And

1 so that's why I ended up voting the way I did.
2 DR. YEH: Ann Yeh. I was very torn in the
3 voting because I too felt that this was an adequate
4 study, but the issues of bias that were brought up
5 by the FDA were compelling.
6 DR. MIELKE: Michelle Mielke. I voted no.
7 I understand the need for additional medications,
8 and I do think the study was possibly adequate.
9 But I just couldn't vote yes that it was well
10 controlled. So I went back and forth, and I
11 decided to vote no.
12 DR. FOUNTAIN: So I believe that's all the
13 voting members.
14 Question 2, has the applicant provided
15 substantial evidence of effectiveness of
16 alemtuzumab for the treatment of patients with
17 relapsing forms of multiple sclerosis? And this
18 has a complicated response, so I'll explain it.
19 Your answer could be yes, or it could be no because
20 the studies are not adequate and well controlled,
21 or it could be no because there is not substantial
22 evidence of effectiveness.

1 So to explain the way you're going to vote,
2 you'll see that there are three buttons lit up,
3 below them is A, B and C, and above them is attend
4 yes and no. And what's blinking is 1, 2 and 3. So
5 1, 2 and 3 corresponds to A, B and C. So the first
6 button on your left is yes.
7 (Vote taken.)
8 DR. FOUNTAIN: Everyone has voted.
9 LCDR JOHNSON: Before I show the results,
10 does anyone have any questions regarding on how to
11 vote?
12 DR. FOUNTAIN: How to use the buttons?
13 (No response.)
14 LCDR JOHNSON: I will now read the results
15 into record. We have 12 As, six Bs and zero Cs.
16 DR. FOUNTAIN: Why don't we go around the
17 room again? This time, let's go the opposite
18 direction. This time, we can start with
19 Dr. Mielke. So if you'll state your name into the
20 record and then how you voted, and if you like, why
21 you voted that way.
22 DR. MIELKE: Michelle Mielke. I voted no

1 because the studies are not adequate and well
2 controlled, as I stated in the last question, the
3 reason I had voted no for that. I had similar
4 reasons for this one.
5 DR. YEH: Ann Yeh. I voted yes here because
6 I felt that the drug was not shown to be worse
7 than -- even with FDA reanalysis, it wasn't shown
8 to be worse than an active treatment, and so I
9 voted yes.
10 DR. ZIVIN: Justin Zivin. I voted yes, and
11 the reason is because I believe it is adequately
12 safe and effective. And what I don't know is
13 whether it is better than the other drugs that are
14 currently available.
15 DR. CLANCY: Bob Clancy. I again voted no
16 because I didn't feel that the methodologies of the
17 study would allow me to conclude that it was
18 effective.
19 DR. ALEXANDER: Caleb Alexander. I'm kind
20 of puzzled. I wouldn't think that one could have
21 voted no on the last question and yes on this
22 question, but regardless, I voted no. I feel if

1 there's not adequate evidence in adequate and
2 well-controlled studies, I couldn't see how I could
3 think that there was sufficient evidence of
4 effectiveness in this question.
5 DR. ROSENBERG: Paul Rosenberg. I voted
6 yes. I think the FDA's concerns about potential
7 bias are valid, but I'm skeptical -- it's a
8 judgment on my part. I'm skeptical that that bias
9 introduced could explain the very substantial
10 effect on relapse.
11 DR. FOUNTAIN: Nathan Fountain. I voted
12 yes, so I'm one of the paradoxical ones that voted
13 no for the first one, yes for this. And so I think
14 the reason is because I interpret it, as
15 Dr. Rosenberg did, that this part required more
16 faith or gut feeling as to do with whether or not
17 you thought the methodology, regardless of how
18 limited it was, did show some evidence of
19 effectiveness whereas the first question was, does
20 it meet sort of the regulatory standard. That's
21 not quite right, but meet the strictest criteria of
22 being adequate and well controlled.

1 So in other words, I thought that on the
2 aggregate, there was evidence that it's effective
3 for MS, probably more effective than Rebif, but at
4 least as effective, which is a little different
5 than are they adequate and well controlled, I
6 thought.
7 DR. BLUMENTHAL: David Blumenthal. I voted
8 yes because although there was variability in the
9 MRI data, I think there was sufficient evidence of
10 efficacy in the MRI data in a way that it -- a type
11 of data that would not have been so affected by
12 flaws in the study design that I felt comfortable
13 voting yes.
14 DR. ASCENSAO: Staying coherent, voting yes.
15 Joao Ascensao.
16 DR. SMITH: Roy Smith. I voted no.
17 DR. KLASSEN: David Klassen. I voted no
18 largely because of my vote on the studies not being
19 adequate and well controlled, although I have to
20 say I was torn. I think that the drug clearly does
21 have activity in multiple sclerosis. And if it was
22 an issue with non-inferiority with the comparator

1 drug, I think I'd have a different feeling about
2 the whole studies.
3 DR. BAGIELLA: Emilia Bagiella. I voted no.
4 I think that the study design has substantial
5 influence on the results.
6 DR. KRYSCIO: Dick Kryscio. I voted yes for
7 the same reasons that Dr. Blumenthal did.
8 DR. LU: Ying Lu. I voted yes, and
9 partially, I think Dr. Yeh answered the same
10 feeling, that's active control and that the other
11 drug has been proved effective. And we're not
12 proving that it's worse than that. Of course, I
13 know it's not designed as a non-inferiority study.
14 The other part is the MRI information seems
15 to be at least the most objective measurement;
16 seems the trend's maintained, and the atrophy use
17 is really an important parameter that shows
18 consistent decreasing.
19 Also, I looked for the relapse rate. When
20 you look for the severe relapse required for
21 treatment, hospitalization, it seems to be
22 beneficial. And I feel there is potential bias,

1 but that piece may be to the level it's very hard
2 to be biased. Thanks.
3 DR. WALLIN: Mitch Wallin. I voted yes. I
4 think there was some consistency across the studies
5 with relapse rate reduction, inconsistencies in
6 disability progression or MRI data. But at least
7 for the major outcome, relapses, I thought there
8 was some effectiveness generated across trials.
9 DR. HOFFMANN: Richard Hoffmann. I voted
10 yes. I think there was definite evidence of
11 efficacy in the relapse rate in spite of the
12 potential bias.
13 MS. SITCOV: Cynthia Sitcov. I voted yes
14 because I also think it's very efficacious, and I
15 think that it's important to have another treatment
16 option available for those who are failing on their
17 current therapies.
18 DR. WOODS: Mark Woods. And I also voted
19 yes. And I thought the Lancet editorial statement
20 that said the real magnitude of the effect is
21 difficult to assess really kind of captured the way
22 I felt about this. I guess at the end of the day,

1 I felt there was more positive than negative.
2 DR. FOUNTAIN: Thank you.
3 The next question is question 3, and so far
4 the questions we've talked about really focus on
5 the things we spent much of our discussion on. So
6 first I'll read question 3, but then maybe it
7 requires more discussion before we vote.
8 The question has to do with the beneficial
9 effect on disability. So has the applicant
10 provided substantial evidence that alemtuzumab has
11 a beneficial effect on disability?
12 Before we vote, are there any more
13 clarifying questions of the FDA or the sponsor that
14 you'd like to ask?
15 Yes, Dr. Alexander?
16 DR. ALEXANDER: Should we read this as
17 beneficial effect on disability relative to the
18 active comparator that it was studied against?
19 DR. BASTINGS: Your business to make the
20 decision is relative to the active comparator based
21 on the studies that you have in front of you, so,
22 yes.

1 DR. ALEXANDER: So essentially, we're being
2 asked about comparative beneficial effect on
3 disability?
4 DR. BASTINGS: Well, in this case, you have
5 an active control. So the question really is: Did
6 the trial show superiority of this drug over Rebif?
7 Forget it's even an active control. The issue
8 would be the same if it was placebo. The question
9 is: Compared to control in this trial, is
10 alemtuzumab showing a significant improvement?
11 DR. DUNN: It's what we usually think of a
12 win. Did this trial win with its design on this
13 outcome measure.
14 DR. FOUNTAIN: As opposed to a win with
15 relapse rate.
16 DR. BASTINGS: No. I think it's the exact
17 same issues for relapse rate.
18 DR. DUNN: It's not as opposed to, unless I
19 misunderstand what you mean by that. The question
20 is designed to assess the outcome of disability in
21 isolation with regard to some of the issues --
22 DR. FOUNTAIN: In isolation separate from

1 its effect on relapse rate or anything like that?
2 DR. DUNN: That's right. It's an
3 independently measured entity, and we're asking the
4 committee to consider this independently.
5 DR. FOUNTAIN: Which is mostly the SAD.
6 DR. DUNN: Yes. I'm sorry. Yes. By way of
7 clarification, we used substantial effect on
8 disability. What we're asking is, did the study
9 win on the outcome measure of sustained
10 accumulation of disability?
11 DR. FOUNTAIN: Dr. Clancy?
12 DR. CLANCY: So those of us who feel that
13 the study is fatally flawed by the unmasking part,
14 then to be consistent, we're going to have to
15 answer no to all of this.
16 DR. BASTINGS: It's a comment I would like
17 to make is that our expectation is that if you
18 answered no to question 1, you would have had to
19 answer no to question 2 because the standard for
20 approval is that you need to have adequate and
21 well-controlled studies. There is no other way to
22 approve a drug.

1 So if you found that the studies were not
2 adequate and well controlled, you cannot conclude
3 that there is efficacy in a regulatory standpoint.
4 DR. DUNN: We value all the input you
5 provided, but the flow of the question, some of you
6 picked up on it, and others were impressed by the
7 biological effect and MRI effects. And we took
8 careful notes on all of that. But our intent was
9 to build up on the vote of number 1, and as
10 Dr. Alexander pointed out, our expectation was that
11 if you voted no to number 1, , that that was
12 inconsistent with a yes vote on number 2.
13 DR. FOUNTAIN: So maybe our discussion about
14 it provides more importance than our votes.
15 DR. DUNN: I'm sorry. What's that?
16 DR. FOUNTAIN: Maybe our discussion about it
17 provides more information than our votes.
18 DR. UNGER: The discussion was actually very
19 helpful. It was very helpful.
20 DR. DUNN: It was. There's no question
21 about it.
22 DR. UNGER: And the discussion's worth a lot

1 more than yes or not.
2 DR. DUNN: Sometimes you can't reduce things
3 to a simple vote, but just by way of how the
4 questions link to each other, we thought that was
5 worth explaining because it caused some confusion
6 on the committee's part. And it may have been that
7 we did not write the question in a way that clearly
8 conveyed the relationship between the two.
9 DR. FOUNTAIN: So now for question 3 --
10 DR. PANZARA: Is there anything we can
11 clarify with this at all?
12 DR. BAGIELLA: So what you're really asking
13 is whether or not the trial was able to show
14 superiority, that's what you're asking in terms of
15 disability.
16 DR. BASTINGS: Again, if you found that the
17 trial is not adequate and well controlled, it's
18 impossible for you to conclude --
19 DR. BAGIELLA: Right.
20 DR. BASTINGS: -- that an effect was
21 demonstrated.
22 DR. FOUNTAIN: Dr. Unger.

1 DR. UNGER: I'd just like to say -- a couple
2 times, we've mentioned trial. There are two
3 trials. And typically from a regulatory
4 standpoint, we want two trials to show efficacy and
5 particularly superiority over another treatment.
6 We want two trials, so it's two trials to think
7 about, not one.
8 DR. ASCENSAO: Can I ask for clarification?
9 We have two trials. One is the naive, and one is
10 the relapse. The request from the sponsor is for
11 approval for relapse disease, though, right, only?
12 DR. DUNN: That's correct. The proposed
13 indication from the sponsor is for treatment for
14 relapsing forms of multiple sclerosis, and the
15 sponsor has discussed that indication with us.
16 DR. ASCENSAO: Which is different than the
17 European trial or the European approval, which was
18 for upfront disease therapy, if I recall correctly.
19 DR. FOUNTAIN: Let's see if I can clarify.
20 I think you're asking if they're treatment-naive
21 patients or treatments that patients have failed
22 previous medication, not about relapsing remitting

1 MS. So has the sponsor asked to include drug naive
2 or --
3 DR. DUNN: No, the proposed indication from
4 the sponsor is, quote, "treatment of relapsing
5 forms of multiple sclerosis." And the specifics of
6 any approved indication obviously would follow
7 later in the review cycle, but that's the proposed
8 indication. And they have come up with that in
9 conjunction with us.
10 DR. PANZARA: Can I clarify anything with
11 this?
12 DR. FOUNTAIN: Dr. Rosenberg?
13 DR. ROSENBERG: So there's nothing in the
14 question about indication to distinguish the 323
15 treatment-naive patients from the 324 treatment-
16 refractory patients. The indication we're talking
17 about is just for relapsing MS, period.
18 DR. BASTINGS: That's correct. The
19 indication is for relapsing forms of MS.
20 DR. DUNN: Right. What this question gets
21 at is whether or not evidence has been provided
22 that would support a description in an approved

1 label of an effect on disability that comes from
2 trials that can provide such evidence. And as
3 Dr. Unger said, assuming that everybody that that
4 these trials were adequate and well controlled,
5 you've heard presentations from the sponsor and
6 from the agency regarding issues surrounding the
7 effect on disability, what our analyses suggest.
8 And you also heard the sponsor and the agency both
9 present to you data that one of the trials did not
10 provide evidence, and that one did. And typically,
11 we require substantiation in two trials for that.
12 DR. PANZARA: Can I provide some
13 clarification, Mr. Chairman? Is it possible?
14 DR. FOUNTAIN: Wait just a minute, and then
15 we'll bring you in.
16 DR. ROSENBERG: Just a follow-up, so I'm an
17 Alzheimer's specialist, so I know a lot about the
18 discussions in Alzheimer's. In Alzheimer's, you
19 can distinguish a symptomatic effect, which you
20 just need a clinical effect. From a disease
21 modifying effect, the rule is you got to actually
22 have two clinical and a biomarker effect.

1 Do you have that same distinction in MS, and
2 are we dealing with that here?
3 DR. BASTINGS: In this case, the answer to
4 your question is based on the disability endpoint
5 that was used in the trial. You don't need to have
6 evidence of disease modification or --
7 DR. ROSENBERG: So the biomarker is extra
8 frosting on the cake. It's just we can interpret
9 it as we wish.
10 DR. BASTINGS: In this case, no, the
11 prespecified endpoint was EDSS, sustained
12 accumulation of disability based on EDSS.
13 DR. FOUNTAIN: So just to clarify because I
14 think -- so many of us, the majority actually, who
15 are a little confused on question 1. So I think
16 maybe the way we might have interpreted it is
17 question 1 would be in the aggregate as everything
18 stands, is it all just as proposed adequate and
19 well controlled.
20 But if you remove everything else and just
21 ask the question, did they have the very narrow
22 evidence that on some level and some way, it's

1 effective for relapsing and remitting MS, that
2 would be how we interpreted question 2. And that's
3 how I anyway could answer question 1 no but
4 question 2 yes. And so that might get at some of
5 these issues.
6 The reason I bring it up now is because it's
7 very hard for me not to just say well, it just
8 seems entirely inappropriate to make it for naive
9 patients since 324 has much more importance for
10 drug-treated patients. And then that leads to
11 modification as opposed -- or disability as opposed
12 to efficacy for preventing relapse.
13 DR. DUNN: I think some of the issues you're
14 speaking to reflect the complexity of the data that
15 emanated from this clinical development program and
16 the fact that we expect and value each committee
17 member's global interpretation of that data in
18 aggregate.
19 DR. FOUNTAIN: So then in regard to
20 question 3, should we assume that if you would have
21 answered question 1 yes, so if you did think there
22 were adequate and well controlled, so those kind of

1 issues of randomization and so forth aside for the
2 data presented, does the data presented have
3 evidence of beneficial effect on disability? Is
4 that the question that you would like us to answer?
5 Otherwise, it would not be possible to
6 register -- 11 people would have to abstain in
7 answering this question otherwise.
8 DR. BASTINGS: Again, I think you have to
9 take into consideration first whether you think the
10 trial is adequate and well controlled, and then the
11 next step is to decide whether you think -- if the
12 answer to the first one was yes, whether an effect
13 of disability has been established in the trial.
14 DR. FOUNTAIN: So you'd like us to apply our
15 gut feeling here just as we did in question 2 in
16 answering question 3.
17 DR. DUNN: We can't and don't want to tell
18 the committee what standard to apply to the data as
19 interpreted. It is worth repeating that we are
20 charged with establishing that substantial evidence
21 as defined in law has been provided, and
22 substantial evidence must come from trials that are

1 adequate and well controlled.
2 DR. FOUNTAIN: So we should answer the
3 question as it stands in the same way we answered
4 the others based on however you feel about the
5 data.
6 (Laughter.)
7 DR. FOUNTAIN: Or have we had enough
8 discussion? We could move on to the next question.
9 Maybe that would be a better way.
10 DR. UNGER: I think you can answer the
11 question based on your judgment. I think part of
12 the problem here may be that in question 1, we
13 asked the committee to dichotomize, is it adequate
14 and well controlled or not. We didn't give you any
15 gray area in the middle to say, well, we have
16 concerns, but.
17 So for question 2, what I think we heard was
18 that despite the fact that it wasn't as well
19 controlled as it could have been or not as adequate
20 as it could have been, et cetera, et cetera. So I
21 don't see a problem in allowing the committee to
22 express similar sentiments with question 3.

1 But I think that's where the disconnect is.
2 We asked for a dichotomous answer on question 1.
3 DR. FOUNTAIN: I think we can understand
4 that.
5 Yes?
6 DR. BLUMENTHAL: Question for the FDA. Is
7 the relevant outcome measure for this question the
8 SAD or sustained accumulation of disability, or are
9 there other outcome measures that you consider
10 relevant to this question, question 3?
11 DR. DUNN: This was a question about the
12 outcome measure of sustained accumulation of
13 disability as presented and discussed during the
14 meeting.
15 DR. FOUNTAIN: All right. I apologize. I
16 should have clarified that before I asked the
17 question, before we met.
18 But given that now we've clarified it, the
19 question 3 is: Has the applicant provided
20 substantial evidence that alemtuzumab has a
21 beneficial effect on disability? And the vote will
22 be yes or no. You can vote now.

1 (Vote taken.)
2 DR. FOUNTAIN: Everyone's voted.
3 LCDR JOHNSON: I will now read the vote into
4 the record. We have two yes, 14 no, two abstain,
5 and zero no vote.
6 DR. FOUNTAIN: Why don't we start again with
7 Dr. Woods? If you'll say your name and your vote,
8 and if you'd like, you can make a comment.
9 DR. WOODS: Mark Woods. I voted no. I
10 think again, the word "substantial" was kind of a
11 hang-up there. I think that the FDA's presentation
12 certainly created some doubt in my mind with
13 respect to that data, and so I voted no on this
14 one.
15 MS. SITCOV: Cynthia Sitcov. I voted yes.
16 I felt that the sponsor made a compelling case on
17 SAD.
18 DR. HOFFMANN: Richard Hoffmann. I voted no
19 because I thought that the results for disability
20 were inconsistent.
21 DR. WALLIN: Mitch Wallin. I voted no.
22 Again, inconsistent results, 323 with a negative

1 disability outcome and 324 with a positive outcome.
2 DR. LU: Ying Lu. I voted no.
3 DR. KRYSCIO: Dick Kryscio. I voted no for
4 similar reasons.
5 DR. BAGIELLA: Emilia Bagiella. I voted no
6 for the same reason I voted no before.
7 DR. KLASSEN: David Klassen. I voted no for
8 the discordant results between the two studies.
9 But again, not to belabor the point, but if it had
10 been an issue of non-inferiority, I would probably
11 vote differently.
12 DR. SMITH: Roy Smith,. I vote no because I
13 think the study was contaminated by bias.
14 DR. ASCENSAO: So this time, I abstained.
15 Joao Ascensao. I'm confused because we're
16 basically looking at results of two different
17 studies with two different patient populations.
18 They're looking at approval for one particular
19 indication. And I think for that particular
20 indication, the study's positive. But then we have
21 another study that's negative.
22 So I think this discussion is perhaps, we're

1 running around the same issues of non-inferiority
2 compared to the benefits. And I'm not sure
3 that -- since we really have different results in
4 two different studies, I feel that I have to
5 abstain in terms of benefits.
6 DR. BLUMENTHAL: David Blumenthal. I voted
7 no because I could not vote yes based on only one
8 positive study.
9 DR. FOUNTAIN: Nathan Fountain. I voted no
10 for the same reasons.
11 DR. ROSENBERG: Paul Rosenberg. I voted no.
12 I want to point out the bugaboo of trials is lack
13 of replicability, and this is a good example.
14 DR. ALEXANDER: Caleb Alexander. I voted no
15 for the reasons stated.
16 DR. CLANCY: Bob Clancy. I'm still stuck in
17 the fact that if the study is flawed at the
18 beginning because of the bias, then everything that
19 flows from this study cannot be trusted.
20 DR. ZIVIN: Justin Zivin. I voted yes, and
21 it depends on what your definition of substantial
22 is. And my belief is that this is as substantial

1 as the other drugs that are currently available but
2 not more. So I believe that they are worthwhile
3 for these patients, and therefore, I decided that
4 it was substantial.
5 DR. YEH: Ann Yeh. I voted no.
6 DR. MIELKE: Michelle Mielke. I voted no,
7 similar to others where I was a little bit confused
8 about where we have the two trials, but this is
9 only for relapsed remitting as opposed for
10 treatment-naive individuals. And so I wasn't quite
11 sure exactly which one to base my judgment off of.
12 But I also just want to clarify too with the
13 second question. So I was under the impression as
14 well that if I voted no for 1, I would vote no for
15 2. And I do -- my main reason for voting no for 2
16 was based on the well-controlled trial gut
17 reaction. I do think that there is some benefit
18 from this, but my problem is still that I don't
19 think that it was completely well controlled.
20 DR. FOUNTAIN: Thank you. And now,
21 question 4: In the context of purported benefits
22 of alemtuzumab, do the safety concerns preclude

1 approval? And I don't know if you want to comment
2 on --
3 DR. BASTINGS: So I would like to make
4 clarification. For this question, we ask that the
5 committee consider the efficacy results as they are
6 on face. So forget concerns about the studies not
7 being adequate and well controlled. Assume, let's
8 say, for argument's sake, that the results are as
9 they appear. And so the question is, in that
10 situation, would the safety profile of the drug
11 preclude approval or not?
12 DR. FOUNTAIN: Are there any -- we talked
13 about this a little bit, but maybe not as
14 extensively as we had before. Are there any
15 questions about this before we vote on it?
16 Dr. Yeh.
17 DR. YEH: I have a question regarding
18 longevity of the effect of alemtuzumab on the
19 immune system. We heard something from the FDA, I
20 believe, from other studies that suggested effects
21 as late as 12 years. Yet the recommendation
22 currently is four years, which seems arbitrary to

1 me. And I'd like to understand a little bit more
2 about that.
3 DR. PANZARA: So the 48-month observation
4 period is driven off of the adverse event profile
5 that we see and not linked to the lymphocyte
6 recovery. But what we do see in our study in terms
7 of lymphocyte recovery, we have over three cycles,
8 two or three cycles, for a period of up to eight
9 years at this point or seven years.
10 Let me show you this slide. Slide 2 up,
11 please. The data that we have based on lymphocyte
12 recovery, the best data we have to date is shown
13 here. And this is from our phase 2 study, patients
14 who entered into our long-term extension study and
15 are continuing to be followed.
16 Each dotted line applies to cycles of
17 treatment and then the recovery of lymphocytes
18 following those cycles of treatment where you have
19 some people who got a third cycle, some people who
20 continued, just got the second cycle and recovered.
21 And what you can see is that the population begins
22 to recover gradually over time.

1 The 48-month monitoring period is linked to
2 the observation that the thyroid events, we've
3 detected those 48 months after last infusion except
4 for those two TSH results, the ITP, all of which
5 occurred within the four-year time frame, and the
6 glomerulonephritis, all of which occurred up to
7 39 months.
8 So they're related, but they're two
9 different things.
10 DR. YEH: Can I follow on that just because
11 we heard from the hematologist that there were
12 cases with the use of Campath arguably at higher
13 doses, but of aplastic anemia, which were thought
14 to be associated much further down the road. So I
15 just for myself to understand what the trajectory
16 is --
17 DR. PANZARA: I think all of those data in
18 other indications, higher doses, cancer patients,
19 transplant patients, it's a very different patient
20 population and a very different dose. So it is
21 difficult to apply what we see here with this lower
22 dosing regimen, less frequent, to that population,

1 which is very different.
2 DR. FOUNTAIN: Dr. Woods, do you have a
3 comment?
4 DR. WOODS: I'd like to build on that
5 because I think we heard during the public session
6 that there have been patients who have been
7 receiving Campath since the early to mid-2000s.
8 And I guess my question is, are there spontaneous
9 reports of adverse events with patients who've
10 received Campath beyond 48 months, or is there any
11 information to be gleaned from maybe those patients
12 who've received it long-term?
13 DR. FOUNTAIN: Does either the sponsor or
14 the FDA or any of the hematologists or anyone else
15 have any information about that?
16 DR. ASCENSAO: We have information as
17 hematologists for Campath, but it's a different
18 disease, different dose. So it's going to be very
19 difficult to extrapolate for this particular
20 situation.
21 DR. PANZARA: What we have is in terms of
22 the long-term effects are what I've shared with you

1 in my presentation in the setting of multiple
2 sclerosis.
3 DR. ASCENSAO: If I can have a question for
4 the FDA. When we're looking at this particular
5 question, are we also talking about including the
6 REMS in the approval process? Is that part of the
7 question or not?
8 DR. DUNN: Explicitly, it's obviously not.
9 I think implicitly, it is. You've heard about the
10 totality of the evidence regarding both
11 effectiveness and safety, and I think the plan for
12 the REMS has been both proposed by the sponsor.
13 And it's been addressed by the agency.
14 So while I think the way we conceived of
15 this question was with a focus on the safety
16 concerns themselves and to what degree did the
17 committee -- how severe does the committee feel the
18 safety concerns are. The existence of a REMS as
19 you envision it based upon what you've heard today,
20 would undoubtedly influence whether or not you
21 think those safety concerns would preclude approval
22 or not.

1 DR. ASCENSAO: The reason I'm asking is two
2 things. One, I didn't see an inclusion, for
3 example, of whether patients with some degree of
4 either immunosuppressed conditions such as HIV or
5 patients with infections that may be worsened by
6 immunosuppression, such as chronic Hep B or Hep C,
7 whether those would be a particular black box that
8 would be addressed upfront.
9 Two, it seemed to me from the presentation
10 from the FDA regarding the REMS that the FDA
11 appears to consider the REMS as it is proposed
12 right now to be inadequate for following these
13 patients. And it's not clear whether that is part
14 of the approval process. So is that a separate
15 discussion that the FDA is going to have with the
16 sponsor?
17 DR. BASTINGS: If you answer yes to this
18 question, it means that you believe that there are
19 conditions under which the drug could be safety
20 marketed. So if you think there is a risk
21 mitigation program that could allow to have an
22 acceptable safety of the product, you could

1 possibly vote yes. But you have to conclude that
2 there are conditions under which the drug could be
3 safely used by patients.
4 DR. PANZARA: So we are proposing box
5 warning for autoimmunity, and also
6 contraindications for HIV and the types of things
7 you're speaking about, as well as black box warning
8 for monitoring, et cetera, in the REMS.
9 DR. FOUNTAIN: Dr. Mentari.
10 DR. MENTARI: Dr. Fountain, I just want to
11 go back to Dr. Yeh's question because I think these
12 are important issues.
13 She mentioned the question of how we came
14 upon the idea that four years of monitoring was
15 adequate. And I think we have to consider that our
16 data beyond four years is only available for a
17 limited number of patients, and that may change in
18 the future.
19 Also, I wanted to comment that that slide
20 that was displayed regarding lymphocyte recovery
21 displayed a median, so that there may be a
22 significant group of outliers who don't display the

1 same level of recovery.
2 DR. FOUNTAIN: Dr. Bagiella.
3 DR. BAGIELLA: I just want to clarify what
4 Dr. Bastings said. So the yes on this number 4
5 means that the risk-benefit ratio is not balanced,
6 that the risk is greater than the benefit, right?
7 DR. BASTINGS: If you answer yes, it means
8 you have concluded that the safety issues are
9 severe enough that they will offer the benefits of
10 the drug as they are presented to you on face.
11 DR. FOUNTAIN: Dr. Wallin?
12 DR. WALLIN: Two quick safety concerns.
13 Long-term cancer risk, there's a very disparate
14 presentation of malignant risk from the sponsor on
15 page 61, the slide of the standardized incident
16 ratios where there was no denominators or time
17 periods presented as opposed to Dr. Mentari's
18 fairly substantial risk with U.S. population data
19 that showed a highly elevated thyroid cancer risk
20 and melanoma risk.
21 At least in the REMS report I heard, there
22 was no specific way to screen for cancers. You can

1 do imaging. You can do skin exams for these
2 things. So that was just a concern.
3 The other thing was how are we going to do
4 risk evaluations for potentially children that may
5 be affected by this drug? We heard that was a
6 potential safety concern.
7 I bring up another approval, mitroxantrone,
8 which has had its issues with cancer in long-term
9 cardiac effects. The FDA has actually asked
10 clinicians to regulate and look at heart scans, and
11 that hasn't been done across the board. And
12 there's been a lot of long-term toxicities that
13 were not seen at the get-go.
14 DR. BASTINGS: Just to clarify, the approval
15 would be only for the other population. So you
16 don't have to worry about issues in pediatrics in
17 making your decision.
18 DR. MENTARI: But, Dr. Wallin, were you
19 referring to my slide about maternal-fetal antibody
20 transfers? Was that the specific --
21 DR. WALLIN: Yes, so I'm looking at
22 autoimmune effects on children of patients that

1 may -- these antibodies may stick around for a long
2 time.
3 DR. MENTARI: Exactly, and there may be a
4 wide variety. I mean, I think with the -- we don't
5 really have a complete picture of what may happen,
6 although it is definitely a concern. So I think it
7 would come down to trying to educate clinicians and
8 have some type of elevated level of suspicion, but
9 I don't know what we could do beyond that
10 considering the variety of things that could
11 happen. Neonatal Graves' disease is something that
12 we could warn about specifically.
13 DR. DUNN: An editorial comment. It sounds
14 like we're hearing a lot of comments and questions
15 that kind of delve into the specifics regarding the
16 safety here, particularly with regard to a REMS,
17 monitoring, special populations.
18 As I'm sure you-all know, six is a
19 discussion question, and a lot of the things that
20 we've listed there as discussion points don't lend
21 themselves neatly to dichotomous or trichotomous
22 answers to vote upon.

1 The spirit of our fourth question is taking
2 the nominal results, the top line results, whatever
3 phrase you like, of the study, we want you to
4 contemplate -- there's relative agreement on the
5 part of the sponsor and the agency that there is a
6 toxicity profile associated with this drug, and
7 we're asking you to consider that in a global
8 sense.
9 This is kind of a global question. We want
10 to get a sense of whether or not the committee
11 feels that the safety profile of the drug globally
12 is sufficient to, again, as it says, to preclude
13 its approval.
14 A lot of these very important details, they
15 may appropriately play a role in what you vote
16 globally, but I wanted to point out that we are
17 eager to hear your discussion about the specifics
18 of those in question 6.
19 DR. FOUNTAIN: Yes?
20 DR. YEH: I have a question regarding
21 the -- Ann Yeh. I'm having trouble not
22 understanding, but knowing if we can actually vote

1 adequately on this question because I think a
2 number of us have a difficult time understanding a
3 risk mitigation strategy that would work. But if
4 there were one in place, we might vote a different
5 way.
6 See what I'm saying? So that's a very hard
7 question for us to answer.
8 DR. FOUNTAIN: So maybe to paraphrase
9 Dr. Dunn from earlier, I think in the back of your
10 mind, you can't help but think about the REMS
11 strategy, whether one's possible. But at face
12 value in the aggregate, is the safety profile so
13 bad it precludes approval even if the study were
14 positive in the way it's purported to be positive
15 in the results.
16 Is that an adequate way to put the question?
17 DR. DUNN: Yes. I think that's a reasonable
18 summary. And I think to follow on to that is that
19 if an individual committee member has concluded
20 internally that no REMS that they can identify
21 could make the safety profile acceptable, then I
22 think that's an individual assessment of the

1 totality of the data that might lead you to reach a
2 certain vote.
3 DR. MENTARI: I think it's important to
4 consider that the proposed REMS does not surpass
5 what was done in clinical trials in any way. And
6 considering that we're -- in a postmarketing
7 setting, we would be expanding the patient
8 population, it would be difficult to expect that
9 the results in the postmarketing population would
10 be better than the clinical trials. I think that's
11 important to consider.
12 I personally could not think of a way to
13 make a REMS that had things in addition to what was
14 done in the clinical trials.
15 DR. FOUNTAIN: Dr. Unger?
16 DR. UNGER: Just if you can get to the point
17 of saying yes, it's plausible to get past the
18 safety issues. Question 6 will give everyone an
19 opportunity to comment on specific risk mitigation
20 strategies for REMS.
21 DR. FOUNTAIN: So it sounds like I think
22 we're in a position to vote on question 4 unless

1 anyone else has anything else. So to repeat
2 question 4 again, the specifics are in the context
3 of purported benefits of alemtuzumab, that is, if
4 you accept that it's a positive study, that it
5 shows what it's purported to show, then do the
6 safety concerns -- do your safety concerns preclude
7 it being approved in any way? I added the any way,
8 but the approval, I guess you get or you don't,
9 approved or not.
10 So now you can vote yes, no or abstain. So
11 please select yes, no or abstain.
12 (Vote taken.)
13 DR. FOUNTAIN: Everyone has voted.
14 LCDR JOHNSON: I will now read the vote into
15 the record. We have zero yes, 17 no, and one
16 abstain.
17 DR. FOUNTAIN: Let's see, starting with
18 Dr. Mielke again. Just state your name, your vote
19 and any comment you'd like to make.
20 DR. MIELKE: Michelle Mielke. I voted no.
21 I think there are potentially serious side effects,
22 but given the disease course and the symptoms that

1 go along with it, I think the patient should decide
2 or should be able to decide what their risks are
3 and determine for themselves.
4 DR. YEH: Ann Yeh. I voted no because I
5 feel that there is still room for discussion about
6 which risk mitigation strategies can be built.
7 DR. ZIVIN: Justin Zivin. I specifically
8 asked this question of both the FDA and the
9 sponsor. The FDA said that they didn't know the
10 therapeutic index, and the sponsor said that they
11 had evidence and showed evidence of greater number
12 of patients to harm than to treat.
13 DR. CLANCY: Robert Clancy. I also voted
14 no. I think the main reason is that there are
15 individual peoples who understand what their own
16 circumstances are and would be willing to say I'm
17 willing to accept these knowing what I'm going
18 through right now, knowing I have a family, knowing
19 where I am with my disability. And that other
20 people would read the same list and say no, that's
21 not for me. But I would not take away that choice
22 for people who had substantial disabilities and

1 were willing to roll the dice and see what they
2 get.
3 DR. ALEXANDER: Caleb Alexander. I voted
4 no. I think this is kind of at the edge of my
5 comfort zone, and I would imagine perhaps of
6 regulators as well. I mean, this would need a
7 pretty impressive ETASU and REMS program if this
8 drug were pursued, and I'm uncomfortable with the
9 absence of any reversibility and more or less
10 you're getting a one-year dose in one shot.
11 But I too could imagine plausibly a
12 well-informed patient and clinician making a
13 reasonable decision that the risks are outweighed
14 by the purported benefits that we've already
15 discussed in other questions. So if those were
16 taken at face value -- I would have enjoyed more
17 discussion about drugs with similarly analogous
18 serious adverse event profiles and how they've been
19 managed, but that's for another conversation.
20 DR. ROSENBERG: Paul Rosenberg. I voted no.
21 I think you have to see risk-benefit, the context,
22 the background is really the disease itself. The

1 risks are substantial, and there are many diseases
2 you wouldn't think about approving this drug for,
3 but this is a really bad disease.
4 DR. FOUNTAIN: Nathan Fountain. I voted no
5 for all the same reasons. And in the struggle that
6 this question really illustrates is that I don't
7 think this is appropriate at all for drug-naive
8 simple, uncomplicated, relapsing, remitting MS
9 patients after their first exacerbation. I just
10 don't think that's appropriate because it's a
11 fundamental principle of drug development and
12 common sense. You identify people who are at the
13 most risk and expose them to the drug first, and
14 after you see it's safe in those people and
15 effective, you have a whole population of people.
16 Then move into a more specific group.
17 So I think for that very specific group of
18 people that are severely affected, that this would
19 be exactly it. Or said differently, do I want to
20 take this drug? No way, but if I have B-cell
21 lymphocytic leukemia, well, sign me up tomorrow.
22 Or if I could get a kidney transplant, 1500 people

1 already have a kidney transplant already got the
2 drug because they're entirely different things,
3 different severe things.
4 So if you have sort of simple uncomplicated
5 MS, if there is such a thing, it doesn't seem
6 appropriate, but for the two dozen people we heard
7 from who have severe MS, it seems very appropriate
8 for them. And they've clearly stated as
9 individuals they're willing to take the risk, and I
10 would personally. And so the great dilemma becomes
11 how to identify what that population is, making
12 sure it's effective for them, which I think what's
13 actually been demonstrated. And then to find a
14 program for regulation, as Dr. Alexander has been
15 referring to, for that specific group so they can
16 get benefit.
17 So I wouldn't want to deny those people, but
18 I wouldn't want to expose everybody else.
19 DR. BLUMENTHAL: David Blumenthal. I also
20 voted no. Though I have to say that I am very
21 impressed with the problems that safe use of this
22 pharmaceutical is going to present, this is a

1 medicine with very long pharmacodynamics that once
2 you give the medicine, you can't take it back. And
3 the next dose is not going to be given for a year.
4 So during those first 12 months, if you have
5 any regrets that you headed down this road, you
6 can't do what is done with many other
7 immunosuppressives and just stop the medicine and
8 let its effect wear off. And there are a lot of
9 impressive, unwanted downstream effects that we've
10 seen in people who are exposed to this medication.
11 We heard testimony earlier today about the
12 current state of Tysabri therapy, where in the view
13 of one particular patient, she's not so sure she
14 would sign up for that today now that 88 people
15 have died of PML. If you go back in time to when
16 only 10 people died of PML, you would not be as
17 aware of the risks.
18 So people will have bad outcomes if they are
19 treated with this medication. Some patients in
20 this study already had bad outcomes, and when you
21 get to the post-approval and marketing phase of
22 surveillance, lots more people are on the drug than

1 the people who have been on it up to now. And I'm
2 sure there will be additional safety concerns that
3 will come out just as it did with Tysabri, for
4 example.
5 But at the end of the day, I did not feel
6 that I could interpose myself between the patient,
7 their neurologist, and access to this medicine.
8 And I think that a properly informed patient and a
9 thoughtful clinician might decide that this is the
10 right choice for certain patients. And I did not
11 see a reason to impose a barrier between them and
12 the medicine.
13 If they can get access to the medicine
14 through the Campath pathway as an off-label use,
15 assuming they can get the insurance company to
16 cover it, I actually would rather prefer that they
17 get the medicine in this environment with a very
18 robust REMS program rather than go off-label and
19 perhaps not have all the protections in place.
20 DR. ASCENSAO: Joao Ascensao. I voted no
21 because I believe that the data as they represented
22 here today suggest that the benefits outweigh the

1 risks, though those may be severe. And as
2 Dr. Blumenthal pointed out and many of the other
3 members of this committee, that once the expanded
4 use of this drug comes on the market, that we will
5 need to be very vigilant about it.
6 DR. SMITH: Roy Smith. I voted no.
7 DR. KLASSEN: David Klassen. I voted no. I
8 think there are substantial risks, and they're
9 somewhat unique. But I think they are potentially
10 approachable.
11 DR. BAGIELLA: Emilia Bagiella. I voted no
12 for reasons that have been already said.
13 DR. KRYSCIO: Dick Kryscio. I voted no for
14 reasons that the clinicians better expressed.
15 DR. LU: Ying Lu. I voted to abstain
16 because I'm not in front line to deal with
17 patients. It's really hard to appreciate. I don't
18 feel comfortable either way.
19 DR. WALLIN: Mitch Wallin. I voted no. As
20 I stated from some of my other comments, I think
21 more surveillance is needed, potentially risk
22 stratification much like is done with natalizumab.

1 But looking for potential lethal consequences, I
2 think is really important and discovering which
3 groups are at highest risk.
4 The drugs that stay around for a long time
5 have negative consequences even on people that sign
6 up. I don't treat anybody with mitoxantrone
7 anymore. That's a drug that stays around a long
8 time. And so this may have its own drum march on
9 its own.
10 So I think it's important to do adequate
11 risk surveillance and follow-up and try to figure
12 out who is at highest risk, especially for lethal
13 consequences.
14 DR. HOFFMANN: Richard Hoffmann. I also
15 voted no because I think a proper REMS will reduce
16 the risk.
17 MS. SITCOV: Cynthia Sitcov. I voted no. I
18 think a proper REMS -- I agree with
19 Dr. Hoffmann -- will hopefully reduce some of the
20 risks.
21 DR. WOODS: Mark Woods, I voted no, and I
22 will reserve my comments for when we get to

1 number 6.
2 DR. FOUNTAIN: Thank you.
3 But before we get to number 6, we can vote
4 on number 5, which is maybe a subpart of the
5 others. But just as we said before, if the
6 available data support approval, so if you were to
7 approve it based on the data available and our
8 other discussions, then should alemtuzumab be
9 indicated as a first-line therapy? If it were
10 approved, would it be indicated as a first-line
11 therapy if you accepted the data as it was
12 presented?
13 So you can vote now, yes, no or abstain.
14 (Vote taken.)
15 DR. FOUNTAIN: Everyone has voted.
16 LCDR JOHNSON: I will now read the vote into
17 the record. We have zero yes, 16 no, two abstain,
18 and zero no voting.
19 DR. FOUNTAIN: Let's start with Dr. Woods
20 again.
21 DR. DUNN: Dr. Fountain, during the
22 discussion, the agency would greatly value not only

1 a discussion on the part of the voters, the
2 committee members, about what constituted the yes
3 or no, but also their thoughts about what their
4 definition of an appropriate line of therapy would
5 be.
6 DR. FOUNTAIN: So if you voted no, which is
7 everyone, what do you think an appropriate
8 indication would be?
9 DR. WOODS: This is Mark Woods. I voted no.
10 And I think, Dr. Fountain, you hit the nail on the
11 head. I don't know that there's enough data at
12 this point that this would be the first thing out
13 of the chute in a newly diagnosed patient.
14 MS. SITCOV: Cynthia Sitcov. I voted no. I
15 do not believe this is something that should be
16 used as a first-line therapy because of the
17 potential serious side effects.
18 DR. HOFFMANN: Richard Hoffmann. And I also
19 voted no because I think the drug does have
20 significant potential for side effects and risks,
21 and there are many other drugs available.
22 DR. WALLIN: Mitch Wallin. I voted no for

1 the same reasons that have been stated by others,
2 but there's a safety profile that needs to be
3 explored further. And as far as the treatment
4 group, for relapsing forms of MS, probably in line
5 with the trials. I would say probably there's no
6 indication for primary progressive MS, but
7 relapsing forms of MS on the earlier side of EDSS
8 scores below 6.
9 DR. LU: Ying Lu. I vote no considering the
10 serious effects, but also, I'm not quite convinced
11 about superiority statements. So I think that's
12 the reason.
13 DR. KRYSCIO: Dick Kryscio. I voted no
14 because I was not convinced that there was a
15 superiority here in this case, and this is a
16 medication that has a lot of serious side effects.
17 DR. BAGIELLA: Emilia Bagiella. I voted no
18 because the evidence in the naive-treated
19 population was very weak, and the side effects
20 outweighed the benefits.
21 DR. KLASSEN: David Klassen. I abstained
22 really, I think, because being not a neurologist, I

1 don't think I have enough clinical expertise to
2 really decide on first-line treatment.
3 However, I have to say I sort of buy into
4 the notion of kind of early, fairly potentially
5 aggressive treatment for diseases like this. I'm a
6 nephrologist, but there are a lot of parallels to
7 treatment of renal diseases. And that concept in
8 nephrology if you wait till the creatinine's risen
9 in the glomerulonephritis, you've missed the boat.
10 And I think potentially, that applies here. But
11 again, I don't think I have the experience to kind
12 of say one way or the other what should be
13 first-line treatment.
14 DR. SMITH: Roy Smith. I abstained pretty
15 much for the same reason that Dr. Klassen has
16 stated. It seems to me like when you think about
17 this rationally, this is probably a drug that could
18 be and perhaps should be applied as early as
19 possible, but there just isn't enough information
20 right now.
21 DR. ASCENSAO: Joao Ascensao, and I voted no
22 primarily based on the results of the 323 trial,

1 which to me did not seem to suggest a beneficial
2 effect upfront, and also concerns that we don't
3 really know the place of this drug. Not being a
4 neurologist, I certainly don't want to comment very
5 much on that, but how it will insert itself in the
6 therapeutic index and range for these individuals.
7 DR. BLUMENTHAL: David Blumenthal. I voted
8 no. I would want to see more post-approval safety
9 data before exposing people who might get adequate
10 control with safer medications.
11 DR. FOUNTAIN: Nathan Fountain. I voted no
12 for all the reasons stated before. And the
13 question then was asked well, what would be the
14 indication if not first line, so I guess you'd make
15 it second line. But what does that mean?
16 So I guess it would at least require, in my
17 mind, one established drug like as in Study 324,
18 and I think you'd imagine that you'd have to have
19 evidence of progression by recurrence episodes and
20 maybe by progression of MRI.
21 So at the very least, it would have to have
22 more episodes on a drug and maybe evidence of

1 progression. That is, if you narrowed it to that
2 very narrow population, then that would be a
3 population that I think everybody would agree is
4 worth the risk. You could make it looser, but
5 those would be the most narrow.
6 DR. DUNN: Can I get you to amplify what
7 you're getting at with failure of an established
8 drug as distinguished from evidence of progression?
9 DR. FOUNTAIN: So you'd have to have -- you
10 couldn't just have another episode; you'd have to
11 have progressed. If you want to make it the most
12 narrow population, people having accumulated
13 disability. So they just didn't have one episode
14 of transient left-sided numbness that went away,
15 and the next year, they have another episode after
16 they've been on a year of Rebif or whatever
17 established drug. And then you wouldn't want
18 to -- well, you could, but in the most narrow
19 sense, you'd say you'd want to have evidence of
20 either a progression on the MRI, additional in my
21 book, anything whether T2 lesions, a new enhancing
22 lesion or a new T1 lesion. Or now a disability you

1 didn't have before, permanent numbness after
2 transient. So that would be the most narrow.
3 I could imagine on the other hand, some
4 would say well, yes, let's give it very early for
5 true disease modification and prevention. That
6 would be the opposite argument.
7 So that would be the most narrow group I
8 could imagine. Because then I could imagine if it
9 were approved for that, then you'd be able to get
10 the data that would, say in another study, show
11 evidence that it was truly disease modifying or
12 curative in some people, that then would launch it
13 on a much larger scale.
14 DR. DUNN: So just for clarity, recurrent
15 relapses alone with a return to baseline, in your
16 mind, would not constitute the progression
17 component of your criterion?
18 DR. FOUNTAIN: I'd have to think about that
19 some more. In the most narrow sense, it wouldn't.
20 If you want to confine it to the most refractory
21 people who I think everybody would stand up and run
22 to get it, then there'd be another group that might

1 run away from it, and there'd be a large group in
2 the middle you'd have to decide among.
3 DR. PANZARA: Mr. Chairman, can I just
4 comment on -- this issue was a real struggle with
5 the European regulators and the same questions.
6 And --
7 DR. FOUNTAIN: Sure. Let us finish the
8 votes and comments, and then we'll let you make a
9 comment.
10 DR. ROSENBERG: Paul Rosenberg, I voted no.
11 Dr. Fountain nailed it. I want to add that the
12 reason I vote no at this time is that the evidence
13 for preventing disability is inconsistent. It's
14 not actually that weak. Frankly, the 324 trial is
15 pretty consistent. And also, the MRI data, which
16 shows a pretty consistent effect in the second
17 year -- or the second dose -- you need the second
18 dose to get that -- suggests to me there could be
19 something there, not strong enough that I could
20 vote yes for it now. But I think if you get more
21 data, you might want to reconsider that because the
22 converse here is if you have evidence for

1 preventing future disability, you may want
2 to -- may change the risk-benefit.
3 DR. DUNN: So again, just to make sure we
4 understand what you're telling us, if the evidence
5 for effectiveness was highly robust with the
6 current safety profile, you could see this as a
7 first-line agent?
8 DR. ROSENBERG: Yes, I think more evidence
9 should be coming in.
10 DR. ALEXANDER: Caleb Alexander. I voted
11 no. I'm not a neurologist, but we did hear that
12 there are many other therapies available. And I'm
13 particularly concerned about some characteristics
14 of the safety profile of the drug. So I think that
15 the labeling ultimately has to be reflective of the
16 populations and the evidentiary standards of the
17 pivotal trials.
18 But with that said, I could not -- I would
19 not suggest that this be labeled as a first-line
20 treatment.
21 DR. CLANCY: Robert Clancy. I also voted no
22 probably for psychological reasons. I know when I

1 treat someone with severe epilepsy, that the family
2 comes back in. They're very invested. They do
3 whatever you want to do. If it's a very, very mild
4 case, they don't take it as seriously. They don't
5 follow the directions as well.
6 So I don't think we'd have a guarantee that
7 the very, very mild case who starts on this would
8 have the same investment in seriousness of
9 follow-up than the person who's scared out of their
10 pants because they see their body decaying.
11 So I think it could be more unsafe in these
12 weak populations where they don't really -- they
13 haven't suffered yet. They're not afraid enough to
14 follow these guidelines.
15 DR. ZIVIN: Justin Zivin. I think this may
16 change over time as to where you would rank it, but
17 for the foreseeable future, I would rank it as a
18 third-line drug. Natalizumab has a black box
19 warning, and it's well deserved. And I think
20 that's the probably the lowest ranked of the
21 available drugs. Others are considerably safer,
22 and so they would go up in first and second line.

1 So that's how I would put them.
2 But with more experience with the drug, it
3 may turn out to be safer than is known from a
4 relatively small sample size from the experiments
5 that have been done so far.
6 DR. YEH: Ann Yeh. I agree with the
7 comments of everyone that was previous to me. The
8 issue of hitting an inflammatory disease early and
9 hitting it hard is one that was brought up by the
10 hematologists and nephrologists, and I think it's
11 an important one. But I don't think we've learned
12 that yet from this set of trials because as we
13 looked at the trials, we have said, well, we're not
14 really sure, but we think probably it's at least as
15 good. Our group seems to have come to the
16 conclusion, or I do, it's as least as good as our
17 existing therapies, but it carries a lot more risk.
18 So my view would be if you're asking the
19 question about first, second, third line, at least
20 second line with failure of a safer drug because
21 there are the safety issues that are attached to
22 it.

1 Then as we learn more about whether it
2 truly -- the earlier thoughts about its high
3 efficacy are borne out, I don't know if that's
4 going to happen with larger trials. Then again, as
5 Dr. Zivin said, there may be a rethinking.
6 DR. MIELKE: Michelle Mielke, I voted no for
7 all the reasons that have been discussed, and I
8 think again, as Dr. Yeh said, based on what we
9 currently know about the drug, I don't think it is
10 good first-line therapy, but second or possibly
11 even third.
12 DR. FOUNTAIN: Now, would you like to make a
13 comment?
14 DR. PANZARA: Yes. The only comment I would
15 make is that when we get into discussions of lines
16 of therapy, this is a very complicated area in
17 terms of that's not sort of where the MS field is
18 going. It's going based on activity regardless of
19 lines of therapy. And when we had this same
20 discussion -- because it's very reflective of what
21 we heard down here, is that when we had these same
22 discussions in Europe about, well, how do you

1 define an appropriate patient, it's very hard for
2 the individual neurologist to say based on whether
3 someone tried a short course of one therapy or
4 another, that means okay, that's enough.
5 It was really more on, what's the clinical
6 picture of that individual based on the disease
7 activity in that individual, independent of whether
8 they might have tried something first or not.
9 Because, as Dr. Rudick and Dr. Fox alluded to
10 earlier, they could have a person come in
11 with -- as we heard from earlier, 25 to 100
12 gadolinium-enhancing lesions. What do you do? Is
13 there an option?
14 So the way it went with the European
15 labeling is that they really focused on you needed
16 to have activity. You needed to have that this was
17 active disease. And it's sort of captures what was
18 discussed here but gets into this lines because
19 lines -- and I'm not commenting about whether
20 that -- that's what we can say. But I just --
21 DR. FOUNTAIN: Thank you.
22 DR. PANZARA: -- that perspective actually.

1 DR. FOUNTAIN: Sure, I think that might play
2 into something else.
3 Dr. Ascensao?
4 DR. ASCENSAO: I want to just comment to
5 that point, which is when it comes to picking
6 orders, though, somebody's chosen because we know
7 what a particular drug is going to be after another
8 drug.
9 So for example, if you bring alemtuzumab
10 upfront, we don't know what the side effects are
11 going to be of people getting interferon. We
12 certainly don't know what the side effects are
13 going to be of getting alemtuzumab.
14 What if all of a sudden your PML rate goes
15 up from 5 percent to 50 percent because patients
16 have Campath first and are now getting a secondary
17 drug? So you got to be -- it's not just patient
18 selection, but we have to be aware of potential
19 safety issues that may be substantially increased
20 by changing the order in which the drugs are
21 currently utilized.
22 DR. PANZARA: Completely understood. And I

1 think that we do have data on about 2 percent of
2 patients who needed something else because we're in
3 a situation where after two courses, most patients
4 didn't need something else.
5 So it's data we're collecting, and I think
6 that when you look at the efficacy and recall that
7 it's -- when we're looking in these active patients
8 that what we're seeing over and above Rebif, which
9 has a disability effect, I think that sort of helps
10 put it in perspective. Also, again, thinking about
11 active patients needing something, and that's where
12 the European Authority felt we should be.
13 DR. FOUNTAIN: Thank you.
14 So now, let's turn to some discussion in
15 question 6, which might amplify that a little bit,
16 but the specific issue, I think, the agency would
17 like addressed is first, are there any strategies
18 that will mitigate the autoimmune serious adverse
19 events and malignancies, given that many of these
20 events occurred after the second course of therapy
21 and with frequent monitoring during the clinical
22 trials?

1 So I guess the nature is what else could you
2 do in the REMS to prevent problems, particularly
3 autoimmune problems that occur late. Either
4 monitor for them or prevent them, I guess, either
5 question.
6 DR. BASTINGS: Just to comment, you've heard
7 from the presentation, the proposal from the
8 sponsor and some comments from the FDA on what the
9 plan is. So the question to you now is really, do
10 you have any additional suggestions on how to
11 mitigate this risk?
12 DR. FOUNTAIN: Dr. Rosenberg?
13 DR. ROSENBERG: Question for the sponsor.
14 It seems like the two most serious and relatively
15 common events we're talking about are ITP and
16 thyroid cancer. I'm not just talking about thyroid
17 abnormalities, but thyroid cancer.
18 Is quarterly monitoring enough for thyroid
19 cancer? Is monthly monitoring enough for ITP? I
20 want to know why you think yes, how do you justify
21 that.
22 DR. PANZARA; Unfortunately, with the hour,

1 we just -- Dr. Braunstein, who is our thyroid
2 expert had to leave. But the quarterly TSH we
3 found to be very sensitive at detecting the
4 changes. And it was actually Dr. Braunstein -- the
5 feedback that we've had after his review of the
6 data is that quarterly because of thyroid disease,
7 you're able to detect signs and symptoms. And
8 because the TSH is so sensitive, 24 percent of
9 patients in Rebif even having an abnormal TSH, it
10 was felt that was the appropriate approach for TSH.
11 Dr. Cuker I could have comment on the
12 monthly CBC for ITP given what we've seen.
13 DR. CUKER: Yes, thank you.
14 So just a reminder that the risk monitoring
15 program that was implemented involved a monthly
16 CBC, education, and then a symptom questionnaire
17 offset by the monthly CBC for two weeks.
18 If I could have slide 1 up, please? So
19 this, if you just direct your attention to the
20 bottom of this slide, you'll see that there were,
21 of course, 28 cases of medically confirmed ITP.
22 The first was the index case. And then the other

1 27 cases all were identified prior to the onset of
2 serious hemorrhagic morbidity or mortality.
3 Twenty-two were identified by the monthly CBC.
4 Five were identified by patient recognition of
5 symptoms, and none were -- the patient
6 questionnaire did not add any value.
7 So while this is a relatively small number
8 of patients, it seemed to be quite successful in
9 the clinical development program. I would also add
10 that as a hematologist, there is an analogy to be
11 drawn here to the patients that we take care of
12 with typical adult ITP.
13 This is a relapsing disease, and we
14 certainly don't -- when we have patients with ITP
15 who are on remission but are at risk of relapse, we
16 don't monitor their CBCs every week. And in fact,
17 we don't even monitor them every month. The key is
18 education. The patients need to be educated so
19 that they can get in touch with us right away if
20 they detect worrisome symptoms.
21 DR. PANZARA: And the other question about
22 thyroid malignancy, also. In terms of that, given

1 the frequent monitoring ongoing of TSH, actually
2 the useful slide that Dr. Braunstein wanted to
3 share -- slide 3 up, please.
4 This is a recent study showing that the
5 increasing incident of thyroid cancer in the United
6 States growing over time, and this is because of
7 the frequency of TSH testing and whenever someone
8 has a thyroid abnormality leading to an ultrasound.
9 So this is sort of the backdrop behind the
10 strong opinion from several of our thyroid experts
11 that this is what's driving the numbers that you've
12 seen.
13 DR. MENTARI: Can I make a comment? But
14 from what I understand, checking for TSH doesn't
15 address the issue of monitoring for thyroid cancer
16 per se.
17 DR. PANZARA: No, but the TSH actually
18 prompts -- the abnormalities are prompting the
19 ascertainment, which is leading to the increased
20 number. The feedback we've had overwhelmingly is
21 that that's what's driving the thyroid cancer, not
22 that there's thyroid cancer that needs monitoring.

1 In fact, one of the cases --
2 DR. MENTARI: So you're suggesting no
3 additional monitoring for thyroid cancer?
4 DR. PANZARA: For thyroid cancer, no. What
5 we're suggesting is that we continue with our
6 thyroid program as part of what we've done in the
7 clinical trials. And you'd mentioned a patient who
8 had a more advanced or a larger lesion, tumor.
9 That patient, as you recall, came in with a
10 submandibular node and an enlarged thyroid.
11 So we had people who came in. These were
12 people at risk of thyroid abnormalities, and we
13 found with the malignancy. So our experts are
14 telling us this is purely ascertainment.
15 DR. FOUNTAIN: Dr. Klassen.
16 DR. KLASSEN: I'd like to point out that
17 these autoimmune events are really very modifiable.
18 I mean, there's a lot of off-label use of Campath
19 in the transplant world, and where I work, we've
20 been using it since 2006 and have given it to about
21 1500 people. And in fact, these autoimmune events
22 really are not seen at all in transplantation.

1 Granted, it's a very different patient
2 population on a lot of different medications and
3 the drug dosing is different, but to my knowledge,
4 I could only find one case report of autoimmune
5 thyroiditis in a transplant recipient.
6 So again, I just think it points out that
7 it's not blocked in stone and that these things are
8 approachable therapeutically and potentially
9 through dosing and alternate --
10 DR. FOUNTAIN: But don't you typically give
11 much larger doses for transplant?
12 DR. KLASSEN: No. Actually, we give a
13 smaller dose. We give 30 milligrams upfront one
14 time. So it's a different environment, and then
15 the patients are chronically immunosuppressed,
16 which certainly probably has activity in
17 suppressing autoimmune things.
18 But it is very -- again, I don't think these
19 things are automatic.
20 DR. FOUNTAIN: Dr. Wallin. Dr. Woods?
21 DR. WOODS: In preparing for this meeting,
22 seeing the 90-plus percent reaction rate with

1 infusion reactions in the infusion center, I
2 thought, wow, schedule a couple of these patients,
3 and you'll have an exciting day in the infusion
4 center.
5 So I think several things with respect to
6 REMS. And Dr. Clancy and Dr. Alexander I think
7 kind of nibbled around the edges of this. But I do
8 think we heard the sponsor say that you need to
9 specify pretreatment in these patients, and how do
10 we ensure that that is done. What are the minimum
11 expectations of a facility that takes these
12 patients, that they should be able to handle?
13 I think there needs to be clear delineation
14 of responsibility of the prescriber, the
15 pharmacist, and the patient. And specifically,
16 with respect to maintaining enrollment status, if a
17 patient doesn't comply with getting lab work done
18 on a timely basis, whose responsibility is it to
19 ensure that that's done in follow-up?
20 One of the issues with some of the REMS
21 programs is you can never find out whether -- or
22 it's very difficult to find out whether the person

1 who sent someone to your infusion center is really
2 an approved prescriber. So a mechanism whereby
3 people receiving those medication orders would be
4 able to tell whether the prescriber was an approved
5 prescriber. And what are the consequences of
6 noncompliance with the REMS? Because again, I
7 think that's sometimes a little bit fuzzy.
8 Finally, I think the duration of monitoring
9 has yet to be determined. We've heard four years,
10 but I think that deserves further exploration. And
11 finally, if we're collecting all this data on these
12 patients, is there some way that we can send that
13 data to a registry so that we can follow that long-
14 term and get more outcome data on patients who
15 receive the drug?
16 DR. FOUNTAIN: Any other comments on that
17 question?
18 I guess the next question really may have
19 already been answered, but it's to modification.
20 The last question is, can the applicant's proposed
21 REMS be modified to ensure adequate
22 monitoring -- which is what you were just talking

1 about, close follow-up, and reporting -- given the
2 proposed dosing regimen and that many of these
3 events occurred after the second course of therapy,
4 which has to do again with the duration of
5 follow-up.
6 Are there any other specific details that
7 anyone on the committee would like to bring up?
8 Dr. Yeh.
9 DR. YEH: Just a very small one, and it has
10 to do with the manning of the infusion centers. If
11 an infusion center was to be proposed, that it be
12 physician manned because of the potential
13 seriousness of the adverse events and not nurse
14 monitored.
15 DR. FOUNTAIN: That's exactly the Part C, is
16 the appropriate infusion setting and duration.
17 That's perfect, leads right in.
18 So any other questions with that?
19 I guess I'd like to ask a question of
20 proportionality, and that is that we've talked
21 about its use as first line or as second line or as
22 third line or something later. And I guess that

1 the comparison population, which has been brought
2 up has been Tysabri, which has a REMS program,
3 which is for patients that have generally failed
4 other things or the circumstance. I know there's
5 kind of an analogous setting.
6 So does anyone know the volume of Tysabri
7 treated patients in the United States and what
8 proportion might be treated outside of an MS
9 center? I don't know if Dr. Rudick would happen to
10 know or have an opinion about that, an idea I guess
11 it would be.
12 DR. RUDICK: Tysabri is not restricted to
13 second-line use, and it is used quite often in
14 patients with active severe disease who are
15 treatment naive. It's always used inside of an
16 accredited infusion center according to the
17 requirements, so it can't be used outside of an
18 accredited center.
19 DR. FOUNTAIN: Do you have a guess about how
20 many patients that would constitute that would be
21 getting Tysabri?
22 DR. RUDICK: In terms of how many patients?

1 DR. FOUNTAIN: Total volume in the United
2 States, or proportion of MS patients, or proportion
3 of your patients, maybe.
4 DR. RUDICK: I think in terms of
5 out-of-the-box therapy with Tysabri, it's probably
6 in the 20 percent or under range. It's people that
7 are worrisome when they first come in. They may
8 look good, but if they've got a lot of -- I
9 mentioned the factors we use, about maybe 15,
10 20 percent.
11 Now, we are stratifying lately for risk for
12 Tysabri, so for patients who are JC virus antibody
13 negative, that threshold gets lowered quite a bit,
14 and it may be used much more often as a first line.
15 But even for JC virus antibody positive, we use it
16 in first-line therapy.
17 DR. FOUNTAIN: So is that proportion of the
18 volume Tysabri might constitute 20 percent of
19 patients treated at an MS center?
20 DR. RUDICK: I'm just giving you a rough,
21 off the cuff --
22 DR. FOUNTAIN: Yes, just in general. It's

1 not -- doesn't seem to be 70 percent or 1 percent.
2 DR. RUDICK: Maybe 10 to 20, I'd say.
3 DR. FOUNTAIN: I was just thinking about the
4 degrees of opportunity, depending on how it was
5 ultimately approved.
6 Dr. Alexander.
7 DR. ALEXANDER: I just wanted to reiterate
8 or express agreement with comments regarding the
9 patient selection for this therapy. I think that
10 to some degree, I haven't heard a lot of
11 suggestions from the group regarding more effective
12 ways to monitor patients.
13 So I think to the greater the degree to
14 which this is kind of a treatment, which has
15 unclear effects and no ability to reverse taking
16 the treatment, I think that the types of patients
17 that are enrolled and the degree to which the
18 agency and clinicians can ensure that they're well
19 informed is maybe more vital than in some other
20 settings where more discretion may be left to the
21 treating clinician.
22 DR. FOUNTAIN: Any other comments or

1 anything else the agency would like us to address?
2 DR. BASTINGS: I think that pretty much
3 covers it.
4 DR. FOUNTAIN: All right.
5 DR. DUNN: We would definitely like to say
6 thank you to the committee. We really appreciate
7 all your input, a lot of hard work and with very
8 complicated issues went in. We thank the sponsor
9 for their detailed presentations and careful, hard
10 work along with the agency on this. And we very
11 much thank the public for their comments. We value
12 them very highly and take them very seriously.
13 Thank you very much.
14 **Adjournment**
15 DR. FOUNTAIN: Thank you for coming, and
16 this concludes the advisory committee meeting.
17 (Whereupon, at 4:56 p.m., the meeting was
18 adjourned.)
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