

ENDOCRINOLOGIC AND METABOLIC DRUGS
ADVISORY COMMITTEE (EMDAC) MEETING

Thursday, March 29, 2012

Location:

FDA White Oak Campus, Building 31

The Great Room (Room 1503)

White Oak Conference Center, Silver Spring, Maryland

Sponsored by:

Food and Drug Administration

Center for Drug Evaluation and Research

Reported by: Rick Sanborn

Capital Reporting Company

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

2 Call to Order and Introduction of Committee

3 DR. THOMAS: Good morning. I would first
4 like to remind everyone present to please silence your
5 cell phones, BlackBerries, and other devices if you
6 have not already done so. I would also like to
7 identify the FDA press contact, Ms. Erica Jefferson.
8 If you're here present, please stand.

9 Good morning. My name is Abraham Thomas.
10 I'm the Chair of the Endocrinologic and Metabolic Drugs
11 Advisory Committee. I will now call the meeting of the
12 Endocrinologic and Metabolic Drugs Advisory Committee
13 to order. We'll go around the room, and please
14 introduce yourself. We will start with the FDA and Dr.
15 Rosebraugh to my left and go around the table.

16 DR. ROSEBRAUGH: Good morning. Curt
17 Rosebraugh, Director, Office of Drug Evaluation II.

18 DR. PARKS: Mary Parks, Director Division of
19 Metabolism and Endocrinology Products.

20 DR. COLMAN: Eric Colman, Deputy from
21 Metabolism and Endocrinology Products.

22 DR. IYASU: Solomon Iyasu, Director, Division

1 of Epidemiology, Office of Surveillance and
2 Epidemiology.

3 DR. KAUL: Good morning. Sanjay Kaul,
4 Cardiologist, Cedars-Sinai Medical Center in Los
5 Angeles.

6 DR. KRAMER: Judith Kramer, Social Professor
7 of Medicine at Duke University in the Division of
8 General Internal Medicine.

9 DR. KONSTAM: Marv Konstam, Cardiology, Tufts
10 Medical Center, Boston.

11 DR. FELNER: Eric Felner, Associate Professor
12 of Pediatrics, Division of Pediatric Endocrinology at
13 Emory University in Atlanta.

14 DR. CAPUZZI: David Capuzzi, Professor of
15 Medicine and Biochemistry, Thomas Jefferson University
16 in Philadelphia.

17 DR. WEIDE: Lamont Weide, Professor of
18 Medicine, Chief, Endocrinology, University of Missouri,
19 Kansas City, School of Medicine and Truman Medical
20 Centers.

21 DR. YANOVSKI: Jack Yanovski, Chief of the
22 Section on Growth and Obesity in the Intramural NIH,

1 and I'm a pediatric endocrinologist.

2 DR. SPRUILL: Consumer Representative Ida
3 Spruill, Medical University of South Carolina,
4 Assistant Nursing Professor and Nurse Educator.

5 DR. BRITTAIN: Erica Brittain. I'm a
6 statistician at the National Institute of Allergy and
7 Infectious Diseases, NIH.

8 DR. THOMAS: Abraham Thomas, Head of
9 Endocrinology at Henry Ford Hospital, Detroit,
10 Michigan.

11 MR. TRAN: Paul Tran, the Designated Federal
12 Officer for the EMDAC Committee.

13 DR. SEELY: Ellen Seely, Director of Clinical
14 Research Endocrinology, Brigham and Women's Hospital.

15 DR. GREGG: Ed Gregg, Chief of Epidemiology
16 and Surveillance Branch and Diabetes Division at CDC in
17 Atlanta.

18 DR. GOLDFINE: Allison Goldfine, Associate
19 Professor, Harvard Medical School, Head of Clinical
20 Research, Joslin Diabetes Center, Boston.

21 DR. WATERS: David Waters, Cardiologist,
22 University of California, San Francisco.

1 DR. BERGMAN: Richard Bergman, Director of
2 the Diabetes and Obesity Research Institute at Cedars-
3 Sinai Medical Center.

4 DR. COOPER: William Cooper, Professor of
5 Pediatrics, Vanderbilt University.

6 DR. PROSCHAN: Michael Proschan. I'm a
7 statistician at the National Institute of Allergy and
8 Infectious Diseases.

9 DR. HIATT: William Hiatt, Division of
10 Cardiology, University of Colorado School of Medicine.

11 DR. JENSEN: Mike Jensen, Endocrinology, Mayo
12 Clinic, Rochester, Minnesota.

13 DR. ALEXANDER: John Alexander, I'm a
14 Cardiologist at Duke University.

15 DR. SAVAGE: Peter Savage, Senior Advisor for
16 Clinical Studies in the Division of Diabetes and
17 Endocrinology at NIDDK.

18 DR. HENDRICKS: Ed Hendricks, Private
19 Practice, Obesity Medicine, Sacramento, California.

20 DR. RASMUSSEN: Mads Rasmussen, Novo Nordisk.
21 I'm the Industry Representative.

22 DR. THOMAS: Ms. McAfee, if you can introduce

1 yourself for the record.

2 MS. MCAFEE: Lynn McAfee, Patient
3 Representative.

4 DR. THOMAS: For topics such as those being
5 discussed at today's meeting, there are often a variety
6 of opinions, some of which are quite strongly held.
7 Our goal is that today's meeting will be a fair and
8 open forum for discussion of these issues and that
9 individuals can express their views without
10 interruption. Thus, as a gentle reminder, individuals
11 will be allowed to speak into the record only if
12 recognized by the Chair. We look forward to a
13 productive meeting.

14 In the spirit of the Federal Advisory
15 Committee Act and the Government and the Sunshine Act,
16 we ask that the Advisory Committee members take care
17 that their conversations about the topic at hand take
18 place in the open forum of the meeting. We are aware
19 that members of the media are anxious to speak with the
20 FDA about these proceedings; however, the FDA will
21 refrain from discussing the details of this meeting
22 with the media until its conclusion.

1 Also, the Committee is reminded to please
2 refrain from discussing the meeting topic during breaks
3 or lunch.

4 Thank you.

5 Conflict of Interest Statement

6 MR. TRAN: Good morning. The Food and Drug
7 Administration is convening today's meeting of the
8 Endocrinologic and Metabolic Drug Advisory Committee
9 under the authority of the Federal Advisory Committee
10 Act of 1972. With the exception of the industry
11 representative, all members and temporary voting
12 members of the Committee are special government
13 employees or regular federal employees from other
14 agencies and are subject to federal conflict of
15 interest laws and regulations.

16 The following information on the status of
17 this Committee's compliance with the federal ethics and
18 conflict of interest laws covered by, but not limited
19 to, those found at 18 U.S.C. Section 208 and Section
20 712 of the federal Food, Drug, and Cosmetic Act is
21 being provided to participants in today's meeting and
22 to the public.

1 FDA has determined that members and temporary
2 voting members of this Committee are in compliance with
3 the federal ethics and conflict of interest laws.
4 Under 18 U.S.C. Section 208, Congress has authorized
5 FDA to grant waivers to special government employees
6 and regular federal employees who have potential
7 financial conflicts when it is determined that the
8 Agency's need for a particular individual's services
9 outweighs his or her potential financial conflict of
10 interest.

11 Under Section 712 of the Federal Food, Drug,
12 and Cosmetic Act, Congress has authorized FDA to grant
13 waivers to special government employees and regular
14 federal employees with potential financial conflict
15 when necessary to afford the Committee essential
16 expertise.

17 Related to the discussions of the meeting,
18 members and temporary voting members of this Committee
19 have been screened for potential financial conflicts of
20 interest of their own as well as those imputed to them,
21 including those of their spouses or minor children, and
22 for the purposes of 18 U.S.C. Section, 208, their

1 employers. These interests may include investments,
2 consulting, expert witness testimony,
3 contracts/grants/CRADAs, teaching/speaking/writing,
4 patent and royalties, and primary employment.

5 The agenda involves the role of
6 cardiovascular assessment in the pre-approval and post-
7 approval settings for drug and biologics developed for
8 the treatment of obesity. This is a particular matters
9 meeting in which general issues will be discussed.
10 Based on the agenda for the meeting and all financial
11 interests reported by the Committee members and
12 temporary voting members, no conflict of interest
13 waivers have been issued in connection with this
14 meeting.

15 To ensure transparency, we encourage all
16 standing committee members and temporary voting members
17 to disclose any public statement that they may have
18 made concerning the topic at issue. With respect to he
19 FDA invited industry representative, we would like to
20 disclose that Dr. Mads Rasmussen is participating in
21 this meeting as a non-voting industry representative
22 acting on behalf of regulated industry. Dr.

1 Rasmussen's role at this meeting is to represent
2 industry in general and not any particular company.
3 Dr. Rasmussen is employed by Novo Nordisk.

4 With the regard to the FDA guest speakers,
5 the Agency has determined that the information to be
6 provided by these speakers is essential. The following
7 interests are being made public to allow the audience
8 to objectively evaluate any presentation that are
9 common made by these speakers.

10 Dr. Robert Eckel has acknowledged that he is
11 a scientific advisor for Eli Lilly, Genentech, and
12 EMINENT, and receives less than \$3,000 per year from
13 each firm. As a guest speaker, Dr. Eckel is not
14 participating in the Committee deliberation, nor will
15 he vote.

16 We would like to remind members and temporary
17 voting members that if the discussion about any other
18 product or firm not already on the agenda for which the
19 FDA participant has a personal or imputed financial
20 interest, the participant needs to exclude themselves
21 from such involvement and the exclusion will be noted
22 for the record.

1 FDA encourages other participants to advise
2 the Committee of any financial relationship that they
3 may have with the firm at issue.

4 Thank you.

5 FDA Remarks

6 DR. THOMAS: We will now proceed with the FDA
7 opening remarks from Dr. Eric Colman. I would like to
8 remind public observers at this meeting that while this
9 meeting is open for public observation, public
10 attendees may not participate except at the specific
11 request of the panel.

12 Dr. Colman?

13 DR. COLMAN: Yeah, Paul, do you have the
14 discussion points?

15 (No audible response.)

16 DR. COLMAN: So eventually we will get to two
17 discussion points. The second point has multiple
18 different subcomponents, and then there is a voting
19 question. So let me run through these.

20 And as we heard yesterday, the current draft
21 Obesity Guidance currently recommends that at least
22 3,000 patients be randomized to investigational drug

1 versus at least 1,500 subjects be randomized to placebo
2 in one-year trials.

3 Now, to date, most of the patients enrolled
4 in the phase 2 and phase 3 clinical trials for obesity
5 drugs under development have very low short-term risk
6 for major adverse cardiovascular events, somewhere in
7 the order of less than .5 percent. By and large, these
8 trials are made up of women in their forties, early
9 fifties; for the most part, they don't have a history
10 of cardiovascular disease; so in some ways they're much
11 healthier than subjects in other trials, cardiovascular
12 disease, for example.

13 So based on that information, we would like
14 you to discuss the potential strengths and weaknesses
15 of actually enriching the phase 2 and 3 clinical trials
16 with subjects who are at higher risk for short-term CV
17 events; for example, including subjects with a history
18 of MI or a history of stroke or individuals with
19 multiple risk factors for cardiovascular disease, and
20 based on that aggregate, perform a meta-analysis of
21 prospectively adjudicated major adverse cardiac events.

22 This, at a minimum, might provide a signal

1 for adverse cardiac effects of a drug, but obviously we
2 will never get to that point with this sample size
3 unless the patients are enriched up to a higher annual
4 MACE rate, perhaps on the order of 1-1/2, maybe even 2.
5 So that's the first discussion point.

6 The second discussion point asks you to
7 assume that if we have a drug that has a signal of
8 concern -- and I'll just, for example, say a drug that
9 raised blood pressure by 3 to 5 millimeters of mercury
10 relative to placebo, and it did that regardless of
11 weight loss, we will be working under the assumption
12 that those drugs would be required to demonstrate lack
13 of CV harm. So what we're asking you here in this
14 scenario is to comment on some of the design features
15 of such a trial.

16 So under 2(a), it has to do with ruling out a
17 certain degree of excess CV risk with a pre-approval
18 analysis of a fraction of the planned number of total
19 events, followed by ruling out a smaller excess CV risk
20 with the post-approval final analysis. So this is
21 similar to what is done with the diabetes drugs.

22 I would add that this assumes that the pre-

1 approval analysis will be based largely on data
2 obtained during the first year of patient exposure,
3 which in most cases would be a period of fewer patient
4 dropouts and maximum weight loss. I think this raises
5 the issue of the constancy of the hazard. It may not
6 be a constant hazard over time, depending on what the
7 body weight changes are over the course of the complete
8 trial.

9 The second component to 2 wants the Committee
10 to discuss setting a non-inferiority margin for excess
11 CV risk on the basis of risk difference versus relative
12 risk.

13 The third component asks you to discuss the
14 use of strict MACE versus MACE-Plus, and MACE-Plus is
15 oftentimes strict MACE plus hospitalized unstable
16 angina or emergent coronary revascularization. And I
17 showed you some data yesterday that you can see
18 different risk estimates depending on if you use strict
19 MACE or MACE- Plus revascularizations. So I think it
20 can have an impact on the estimate of the treatment.

21 The fourth component has to do with the
22 population that should be analyzed. The primary

1 analysis population that incorporates on-treatment and
2 off- treatment information -- the total time analysis -
3 - versus a population that incorporates only on-drug
4 information. So this is an intention to treat versus
5 strictly an on-drug analysis. So we would like to hear
6 your thoughts on those two approaches.

7 Finally, under this second discussion point -
8 - and this was also touched upon yesterday -- we want
9 to hear your thoughts in terms of the proposal to
10 discontinue from study drug patients who do not achieve
11 a certain degree of weight loss within, say, the first
12 3 to 6 months of a trial. Those who withdrew from
13 study drug would remain in the trial and would be
14 continued to be followed for vital status and endpoint
15 accrual.

16 But this is an issue that gets to what may be
17 the real-world situation, where if you put someone on a
18 weight loss drug, you give them a good trial on the
19 drug, but they don't lose weight, most people would
20 argue, "Well, I'm not going to keep this person on the
21 drug, it's not working." In the context of a trial,
22 that has implications obviously, so we would like you

1 to think about that and discuss that.

2 And then the voting question; it reads, "Do
3 you believe that obesity drugs without" -- and this is
4 underlined -- "without a theoretic risk or signal for
5 CV harm should be required to rule out a certain degree
6 of excess CV risk with a cardiovascular outcomes trial
7 or an appropriately sized meta-analysis of phase 2 and
8 phase 3 MACE data?"

9 So the options here are to vote no, and if
10 you vote no, please explain why you voted no. If you
11 vote yes, we would like to know if you think it should
12 be done through a dedicated cardiovascular outcomes
13 trial or through a meta-analysis of phase 2 and 3 data,
14 or perhaps a combination of the two. And we would also
15 like to know when you think these data should be
16 obtained. Should they all be obtained pre-approval?
17 Should some degree of risk be eliminated pre-approval
18 and then a more stringent level of risk ruled out post-
19 approval? This is the two- stage approach, again
20 similar to what the diabetes drugs have done. Or
21 perhaps if you're in favor of this concept, you think
22 it would be reasonable to approve the drug and have

1 this cardiovascular safety conducted solely as a post-
2 approval requirement.

3 So those are all the items that we would like
4 you to address, and hopefully you've had time to think
5 about these after yesterday's meeting.

6 And that's all I have to say. Do you want to
7 go to the Open Public Hearing?

8 Open Public Hearing

9 DR. THOMAS: Thank you, Dr. Colman. Both the
10 Food and Drug Administration and the public believe in
11 a transparent process for information gathering and
12 decision making. To ensure such transparency at the
13 Open Public Hearing session of the Advisory Committee
14 meeting, the FDA believes that it is important to
15 understand the context of an individual's presentation.
16 For this reason, the FDA encourages you, the Open
17 Public Hearing speaker, at the beginning of your
18 written or oral statement, to advise the Committee of
19 any financial relationship that you may have with the
20 sponsor, its product, and if known, its direct
21 competitors. For example, this financial information
22 may include the sponsor's payment of your travel,

1 lodging, or other expenses in connection with your
2 attendance at the meeting. Likewise, FDA encourages
3 you at the beginning of your statement to advise the
4 Committee if you do not have any such financial
5 relationships. If you choose not to address this issue
6 of financial relationships at the beginning of your
7 statement, it will not preclude you from speaking.

8 The FDA and this Committee place great
9 importance in the open public hearing process. The
10 insights and comments provided can help the Agency and
11 this Committee in their consideration of the issues
12 before them. That said, in many instances and for many
13 topics, there will be a variety of opinions. One of
14 our goals today is for this Open Public Hearing to
15 conducted in a fair and open way where every
16 participant is listened to carefully and treated with
17 dignity, courtesy, and respect. Therefore, please
18 speak only when recognized by the Chair. Thank you for
19 your cooperation.

20 We will now have our first Open Public
21 Hearing speaker.

22 (No audible response.)

1 DR. THOMAS: Okay, I don't think they're here
2 right now. Can we move on to Open Public Hearing
3 speaker number two?

4 (No audible response.)

5 DR. THOMAS: Okay. We'll move to Open Public
6 Hearing speaker number three?

7 DR. O'NEIL: I'm worried about what they know
8 that I don't know.

9 (Laughter.)

10 DR. O'NEIL: Good morning. My name is
11 Patrick O'Neil. I'm here to represent the Obesity
12 Society, and currently I'm that group's president.
13 We're the primary professional and scientific
14 association devoted solely to obesity. By day, I'm a
15 clinical psychologist and professor at the Medical
16 University of South Carolina. And personally I should
17 disclose that I've been an investigator on a large
18 number of clinical trials of obesity medications for a
19 variety of sponsors and have served on advisory boards
20 for a few of those pharmaceutical companies.

21 The Obesity Society wishes to thank the
22 Committee and the FDA for your efforts here to create a

1 rational and scientifically valid approach to
2 evaluating cardiovascular risk of potential obesity
3 medications. Obviously, cardiovascular risk is
4 tremendously important, and as we all know, obesity
5 itself is a proven cardiovascular risk factor.

6 But we believe that when considering
7 treatments for obesity, we should also consider the
8 pervasive consequences of obesity beyond the
9 cardiovascular system. As you know, obesity damages the
10 body literally from head to toe, from idiopathic
11 intracranial hypertension to gout, from sleep apnea to
12 lower joint osteoarthritis, fatty liver, urinary
13 incontinence, sexual dysfunction, increased risk of
14 numerous cancers, and of course, we know the mortality.
15 Obesity causes 100,000 excess deaths a year. That is a
16 number that's really so big it's hard to appreciate,
17 but what it represents is that 100,000 times a year
18 somebody is losing a mother or a father, a husband or a
19 wife, a sister, a brother, employee, a friend, or even
20 a child, 100,000 times a year.

21 Beyond shortening lifespan, though, obesity
22 also damages its quality. Our patients speak of their

1 hopes of one day doing things that we all take for
2 granted, whether it's a short hike with their children,
3 playing in the park with their grandkids, joining
4 friends at a restaurant without enduring stares, having
5 enough energy after work to go out with friends, and
6 shaking the pervasive depression and self-esteem
7 problems and hopelessness that many people with obesity
8 suffer.

9 So we really think that a second type of risk
10 needs to be considered as well, the risks of doing
11 nothing, which can lead to continuing increased
12 needless deaths and medical problems throughout the
13 body as well as lives that needlessly fall short of
14 what they promised.

15 We think, then, that assessments and
16 benefits, although that we understand is not your
17 mission at this meeting, but in context, we think that
18 assessments and benefits should include data on the
19 myriad non- cardiovascular medical problems that may
20 improve with weight loss as well as on the equally
21 numerous ways that functioning, feelings, and living
22 improve.

1 Here's an example from our clinic in
2 Charleston. We, about a year or two ago, had a
3 gentleman join one of our programs, he's in his
4 fifties, he came in weighing 455 pounds, and we
5 discovered on screening that he had terrible diabetes
6 with a fasting blood sugar of 391. He was able to lose
7 a little more than 100 pounds, down to 345 pounds. He
8 had started on metformin after his diagnosis of
9 diabetes but was able to come off of that medication,
10 and without medication, was stable, had a stable blood
11 sugar at 83. His cholesterol showed the kind of
12 improvement we would expect as well, falling from 207
13 to 131.

14 But his proudest achievement with his weight
15 loss was that for the first time in years he could fit
16 in an airplane seat, and so he took advantage of that
17 to fly across the country to see his mother, and 2
18 weeks later she died. So I don't know how you would
19 come up with a metric for evaluating one last visit
20 with your mother, but I do know that this is the kind
21 of benefit that many people with obesity look for when
22 they're seeking help for their obesity.

1 So we, at the Obesity Society, do thank you
2 for your efforts to provide obese people with access to
3 more treatment options so that they can achieve better
4 health and better lives.

5 Thank you very much.

6 DR. THOMAS: Thank you, Dr. O'Neil.

7 We'll now go on to Open Public Hearing
8 speaker number four.

9 (No audible response.)

10 DR. THOMAS: Okay. We'll go on to Open
11 Public Hearing speaker number five. Dr. George
12 Grunberger, representing the American Association of
13 Clinical Endocrinologists.

14 DR. GRUNBERGER: Thank you very much, Dr.
15 Thomas. I'm George Grunberger, and I represent the
16 American Association of Clinical Endocrinologists. I
17 don't have any personal financial conflicts. But if
18 you don't know, AACE is the world's largest
19 organization of clinical endocrinologists and its
20 mission statement reads it's a professional community
21 of physicians who specialize in endocrinology,
22 diabetes, and metabolism committed to enhancing the

1 ability of its members to provide the highest level of
2 patient care.

3 We already heard that obesity and type 2
4 diabetes have reached epidemic levels and are the most
5 prevalent diseases of our time, and they now affect
6 over two-thirds of U.S. adults. And we noted a
7 proportion of children, adolescents, that is affected
8 continues to increase, and for the first time children
9 have a lower life expectancy than their parents. And
10 we already heard yesterday about the medical problems
11 which come from excess weight, including type 2
12 diabetes, high blood pressure, cholesterol excess, and
13 cardiovascular disease, and they're affecting younger
14 age groups, which lead to more increases in our health
15 care costs.

16 So we know there is an urgent need to develop
17 novel ways to treat the obesity epidemic, including
18 medications. And the hope, of course, is that
19 prevention and treatment of obesity early on could
20 decrease or prevent the catastrophic cost of care and
21 complications of the serious medical consequences of
22 obesity.

1 Now, the advocates of the long-term
2 cardiovascular trials apparently believe that obesity
3 drugs are basically diabetes drugs, and the same rules
4 that apply to diabetes drugs in terms of cardiovascular
5 risk should apply to obesity drugs, but I think that
6 this view ignores the tremendous clinical need for
7 these drugs -- so that's the benefit side of the
8 equation, which is a known entity -- for risks that are
9 theoretical and non- data driven.

10 And we already heard also the contrast
11 between the usual cardiovascular study design in high-
12 risk populations which calls for enriching those
13 populations with older, sicker populations to have
14 sufficient number of events versus a clinical
15 population that is usually seen in obesity practices,
16 which is healthier.

17 Now, we know, to complicate issues, that if
18 you actually lose weight, you can ameliorate the CVD
19 risk factors and can reduce events. From the SCOUT
20 trial, we know that short-term and long-term moderate
21 weight loss can be associated with reduction in
22 subsequent cardiovascular mortality for the following 4

1 to 5 years even in those who had preexisting
2 cardiovascular disease.

3 So the cardiovascular trials will be
4 problematic because we will have to treat -- I don't
5 think we can ignore the associated dyslipidemia,
6 hypertension, glucose intolerance, and diabetes while
7 investigating these drugs, and these co-variables will
8 be make these studies hugely expensive and probably not
9 very feasible.

10 Now, obesity per se, if you strip all the
11 associated cardiovascular disease risks, just the
12 obesity itself, as we heard, there are not substantial
13 risk factors for coronary heart disease, so if you're
14 starting with low-risk population, any cardiovascular
15 trial will necessarily involve a large number of
16 subjects for a large number of years, and even then
17 will likely be inconclusive because of these low-event
18 rates and the question of undercurrent therapies with
19 statins, antihypertensives, or antidiabetic drugs in
20 those subjects who require those therapies.

21 We heard about the retention rates in these
22 kinds of studies, and in short, we believe that such

1 studies will be technically difficult to do.

2 And the concern, of course, is, as we heard
3 from the previous speaker, the unintended consequence
4 of this requirement might be delays in individual drug
5 availability for years while these cardiovascular
6 trials are underway and potentially might hinder the
7 new drug development.

8 Thank you very much for your consideration.

9 DR. THOMAS: Thank you for your comments.

10 We'll now go to Open Public Hearing speaker
11 number six, who is Morgan Downey, who is the Obesity
12 Policy Consulting Publishing Editor of the Downey
13 Obesity Report.

14 MR. DOWNEY: Thank you, Mr. Chairman. It's
15 an honor to be here today. I have no financial
16 interest at all in this topic, and no one paid for my
17 participation.

18 Following the previous comments, I would like
19 to describe the two models that I think are before the
20 Committee in terms of addressing this important
21 question. The first is the Avandia-rosiglitazone model.
22 And as you recall, I'm sure, maybe painfully, in July

1 2010, the Committee reviewed the status of
2 cardiovascular diseases associated with rosiglitazone
3 and involved analyses, I think, of something like 40
4 different studies over a long period of time. There
5 were two camps of analyses, including within the FDA,
6 and the conclusion was that there were known risk
7 factors associated with the drug, but it was kept on
8 the market anyway, albeit with some restrictions on its
9 marketing or distribution with a statement of
10 confidence that doctors and patients could figure out
11 the risks that hundreds of biostatisticians seemed to
12 have trouble with. My conclusion was long-term studies
13 produce long-term noise, and I haven't been dissuaded
14 from that recently.

15 The other model is the sibutramine-Meridia
16 model, where, in contrast to rosiglitazone, the
17 population under study was not the intended population
18 and was dramatically different than the clinical
19 population. The FDA materials have indicated that only
20 a half of a percent of the recent NDAs have shown a
21 MACE event.

22 In contract, in the SCOUT trial, if I recall

1 correctly, yesterday was commented on, that 3 to 4
2 percent of the controls in the SCOUT trial had had a
3 MACE. So this is a dramatically different population.
4 This is not a matter of the 99 percent versus the 1
5 percent; this is a matter of the half percent against
6 the 99.5 percent.

7 At the end of the day yesterday there was a
8 brief discussion, I was tired and I'm not sure I
9 understood it all, but I believe Dr. Rasmussen asked
10 Dr. Colman about how the benefits were weighed in the
11 SCOUT trial, and I'm not exactly sure of the response,
12 but I do remember the discussions and the statements
13 from the FDA, and clearly the Committee and the FDA
14 took the benefits in the SCOUT study against the risks
15 in the SCOUT study. So you have a total population that
16 is totally different from the clinical population
17 reality, and you're weighing risks and benefits both in
18 that, and it's hard to see how you could go back to a
19 different study and a different population and pick out
20 benefits against risks.

21 So this has to be resolved, and the fact, as
22 mentioned already, cardiovascular events in this

1 population that typically take these drugs should be
2 considered a rare event, and any research done in the
3 unintended populations are going to lose credibility
4 for not being clinically relevant.

5 I also have to say I found some questions
6 yesterday about this process of changing the protocol
7 in mid-study. This was part of the SCOUT experience
8 where they didn't have enough events in the middle of
9 the study, and they had to expand the population. We
10 heard yesterday this was also true in Look AHEAD. I'll
11 tell you, as a lawyer, it's troubling, and I think it
12 can reveal a lack of confidence in the validity of some
13 of these findings.

14 Thank you.

15 DR. THOMAS: Thank you for your comments.

16 Dr. Temple, if you could introduce yourself?

17 DR. TEMPLE: Hi. Good morning. Sorry I was
18 late. Bob Temple, Deputy Center Director for Clinical
19 Science.

20 DR. THOMAS: Thank you.

21 We'll now move on to Open Public Hearing
22 speaker number seven, Dr. Wolfe, from the Health

1 Research Group at Public Citizen.

2 DR. WOLFE: Good morning. Ten years ago this
3 month we petitioned the FDA to ban sibutramine based on
4 randomized trial data before approval showing increased
5 hypertension, tachycardia, and arrhythmias. The
6 predecessor of your Advisory Committee voted narrowly
7 that it shouldn't come on the market because of the
8 risk, and the medical officer, Dr. Colman, said the
9 same thing.

10 We included this in our petition just to note
11 that back in 1968, another FDA medical officer had
12 refused to approve a drug and was transferred to
13 another part of the FDA. His statement, which is
14 relevant to the discussion yesterday and today, is that
15 obesity is a chronic disease, and there is no evidence
16 that these drugs affect the course of the disease over
17 the long term.

18 This has been gone over by several speakers,
19 but just to point out that these are the last four
20 drugs for treating obesity. They were taken off the
21 market. It was all because of cardiovascular problems
22 with the exception of sibutramine. There was no

1 randomized trial with phenylpropanolamine. There was a
2 case control study, lots of cases with ephedra. We are
3 the group that petitioned to ban ephedra in 2001, and
4 both in 2002 and 2009 to ban sibutramine. So the
5 history of these drugs, not surprisingly, involved some
6 cardiovascular problems.

7 We strongly support the current statement in
8 the briefing materials. Any drug developed for obesity
9 should not only be effective but should demonstrate
10 safety for long-term or chronic use in a large diverse
11 population.

12 These are persistent curves. They happen to
13 be from a single player database in Canada, British
14 Columbia. Almost identical data come from Israel. The
15 point is that by 6 months, only 30 percent or 25
16 percent of the people that have started using one of
17 these drugs are still using it. By a year, it's down
18 to about 10 percent, and by 2 years, it's down to 2
19 percent, and these curves, one is for sibutramine and
20 the other is for orlistat.

21 What we learned from this -- and you'll see
22 in the next slide -- is that for most of the people,

1 because they don't use the drug for very long, there
2 can't be any benefit at all, once they stop using it,
3 they may have lost a few pounds, but when you're
4 losing, most of the people by a year, let alone 2 years
5 where they only have 2 percent, but even during the
6 relatively short time that most people are on the drug,
7 significant harm is already occurring, and as I said,
8 the next slide will show some of this. Thus, for most
9 of these people, there are risks without any chance of
10 a benefit. Long-term use on a large population is
11 really an artifact of trial design, as it should be, as
12 in SCOUT, but is necessary to establish the risk for
13 longer term use, chronic disease.

14 These are data from SCOUT, and there are a
15 lot of numbers on here, but if you just look, that by 6
16 months you already have a statistically significant
17 increased hazard ratio for non-fatal stroke, and it
18 continues at 12 months. So during a time when people
19 have stopped using it, there is still 25 percent at 6
20 months, there are already clear harms occurring, in
21 this case, non-fatal stroke.

22 These are data just showing outpatient

1 utilization of sibutramine from 1.3 million
2 prescriptions in the first year after it was approved
3 down to 250,000.

4 And the next slide, just looking at one year,
5 in that one year, there were still -- 2009, the last
6 year it was on the market, full year -- 94,000 patients
7 were using it, and they were largely women, 83 percent.

8 So using these two pieces of data, which are
9 from FDA briefing materials from last year, we estimate
10 that there are about 3.6 million patients who used
11 sibutramine at one time or another.

12 This is Dr. Colman's paper, 5 years ago, 7
13 years ago, saying we're in the process of doing a
14 guidance for clinical evaluation. It is here now, it's
15 subject to this meeting, and these are the conclusions.
16 There is little doubt that many thousands of people of
17 the 3.6 million U.S. patients using sibutramine suffer
18 heart attacks, strokes, or other life-threatening
19 adverse events. Had SCOUT been completed before
20 approval instead of 12 years after, most of this damage
21 would have been prevented. And given that no long-term
22 randomized placebo-controlled study of any obesity drug

1 has shown cardiovascular benefit, the benefits of doing
2 future adequately powered trials before approval
3 greatly outweigh the cardiovascular risks of waiting
4 until there have been large-scale, post-approval
5 exposure.

6 I thank you. And as other people have
7 alluded to, there are other considerations, such as
8 increased suicidality, which is what kept rimonabant
9 off the market, and other problems.

10 Thank you.

11 DR. THOMAS: Thank you for your comments.
12 We'll now move to Open Public Hearing speaker number
13 eight, Kelly Close, Editor-in-Chief of diaTribe.

14 MS. CLOSE: Good morning, Chairman Thomas,
15 Committee Members, and FDA Officials. My name is Kelly
16 Close, and I want to thank you for the chance to talk
17 today.

18 So why I'm here. I've been the editor of
19 three diabetes and obesity publications for the past
20 decade. I'm an obesity advocate. I've had diabetes
21 myself for over 25 years. By way of disclose, a number
22 of sponsors of obesity drugs have subscribed to our

1 newsletters over time. I attend all EMDAC meetings at
2 my own expense.

3 So as I think about everything presented
4 yesterday from a patient perspective, it occurs to me
5 that some of the questions are especially challenging
6 with regard to consistency across obesity, diabetes,
7 and other therapeutic areas. First, you're being asked
8 to figure out to what degree should anti-obesity drugs
9 show that they're free of cardiovascular disease risk.
10 The simplest answer is that since obesity and diabetes
11 are associated with so many of the same risks and
12 affect so many of the same people, therapies for both
13 conditions should play by the same rules. But should
14 they?

15 In the case of diabetes drugs, the goal is to
16 try to lower blood glucose so as to prevent the
17 complications related to the disease. It is therefore
18 important that any glucose-lowering drug not be
19 associated with increased risk of a complication,
20 especially cardiovascular disease, the most serious
21 diabetes-related complication today.

22 The case is not so clear-cut with obesity,

1 which is a major risk factor for dozens of grave
2 disorders, as you know. To what extent should we
3 require an obesity drug to not show signal for each of
4 these comorbidities? Why should we focus on
5 cardiovascular disease when obesity is also associated
6 with an increased risk of cancer, which has a similar
7 morbidity and mortality, each killing over half a
8 million Americans last year? Why not run an outcomes
9 study to rule out malignancy signals for every new
10 obesity drug?

11 Well, such trials would be impossible. The
12 incidence rates would be too low, the statistics too
13 complicated, the costs too daunting. No sponsor could
14 overcome such a hurdle and no investors would support a
15 sponsor that wanted to try.

16 None of us likes uncertainty, especially
17 about matters about life, death, and chronic disease,
18 yet we have accepted that we can know only so much
19 about a new drug's cancer risk before it goes up for
20 FDA approval. So why do we think differently about
21 cardiovascular disease as it relates to obesity? When
22 FDA's guidance on CVOT for diabetes therapies went into

1 effect, at least eight different classes of diabetes
2 medications had been FDA-approved. There were
3 alternatives for patients. Arguably, they weren't the
4 best alternatives, but there were alternatives. That's
5 very different than in the case for obesity, although
6 it's quite likely that early- stage development of
7 diabetes drugs has been slowed by these new rules.

8 And certainly cost and time to development
9 have increased, as Dr. Parks acknowledged yesterday.
10 Fortunately, patients with type 2 diabetes still have
11 some medical options. The case is very different for
12 obesity. Only one obesity drug, and not a particularly
13 effective or tolerable one, is approved for long-term
14 use in America. Just 40 compounds are in clinical
15 development for obesity today, down from nearly 60 in
16 2008, due, at least in part, to regulatory
17 uncertainties, and this compares to hundreds of drugs
18 in development for cancer and cardiovascular disease,
19 over 700 and over 150 to be specific.

20 How would those numbers change for compounds
21 in development for obesity if the price tag for
22 clinical development was increased by the hundred to

1 two hundred million that it costs to run a pre-approval
2 cardiovascular outcomes trial? I love data, but do we
3 really want to know the answer to that? I'm not really
4 sure that we do. I surely suspect, as someone who has
5 studied and written about life sciences innovation for
6 over 20 years, that would put the nail in the coffin
7 for obesity drug development.

8 Although it's tempting to create a cut-and-
9 dried rule in order to simplify things and increase
10 predictability, I would urge you not to make choices
11 that will increase the time to approval significantly
12 for drugs with a positive benefit-risk profile, or
13 perhaps one day we'll be without obesity drugs and
14 development altogether.

15 Given all of the complexities outlined
16 yesterday, I would advocate thinking more creatively
17 about a staged approach, where warranted, that enables
18 FDA to work with companies on a compound-by-compound
19 basis and to allow post-approval cardiovascular outcome
20 trials where efficacy and safety warrant it. It's not
21 a matter of if these trials will happen; it's a matter
22 of when.

1 In closing, some very fast patient data that
2 I believe is really instructive. As part of our
3 research organization called DQ&A, Diabetes Questions
4 and Answers, we conduct a patient survey every quarter.
5 Four days ago, we asked 2,400 type 2 diabetes patients,
6 the vast majority of whom are overweight or obese,
7 about their experiences with weight management. In
8 that time, we've gotten nearly 1,000 responses, as of
9 this morning, it was just below that. The numbers are
10 really daunting, two-thirds of these respondents said
11 that they don't have confidence that their doctors and
12 health care teams have the tools to be able to help
13 patients manage their weight successfully. Only 14
14 percent said that their own doctors have been very
15 helpful in managing their weight, and 63 percent said
16 outright that the doctors and health care teams had not
17 been able to be helpful. Why is that? They don't have
18 the tools. This doesn't speak to cardiovascular
19 outcome trials assessment, but I share this data with
20 you so that you understand a little more the
21 difficulties that patients go through.

22 Thank you very much for your time. I admire

1 your courage on being on this Committee today.

2 DR. THOMAS: Thank you for your comments.

3 We'll now move to Open Public Hearing speaker
4 number nine, Dr. Denise Bruner, from the American
5 Society of Bariatric Physicians.

6 DR. BRUNER: Good morning, everybody. And I
7 want to thank the Committee for inviting me here to
8 speak. It's an honor and a pleasure to be before you
9 again. And I'm here to represent the views of the
10 American Society of Bariatric Physicians, which is the
11 oldest U.S. medical society that is dedicated to
12 obesity. I am here on behalf of them. I have no
13 financial interest in the sponsor or any drug
14 companies.

15 We have over 1,430 members, and our mission
16 is really to provide obesity management education to
17 physicians and mid-level practitioners. We all know
18 that excess adiposity contributes to a number of
19 deleterious cardiovascular events, and people and obese
20 people with cardiovascular disease, when they do lose
21 weight, these are some of the benefits that are
22 outlined with weight loss, and we know LVH is the

1 strongest predictor of cardiovascular morbidity and
2 mortality short of age.

3 So we conclude that really in medical weight
4 loss, when patients are managed also with
5 pharmacotherapy, the major incidences of cardiovascular
6 events will be reduced, and ultimately mortality. Now,
7 where is the evidence for that? Well, I point to you
8 three recent studies: the SCOUT trial, the QNEXA
9 trial, and a long-term obesity phentermine study.
10 Well, in the first trial, sibutramine was removed in
11 2010 because of the findings, but weight loss was not
12 considered in the final analysis. In the second trial,
13 recently published, they stratified the data for weight
14 loss, and the sibutramine patients who lost weight
15 experienced a reduction in cardiovascular mortality and
16 morbidity. And, again, the conclusion of that SCOUT
17 trial we saw earlier. But again to note, the decrease
18 in cardiovascular risk that followed 4 to 5 years after
19 the trial was ended.

20 And these are the QNEXA data, which we saw
21 earlier, looking at the reduction in hypertension in
22 obese patients, and this is over a year, and the

1 changes followed in a 2-year period of time.

2 When we look at the long-term phentermine
3 study that was published by Dr. Hendricks and parties,
4 this was in private practice. This is kind of what we
5 see every day, of 300 patients. And we looked at the
6 weight loss over 7 years, this is 7-year data, and
7 basically the changes in systolic and diastolic blood
8 pressure persisted during weight loss and maintenance,
9 again over 7 years.

10 This data was stratified according to JNC-7
11 criteria for systolic blood pressure, and we see in
12 this group again a 7-year -- 7-year, remember that
13 number -- data. The people with hypertension
14 experienced significant reduction in their blood
15 pressure. The pre-hypertensives also had an
16 improvement, but basically the normotensive patients
17 remained stable.

18 So what can we say in terms of these shifts?
19 If we look at what the American Heart Association
20 published as guidelines for 2012, there was a reduction
21 in progression from normal hypertensive to hypertensive
22 and pre-hypertension to hypertension in the study, and

1 again what we saw is the reduction in pre-hypertension.
2 Really, we can conclude, or this study does suggest,
3 that over the long term phentermine induced weight loss
4 and maintenance will translate into reduction in
5 cardiovascular mortality.

6 Well, the ASBP recommends that the
7 cardiovascular outcome trials really should be part of
8 the approval process but the data stratified by weight
9 loss, and that initial JNCBP criteria, the category B
10 included, and that again, as changes occur, transitions
11 occur, that be included in the data analysis. And we
12 realize that this has to be done, but suggest that this
13 not prolong an already too lengthy process.

14 Phentermine is so widely used. Perhaps NIH
15 should fund a phentermine cardiovascular outcome trial;
16 that would be of great public interest.

17 So thank you very much for allowing me to
18 speak, and thank you for your work.

19 DR. THOMAS: Thank you for your comments.

20 We'll now move to Open Public Hearing speaker
21 number ten, Preston Klassen, from Orexigen
22 Therapeutics.

1 DR. KLASSEN: Good morning. My name is
2 Preston Klassen. I'm a physician and clinical
3 nephrologist, and I lead drug development activities at
4 Orexigen Therapeutics, where I'm an employee. Orexigen
5 currently has two obesity drugs in development.

6 Many members of this panel are familiar with
7 Orexigen's EMDAC meeting in December of 2010, where our
8 combination therapy bupropion/naltrexone received
9 majority vote for approval along with a majority vote
10 for the conduct of a post-approval outcomes trial to
11 evaluate the theoretical risk related to the known and
12 well- characterized sympathomimetic activity of
13 bupropion.

14 On our PDUFA date the following month, FDA
15 required that this cardiovascular trial be conducted in
16 the pre-approval setting. Although this was a major
17 setback, we've been able, since, to make great progress
18 with FDA in defining the requirements for a large
19 streamlined trial, and we plan to enroll our first
20 patients by the end of June.

21 Orexigen's experience highlights several
22 critical questions that we urge the panel to consider,

1 and these questions center on the need for developing a
2 clear logic for any guidance on risk assessment that
3 maintains an appropriately high standard for safety but
4 that is also feasible for drug development. It is
5 critical that this logic be clear enough that it can be
6 consistently applied for obesity drug development
7 across various modes of action or magnitudes of effect.

8 And with all due respect to Dr. Colman's
9 guidance to the Committee yesterday, I would submit
10 that discussion of what actually constitutes a signal
11 for theoretical cardiovascular risk is in fact at the
12 heart of this entire discussion. It's not clear how
13 this panel can opine on Question 2 and vote on Question
14 3 without at least knowing what constitutes a signal or
15 theoretical risk and, perhaps, more importantly, what
16 actually constitutes the absence of a signal or absence
17 of theoretical risk. Without that discussion and
18 setting some common ground, each of you may have very
19 different ideas on what is or is not a signal or a
20 theoretical risk. Is it imbalance of MACE? Is it an
21 increase in blood pressure alone? heart rate alone?
22 only if both are combined? Is it simply a worrisome

1 mechanism? What about putting all of these factors and
2 other biomarkers into a Framingham-like risk equation?

3 In the case of Orexigen's combination drug
4 bupropion/naltrexone, we know that a key factor in the
5 Review Division's decision to require a pre-approval
6 trial was the outcome of SCOUT, where a drug with
7 sympathomimetic activity resulted in increased major
8 cardiovascular events, but we also know from prior
9 discussion that changes in blood pressure and heart
10 rate did not correlate with these MACE outcomes. This
11 indicates that we may not know enough about biological
12 plausibility to make a distinction in what does or does
13 not constitute a theoretical risk based on observed
14 changes in biomarkers.

15 So here is a very practical example of why
16 this is so important. Take the bupropion/naltrexone
17 combination. It has the same sympathomimetic activity
18 and hemodynamic profile of bupropion alone, and as we
19 learned last year, FDA believed that this combination
20 drug required a pre-approval outcomes trial. Now take
21 the same dose of bupropion but combine it with an
22 anticonvulsant. We know that anticonvulsants lower

1 blood pressure, so the sympathomimetic activity isn't
2 changed but it may be partially masked. Heart rate is
3 still elevated to the same degree, but now blood
4 pressure goes down a bit compared to placebo. So a
5 different hemodynamic profile and sympathomimetic
6 activity would appear to be diminished, but how do you
7 judge the potential for risk? On the mechanism? On
8 the blood pressure? On the heart rate? On something
9 else? Do we have enough understanding of biological
10 plausibility to make a decision that there is no signal
11 or theoretical risk? This example is entirely relevant
12 to Orexigen because our second compound combines
13 bupropion and the anticonvulsant zonisamide. It has
14 completed phase 2 with the hemodynamic profile I just
15 described.

16 Now, these issues, of course, are not unique
17 or exclusive to just Orexigen. We and other industry
18 sponsors need to hear from this panel and FDA on these
19 topics, and we applaud FDA for convening this meeting.
20 I urge this panel and FDA to provide companies clear
21 standards for approval that can be consistently applied
22 across agents with differing profiles. Most new agents

1 in obesity today are being developed by small
2 companies, and the funding of these high-risk ventures
3 is greatly aided by clarity and consistent application
4 of efficacy and safety standards. Those standards
5 should be high; however, ambiguity in these standards
6 or in how they are applied across different drugs would
7 have a chilling effect on the ability to attract the
8 necessary capital to develop these new therapeutics.

9 In closing, I again submit that central to
10 this entire discussion is what constitutes a signal or
11 theoretical risk and, more importantly, what actually
12 constitutes the absence of these. I know that we would
13 greatly regret missing the opportunity to hear this
14 panel's opinion on these critical concerns.

15 Thank you for your thoughtful deliberation,
16 and I appreciate the opportunity to provide these
17 comments. Thank you.

18 DR. THOMAS: Thank you for your comments.

19 Is Open Public Hearing speaker number one in
20 the room?

21 (No audible response.)

22 DR. THOMAS: Okay. The open public hearing

1 portion of this meeting is now concluded. We will no
2 longer take comments from the audience. The Committee
3 will now turn its attention to address the task at
4 hand:

5 the careful consideration of the data before
6 the Committee, as well as the public comments.

7 Since we have some time on the agenda, what
8 we have decided to do is actually open up for questions
9 from any of the speakers from yesterday for the panel.
10 So if you have questions related to the specific
11 presentations yesterday, remembering that three of our
12 speakers are not here today, please let Dr. Tran know.

13 And then I also just wanted to add some
14 clarification. There was a question yesterday about
15 the results from a JAMA article in 2012 from the
16 Swedish Obesity Society, and what I'm going to do is
17 just read the results from the abstract in case that
18 helps people in clarification of these issues. And the
19 question was whether there was improvement in death
20 versus events in the Swedish obesity study in the paper
21 published in 2012, and this is just from their results.

22 The bariatric research showed a reduced

1 number of cardiovascular events in the surgery group
2 versus the controlled, 28 events among 2,010 patients
3 versus 49 events among 2,037 patients in the controlled
4 group," and this is statistically different. And the
5 number total first-time events was also reduced in the
6 surgery group, 199 events in the surgical group out of
7 2,010 patients versus 234 events among 2,037 patients.
8 So both cardiovascular events in the publication that
9 had some questions about yesterday. And the reference,
10 for those who would like to look that up, is Journal of
11 American Medical Association 2012, Volume 307, pages 56
12 to 65. Questions to the Committee

13 DR. THOMAS: So we'll now go on to questions
14 from the panel.

15 Dr. Brittain?

16 DR. BRITAIN: Yeah. I'm not quite sure who
17 to direct this to, but there was a lot of concern
18 yesterday about the lack of follow-up data from a hefty
19 proportion of the patients started, but that was in
20 terms of the weight loss data. Now we're talking about
21 cardiovascular events, and I'm not quite sure whether
22 that's harder or easier. I'm assuming it's harder, but

1 I don't know if someone can speak to that.

2 DR. THOMAS: Anyone from the FDA or --

3 DR. COLMAN: Yeah, if you can just give me
4 one minute. If you can tell a joke or something for a
5 minute.

6 DR. THOMAS: Okay. Well, while you think
7 about that, Dr. Bray, do you have any comment about --
8 the question was related to the lack of follow-up in
9 obesity trials, and does that make it harder to assess
10 for cardiovascular events or does it have an impact? A
11 clarification from your presentation yesterday.

12 DR. BRAY: I don't think my presentation
13 dealt with that issue. The follow-up one is a serious
14 one. In all of the obesity trials, look ahead, and for
15 whom I can't speak exactly, I'm only a PI on the
16 project and DPP both have exceptional follow-up. The
17 95 percent is very unusual. There are just very few
18 trials that can manage that. All of the obesity trials
19 that I am familiar with have less than 80 percent
20 follow-up, and that's as good as I know of. Most of
21 them are in the range of 50 percent at one year, and
22 that will certainly impact the outcomes because you

1 don't know what happened to the people who aren't there
2 to evaluate.

3 DR. THOMAS: Thank you. And we'll come back
4 to Dr. Colman in a few minutes.

5 Ms. McAfee?

6 MS. MCAFEE: This is not a question, but I
7 really feel it's incumbent on me, as a patient
8 representative, to address some of the issues that were
9 brought up by the public opinion speakers, who are some
10 of our excellent advocates for us, and I'm particularly
11 thinking of Pat O'Neil, who has been wonderful.

12 Social prejudice has been brought up, and
13 that's a very important issue, and one I've spent my
14 entire adult life dealing with as an activist, but I
15 have to wonder whether it's really appropriate to bring
16 it up in this connection. Is it appropriate to use a
17 diet drug to end social prejudice? And although it's
18 tempting for me, as the activist, to say, "Yes, we'll
19 use any tool," I have to say that I think it's not
20 appropriate to consider that at this time. And that's
21 something that probably should be discussed more among
22 activists, but it really is not.

1 This is something that affects appearance,
2 and while we do take these things into account,
3 prejudice, when we look at things like facial
4 disfigurement and things like that, this is a very
5 different issue. These drugs are not to deal with our
6 appearance, they are to deal with underlying medical
7 conditions, many of which, frankly, I have. So I just
8 think it's important to put that in a kind of context.
9 And also be aware that some of these health conditions
10 that are so serious are made more serious by the
11 tremendous medical prejudice that we have, which is
12 very well documented.

13 And then the other issue I want to bring up -
14 - and it's not really appropriate, but I'm going to do
15 it anyway -- is cost. As a consumer, that's a big
16 concern of mine, and I think one of the things that I
17 need to balance today is how much testing needs to be
18 done versus how much cost that's going to add to the
19 medication, and is that something that I need to think
20 about, perhaps not for today but just in general, that
21 we need to really think about? And particularly this
22 drug has very, very broad indications, and I wonder if

1 maybe some of this cardiovascular testing could be tied
2 to the indications in some way.

3 That's it.

4 DR. THOMAS: Thank you.

5 Dr. Proschan?

6 DR. PROSCHAN: Yeah, this is a question I had
7 from yesterday about the DPP trial, the 10-year follow-
8 up, and Dr. Knowler mentioned that the lifestyle
9 intervention was offered to anyone in any of the three
10 groups during that time, and I was just wondering how
11 many people did partake in the lifestyle intervention,
12 in, for example, a metformin group.

13 DR. THOMAS: I don't know if anyone from the
14 FDA would want to comment.

15 DR. BRAY: Yeah. I'm a PI on that trial as
16 well, and I --

17 DR. THOMAS: Would that be okay with you? I
18 think that's okay then.

19 DR. BRAY: In the bridge period between DPP
20 and DPPOS, it was offered to all participants,
21 including the former lifestyle individuals, and the
22 paper by Venditti, which he didn't refer to, we

1 examined the frequency with which the various arms --
2 placebo, metformin, and the original lifestyle -- took
3 it up, and it decreased. People who had the original
4 lifestyle volunteered, if I remember, about 30 percent
5 for the second lifestyle program. The volunteer rate
6 for the other two was closer to 60 percent. There were
7 some other variables in it. That was a 6-month trial.
8 After that point, the intensive lifestyle was offered
9 in a much lower level but only to those who had the
10 intensive lifestyle, so they were maintained in the
11 group. Metformin was only provided for those who had
12 been in the metformin group and were still eligible.
13 All groups received booster sessions twice during the
14 year, lifestyle placebo, and metformin. So the
15 lifestyle was reduced in intensity from the end of the
16 bridge period onwards. Boosters were available for
17 everybody. Is that clear?

18 DR. PROSCHAN: Thank you.

19 DR. THOMAS: Dr. Kaul?

20 DR. KAUL: Thank you. In the briefing papers
21 that were sent to us by the FDA, on page 16, the first
22 paragraph, it says, "In order to identify off-target

1 cardiovascular toxicity, the evaluation of
2 cardiovascular risk applies even if there is no known
3 cardiovascular signal with the investigational agent in
4 animals or humans or a history of concern with this
5 pharmacologic class." Could you please expound on
6 that? What do you mean by "off-target toxicity"?
7 Well, I'm trying to understand what is "off-target
8 cardiovascular toxicity" and whether that also applies
9 to the obesity guidance, and how does the FDA
10 anticipate off-target toxicity, and how does the FDA
11 adjust or account for that in the clinical trial
12 design?

13 DR. PARKS: So specific to the diabetes
14 programs -- and I imagine that this could be applied to
15 other therapeutics for chronic conditions -- is that
16 when we talk about off-target of things that we have
17 not been to or companies have not been to identify in
18 their development program, development program meaning
19 not only the clinical program but the non-clinical
20 program. And keep in mind that these non-clinical
21 programs for the chronic conditions are very, very
22 extensive. You're not looking at just the biomarkers,

1 but these analysts are also looking at for blood
2 pressure, ECG changes, heart rate, et cetera. And this
3 came about with the diabetes program, that was the
4 question, is that if we can't identify this in the
5 extensive pre-marketing application, does the panel
6 still believe that those drugs, the diabetes drugs, and
7 the patient population which it's intended for, that
8 there is merit in evaluating cardiovascular risk?
9 Because we already stated up front that if there is a
10 known signal, that we will ask for it, similar to what
11 Eric has mentioned in the discussion for obesity drugs.

12 So saying what an off-target toxicity is, in
13 some ways it's apparent, self-apparent; that is, we
14 haven't been able to identify it in the extensive pre-
15 marketing testing, but because of its very broad use in
16 a patient population, which there is a high background
17 rate of cardiovascular disease, should there be a more
18 formal testing done in a clinical development program;
19 that is, these rule out excessive cardiovascular risk
20 trials that we've been imposing on companies in the
21 past couple of years to give us further reassurance
22 that we had not missed anything in the pre-marketing

1 program.

2 With respect to the obesity guidance, that's
3 actually the reason why we're here today. I can't
4 really comment on that.

5 DR. KAUL: But there is always a potential
6 for off-target cardiovascular toxicity. And we love to
7 use the word "off-target" after we have become wiser
8 after the fact. I mean, we talk about torcetripib and
9 the off- target effects, which I'm not quite even sure
10 if all of those excess risks in torcetripib can be
11 attributed to aldosterone pathway because there was an
12 excess in non- cardiovascular events, and it's hard to
13 link aldosterone to non-cardiovascular events.

14 So, I mean, it's a dilemma because
15 potentially anything can have anticipated or
16 unanticipated risks.

17 DR. THOMAS: Dr. Temple?

18 DR. TEMPLE: That's true, of course, and the
19 cardiovascular ones have been most stunning, probably
20 because they're most detectable. So, you know, a whole
21 bunch of beta-agonist type drugs or their relatives in
22 treatment of heart failure decrease survival. Nobody

1 really expected that. Our requests for outcome studies
2 in those cases were severely criticized as being
3 unethical because we were delaying important drugs for
4 heart failure, and torcetripib is certainly another
5 exciting example, as is CAST and all the other things.

6 The usual explanation for them is that
7 they're doing something other than what you were using
8 them for. That's why they're called off-target. But
9 you're absolutely right, the reason so many of them are
10 cardiovascular, I think, is that you can detect
11 cardiovascular effect, it's harder to detect increases
12 of cancer rate. But, you know, you find other things.
13 More people went to the hospital when they were on
14 long-acting beta-agonists maybe? So that's another
15 unexpected effect certainly.

16 But the question in all of these things is:
17 How sure do you have to be that there isn't one of
18 those? And that's really what a lot of this is about.

19 Cardiovascular comes up I think mostly
20 because we know, but, including the right population,
21 how do detect them? But certainly what's on people's
22 mind is things like, what does an increase in heart

1 rate mean? Is that worrisome? If you believe beta-
2 agonists are a problem for people with heart failure,
3 maybe you think anything that raises heart is
4 sympathomimetic in some ways, and maybe that should
5 make you nervous. But you're in uncharted territory
6 in most of these things, it's certainly true. I think
7 what people are noticing is the experience with these
8 drugs, and that is enough to make you nervous, as Sid's
9 testimony pointed out, there have been a fair number of
10 troubles with a lot of these drugs. So everybody gets
11 nervous.

12 DR. THOMAS: Dr. Colman, your follow-up?

13 DR. COLMAN: Yes. This gets to the question
14 earlier about the dropout rates. So in SCOUT, where
15 there were about 5,000 patients per treatment arm, 60
16 percent of the subjects in each treatment group
17 completed the study on drug. Another 20 percent came
18 off of study drug, but they were followed in the trial,
19 so they were able to accrue information in terms of
20 cardiac events. And there were a total of 96 percent of
21 all trial participants where they actually had vital
22 status information at the completion of the trial. So

1 I think that's pretty good.

2 DR. THOMAS: Dr. Kramer?

3 DR. KRAMER: I would like to hear what the
4 FDA's thoughts are regarding the question that was
5 raised in the Open Public Hearing about everything
6 hinging on defining whether or not there is a signal.
7 And it appears from all the data that's been presented
8 that they have been any individual thing that makes
9 people nervous or any prior history that relates to the
10 compound under study may be enough for people to say
11 there is some signal, we need to do something. But I
12 think that's a really important question for us to
13 understand, given that you've segmented our questions
14 based on if there is any signal of a cardiovascular
15 risk in terms of what we would recommend. And I would
16 like to hear what your thoughts on these suggestions,
17 for instance, that we might use an integrated
18 Framingham score or something else.

19 DR. COLMAN: The first discussion point
20 really is we want to get your thoughts, if you think
21 it's worthwhile to make an effort to enrich the current
22 population of patients who enroll in phase 3 trials for

1 obesity drugs to try to get a sufficient number of
2 adverse cardiovascular events such that that in and of
3 itself may provide a signal because the way the trials
4 are currently run, the subjects are young, they don't
5 come in with a history of cardiovascular disease, and
6 they're only followed for a year. So you're going to
7 see very few cardiac events, so you'll never see a
8 signal for cardiac problems in the phase 2 and 3
9 programs that are currently implemented.

10 The second discussion point, we've asked you
11 to answer design questions when the assumption is that
12 everyone has agreed that there is a signal of concern
13 and that the trial will have to be done. So, again,
14 we're not asking you to weigh in on whether you think
15 there is a signal or not; we're asking you to assume
16 there is a signal and then provide feedback on study
17 design for a trial with that drug with a signal.

18 So the issue with the third, the voting
19 question, is the other side of the coin, which is, if
20 we have a drug and everyone agrees there is no
21 theoretical risk or a signal for CV harm, do you think
22 they should still be required to conduct a

1 cardiovascular outcomes trial? And if yes, when should
2 that be done? Or, no, if you feel no, then that's no.

3 DR. KRAMER: But in follow-up, Question 3
4 hinges on this statement, assuming that everyone agrees
5 that there is no theoretic risk, and that's the meat of
6 my question, which is, what should we assume that that
7 is based on? Is it any individual thing that makes
8 people nervous, an increase in heart rate or blood
9 pressure, or is it integrated, is it a prior history of
10 a similar mechanism?

11 DR. COLMAN: Well, again, I suspect that, in
12 reality, we would not get a room full of 100 people to
13 all agree, but I think if we had another sibutramine
14 where the mean increase in blood pressure, systolic and
15 diastolic, was 1 to 3 millimeters of mercury, and the
16 pulse was increased 3 to 5 beats per minute on average,
17 I think most people would agree that was a signal.
18 Would you agree that's a signal?

19 DR. KRAMER: I guess I'm wondering about
20 bupropion, which is on the market for another
21 indication currently, right?

22 DR. COLMAN: Mm-hmm.

1 DR. KRAMER: So we don't require outcome
2 studies for those.

3 DR. COLMAN: Well, Dr. Klassen may want to
4 comment on the trial that the Orexigen folks are
5 planning to do. But, again, I think we're going to
6 lose focus if this devolves into a discussion of what's
7 a signal. Is a 2-beat-per-minute increase in heart
8 rate a signal? Is a 1-beat-per-minute? Is a 3-
9 millimeter of mercury increase in blood pressure? Is
10 an elevated CRP a signal? I mean, there are a lot of
11 potential situations when there might be a signal, so,
12 again, we're asking you to -- for 3, you could assume
13 that this is a squeaky clean drug, there is absolutely
14 no reason to believe that it would increase the risk
15 for cardiovascular disease.

16 DR. THOMAS: Dr. Parks?

17 DR. PARKS: I don't know if in your question
18 here you're concerned about whether or not we have a
19 ranking system for biomarkers or CV risk, because I
20 can't answer that question. But if it can be
21 reassuring to the panel, again, these programs, before
22 they come in to us an NDA, they have to be tested very

1 rigorously in pre- clinical and the clinical program.
2 And so a lot of the traditional cardiovascular risk
3 factors are being assessed both in animals and humans.
4 And so we're seeing those things going in the wrong
5 direction. Those are the theoretical risks that may
6 rise to a level where we make that determination that
7 they've got to do more as opposed to what you're being
8 asked for right here.

9 I can speak a little bit about the diabetes
10 program; that may give you a sense of direction. So
11 setting aside that even before the guidance they had to
12 do all the extensive non-clinical evaluations, so we
13 know about the lipid effects, we know about blood
14 pressure, heart rate, pulse of these products. All of
15 these products had to do a thorough QT study. But it
16 comes down to how did their clinical program, how was
17 it designed to put into perspective whatever signals we
18 saw from either the PK studies, the early phase 1
19 studies, or animal studies? And it was really
20 difficult before companies were asked to more robustly
21 design their phase 2 and 3 program to meet the current
22 guidance, because we were getting events in the range

1 of like 20 to 30 at best, and I don't even want to call
2 -- as Dr. Guettier pointed out yesterday, in quotes,
3 we're not really sure if we want to call those MACE
4 events because those were adverse events collected by
5 investigators on case report forms never formerly
6 adjudicated, and they could have, there was a lot of
7 noise there. So I would venture a guess that they were
8 probably even lower than that. And we're being asked
9 to opine whether or not that was a sufficient signal.
10 But going forward, these programs, you have
11 adjudication committees set up with definitions,
12 standard definitions, prospectively adjudicating these
13 events so that the hope -- and this is getting to
14 discussion point number 1 -- is whether or not that
15 will help us define that risk to determine whether or
16 not if you see something from that very, very robust
17 evaluation in the phase 2 and 3 program, and if you're
18 comfortable with that, does that constitute without a
19 theoretic risk and do they have to do more? I don't
20 know if that helps.

21 DR. THOMAS: So fair to say that the task to
22 the Committee is to not really quibble over what those

1 signals might be and use the pre-marketing and other
2 examination that the FDA does with the sponsor for
3 their studies, and rely that there is enough testing
4 done to pick up potential signals, and if nothing is
5 picked up, then should an additional trial be done and
6 let other committees or FDA decide what are appropriate
7 signals?

8 Dr. Weide?

9 DR. WEIDE: Thanks, Ed. You know, I didn't
10 say anything all day yesterday because I was listening.
11 I promise to make it up today.

12 (Laughter.)

13 DR. WEIDE: I have two pages of issues here,
14 and I'll just take a couple at a time.

15 So, you know, the question -- I want to
16 bring up a couple things to stimulate people's thinking
17 process because I'm a little concerned. As Lynn said,
18 the goal for weight loss medicine should be to improve
19 health. Okay? So if we assume that, I don't know that
20 we're always measuring that. Sibutramine was on the
21 market for 10 years, was taken off. When I asked the
22 question, "Can you tell me one other thing that

1 occurred in these patients other than the weight loss
2 that was an improvement, metabolic parameter,
3 anything?" the company could provide nothing. That's a
4 concern. In the DPP that was talked about yesterday,
5 there was an arm left off. The Rezuline arm was left
6 off, and I know Rezuline was pulled from the market,
7 and when they talk about the
8 DPP results, they usually ignore that. If
9 you look at the Rezuline arm, however, which they did
10 in retrospect, it prevented progression to diabetes by
11 over 60 percent, and, indeed, all the TZDs have
12 decreased the progression to diabetes in high-risk
13 patients and look to be the only drugs that have 5-year
14 stability in glucose control in diabetics. They do not
15 cause weight loss. It appears that, among other things
16 -- and we can get into a major discussion -- that they
17 do change where the fat is, and that intra-abdominal
18 fat is bad from a metabolic standpoint; subcutaneous
19 fat you could think of as an insulator and does not
20 have the same metabolic badness that intraperitoneal
21 fat has. So that brings up the question: Does it
22 matter how we lose weight, where we lose weight, and

1 how this goes on? That is not part of what people are
2 looking at, they're just looking at weight loss, and
3 perhaps that is a much bigger issue than where we go
4 on. So losing intraperitoneal fat would be highly
5 beneficial. Subcutaneous fat, like liposuction and
6 other things, or medication that causes subcutaneous
7 fat loss but no intraperitoneal fat loss may not at all
8 be beneficial, and we're not really addressing that.
9 So I would really appreciate other comments.

10 The other thing that I'm concerned about is
11 we saw some great compliance as far as people returning
12 for follow-up, 90 and 95 percent. That's incredible.
13 I mean, those investigators are angels or miracle
14 workers. I have no idea how you get that. I know you
15 paid them, but even that, I find those retention rates
16 incredible. However, having said that they have those
17 retention rates, they all also said that the patients
18 weren't following through on the programs. So they
19 weren't doing the exercise, or in the case of drugs,
20 they weren't compliant with the drugs. They were just
21 showing up for the appointments. And so it looks like
22 we have a very low success rate in people who are going

1 to stay on medications, and therefore, when you look at
2 the studies, it becomes much more complex. Do we look
3 at people who stayed on? Do we look at everybody who
4 got put on? Because it radically will change how we're
5 looking at.

6 And when we look at some of the breakdowns in
7 those studies, what is very clear is that patients who
8 were most compliant with adherence to whatever
9 protocol, whether it was lifestyle changes or the
10 medication, tended to lose the most weight, and they
11 balanced out the patients who did not adhere to the
12 plan. And if you look at those cutoffs and look at
13 what happened, it really looks like you have to achieve
14 10 percent. Those patients who did well all exceeded
15 the 10-percent mark, and the other patients were 2 to 4
16 percent or less and didn't do as well.

17 So I guess what I wonder is if we have the
18 wrong cutoffs, if we are looking at the wrong things,
19 and we ought to shift. Perhaps we ought to say if you
20 don't lose weight by 6 months, you can't continue on
21 the drug, and then if you do, we have to see that that
22 drug provides 10 percent weight loss, not 5. We're not

1 getting what we need, we're not getting what the
2 patients need, we're not getting what we want, and we
3 have to see the metabolic changes.

4 This is not where we are now. I think it's
5 the right thing to do. I bring these two concepts up,
6 which sort of wrap together, because I want to hear
7 what other people think to make a radical departure and
8 change like this. I think it would be the right thing
9 to do, but it is different than what we're doing now.

10 DR. THOMAS: Dr. Konstam?

11 DR. KONSTAM: Yeah, thanks. You know, I just
12 was thinking, I was wondering what other help the FDA
13 could give us regarding the feasibility for sponsors
14 for some of the recommendations that we might be
15 making. And so we did see the SCOUT and CRESCENDO
16 trials yesterday, so those are sort of sets of
17 information that trials that provide cardiovascular
18 signals can be done, but there continues to be, I
19 think, an understandable concern that we may be making
20 a recommendation that could significantly delay
21 development of these drugs and the feasibility of
22 bringing them to market.

1 And so let me just point out, I think we're
2 talking about two different things when we get into
3 that discussion. One is the wisdom of enriching the
4 population with patients at high cardiovascular risk in
5 order to get the events, and thereby creating a
6 population that's not representative of the typical
7 target population of the drug, and I get that, and I
8 think we all get that, and we're going to have to
9 grapple with that. But accepting the fact that if you
10 want to see the endpoints, you're going to have to do
11 that, if we could just accept that for a second, I'm
12 still not clear about the burden that that's going to
13 create in terms of moving drugs forward for sponsors.
14 Let's assume guidance is given to sponsors, okay, you
15 need to enrich your population with patients at high
16 risk for cardiovascular disease, okay, go do it. I
17 don't have a sense for, based on your experience, how
18 burdensome is that really going to be? How much delay
19 is there really going to occur? Is it going to take
20 twice as long with twice as much money? in order of
21 magnitude, more difficulty? I don't have a good sense
22 of that, and just any help you could give us about that

1 would be really helpful.

2 DR. PARKS: So this will have to come from
3 our experience with the diabetes drugs. I think we
4 have to be very clear that the programs had to increase
5 in scope and size. And I think from what Dr. Guettier
6 had pointed out yesterday, we're talking about at least
7 a doubling of patients exposed to drug in these
8 programs, the diabetes programs, to be able to meet
9 that pre-marketing goalpost. I can't really speak to
10 what it has done with respect to the duration or the
11 costs. I don't know, Mads, if you have that
12 information, being the industry rep, but I think one
13 should expect there is going to be an increase to the
14 companies pre-marketing.

15 DR. KONSTAM: Okay, but that's helpful to a
16 certain point. So you're saying there would be
17 obviously a shift in the population to include patients
18 at higher risk, but you think that in addition to that,
19 there probably would -- and I guess, let's say, we're
20 talking about getting to the 1.8 upper confidence
21 level, you think roughly the development program would
22 wind up being doubling in terms of the total patient

1 population. Is that a rough approximation?

2 DR. PARKS: A doubling in patients exposed.

3 In terms of patient-year exposure? That depends on the
4 patient -- the event rates, because if you enroll a
5 patient population in your phase 3 program that is
6 very, very high risk so that you have a high event
7 rate, you may actually have a slightly lower patient-
8 year exposure.

9 I don't know, Paul, if you can put up Jean-
10 Marc's slide number 39, but a striking example of drug
11 C and D -- wait for it to come up -- drug C and D, as
12 you can see, the total patient-year exposure is much
13 lower in drug D versus drug C, whereas the total
14 exposed is pretty comparable. And that really speaks
15 to the event rate or the background risk of the patient
16 populations in D if you're going to be able to get a
17 lot more events in an earlier period of time, so less
18 duration in terms of exposure, then you may be able to
19 achieve. So clearly there are going to have to be more
20 patients, but the duration of exposure depends on the
21 patient population, the at-risk population you want to
22 enroll.

1 DR. KONSTAM: Well, I mean, that's really
2 helpful, and I know Dr. Kaul questioned what is it that
3 actually went on in drug D that got them the higher
4 event rate, but let's go with it. Somehow or other
5 they managed to get a reasonably high event rate, with
6 total patient-years exposed, it was no different than
7 in the drug A/drug B year; right?

8 DR. PARKS: Yeah, and, again, I have to
9 caution that drug A and drug B, one, it's hard to
10 compare across these different programs, but drug A and
11 drug B were not designed with this guidance in mind, so
12 even looking at the MACE events here, as I pointed out
13 earlier, 26 and 40 events may actually be a lot lower
14 because those were not prospectively adjudicated, not
15 meeting the same types of case definitions that
16 programs C, D, and beyond are now expected to face.

17 DR. KONSTAM: Well, one of the key issues, by
18 the way, that I think we're going to have to grapple
19 with is keeping patients on the drugs, you know, so
20 patient- years of exposure is not only the number of
21 patients you enroll but the fact that they're kept on
22 the drug for a year. So that's one of the points we'll

1 have to come back to, but I have to say, looking at
2 this, you know, I'm not getting a sense that there is
3 going to be an extraordinary increase in the demands on
4 sponsors and an extraordinary delay in moving these
5 drugs to an NDA. I don't really even see a doubling
6 there in terms of the patient population. So I don't
7 know if that sense is correct, but I'm not seeing that.

8 DR. THOMAS: Dr. Guettier, do you want to
9 comment?

10 DR. GUETTIER: So I'm not sure if actually
11 taking the diabetes drug example and applying it to the
12 obesity drugs is actually fair because a lot of these
13 trials are actually done to -- you know, we require
14 sponsors to do comparison to placebo, and so that would
15 be a monotherapy trial comparing it to placebo, and
16 then a lot of sponsors do add-ons to additional therapy
17 just because that's how we treat the patients, so there
18 would be a trial add-on to metformin, if the second-
19 line agent is a sulfonylurea, we would sort of expect
20 sponsors to do a trial add-on to sulfonylurea. So all
21 these additional trials actually just for diabetes
22 itself add to patients and patient exposures. I can't

1 speak for the obesity drugs, but drug A and drug B had
2 to do a lot of trials just to --

3 DR. KONSTAM: Well, except your current
4 guidance is 3,000 patients randomized to active drug;
5 that's your current guidance without -- and then we get
6 back to how long they're on the drug. But that's --
7 you know, I mean, it's sort of ballpark here as far as
8 I can tell, if you were to change the nature of the
9 population.

10 DR. THOMAS: Dr. Temple?

11 But can I also just clarify the 3,000
12 patients on active drug, that's with an expectation of
13 about a 50- percent dropout? So really you're looking
14 at 1,500 patients? Is that correct?

15 DR. TEMPLE: Yeah. Mary will need to correct
16 me if this is wrong, but I think the main change that
17 we're talking about here is a different population. I
18 mean, it was already a fairly demanding -- you know,
19 3,000 patients, that's a fair number, and it doesn't
20 sound like it would be markedly different if you got
21 the right people, or what we think the right people to
22 assess cardiovascular risk is. Does that sound like --

1 and that's not that different from the number of people
2 that are in the first phase of the diabetes programs,
3 with the pooled data. It's the same neighborhood,
4 right?

5 DR. PARKS: That's correct. You're really
6 seeing a different type of patient population enrolled
7 in these programs now. Companies may not agree with my
8 saying this, but I think that in some ways it may not
9 necessarily be difficult for them to promote those type
10 of studies because it reflects the general patient
11 population. So, for example, they now have to enroll
12 an older patient population. A lot of these companies
13 are actually doing dedicated studies in renal impaired
14 patients of one-year duration. Or they'll have a
15 dedicated study where it's specifically in just high-
16 risk cardiovascular disease patients. That really
17 wasn't seen before the guidance.

18 DR. THOMAS: Dr. Rasmussen? If you could
19 also comment if you have any information about the
20 question

21 I --

22 DR. RASMUSSEN: Yes, thank you. I just

1 thought it would be appropriate for industry to give
2 its perspective as well. And I think -- I mean, you
3 accurately, on this slide, presented there are
4 different approaches to achieve the target number of
5 events. One of them is to somewhat drastically shift
6 the population, and I think that's what we're seeing in
7 column D up here with a very high-risk population.

8 I would say in the diabetes field, I believe
9 that it's most predominant to take kind of a middle-of-
10 the-road approach where the duration of exposure and
11 the patient numbers, like you mentioned before,
12 approximately are doubling and adding potentially a
13 year or two to the pre-approval assessment. And, I
14 mean, to the extent that anyone is interested in cost,
15 these things usually would cost around \$100 million.

16 (Off-mike comment.)

17 DR. RASMUSSEN: To expose twice as many
18 patients for 3 to 5 years.

19 DR. THOMAS: So just because part of that
20 wasn't on the mike, so it was \$100 million extra for
21 the increased number of patients.

22 DR. RASMUSSEN: I mean, it's different from

1 company to company, and depending on both the
2 population and how many assessments you make, but I
3 think that's a fair estimate.

4 DR. THOMAS: Thank you.

5 Dr. Goldfine?

6 DR. GOLDFINE: I'm going to address this and
7 then come back to the other point that I wanted to
8 make, and that's that I also think that you have a
9 physiologic problem when you move into these very high-
10 risk patients where we think that the weight loss may
11 have its benefit subsequent to the weight loss, so
12 there is a time lag between administering the drug and
13 the potential benefit, and when you move into the very
14 high-risk patients -- for example, those with renal
15 disorder or acute coronary syndrome, or whatever you
16 need to get to an event rate of 4 percent in today's
17 day and age -- you'll have an acute difference in the
18 risk-benefit because any risk would not have the
19 potential to have benefit in these very short- turnover
20 trials. So that's my one concern there.

21 The other comment that I actually had wanted
22 to make is there is sort of an unspoken comparison that

1 hasn't actually been brought up that I think is
2 important for the group to consider, and that's that
3 the use of the approved agents has really been only in
4 about 2.7 million people, so really a very small
5 minority of the individuals who have obesity in the
6 U.S. today, and I think that there has been difficulty
7 with some of their potential adverse effects and their
8 tolerability and the magnitude of the benefits so that
9 when people weigh that, they haven't really used them,
10 and I think that that bespeaks a real need and that we
11 really have very few options.

12 So what we're really comparing to in some
13 ways are the options of bariatric surgery, which have
14 only been touched upon. And if you look at the entire
15 use of sibutramine just using Dr. Wolfe's, there were
16 94,000 patients in 2009, well, well, under the numbers
17 of patients either having Roux-en-Y gastric bypass or
18 band, and there is acute morbidity and mortality
19 associated with surgery, many of them needing re-
20 operations, there are uncertainties on long-term risks
21 with potential for weight regain and the band slipping
22 and needing to be explanted and with the nutritional

1 absorptions with these procedures.

2 And if you compare, there was a device
3 meeting, I was not at it, but I did look at the
4 minutes, where basically based on the experience in the
5 population in 150 patients in an open one-year labeled
6 trial where the band was recommended to lower the
7 guidelines for BMI.

8 So I think when we actually consider our
9 risk- benefits, I think we actually also need to
10 consider what are our other clinical alternatives to be
11 offering to our patients, and I think that it's just an
12 important point. As we said, we all want a very good, a
13 very effective, and a very safe drug, and yet to really
14 have very clear knowledge is something that takes some
15 time and may need to be split between the pre and the
16 post.

17 DR. THOMAS: Dr. Kaul?

18 DR. KAUL: Thank you. My uncertainty -- or
19 maybe perhaps the better term should be my anxiety --
20 around Question Number 3 would be alleviated to some
21 extent if I knew if the FDA had firmed up its mind
22 about what to do with obesity drugs with a theoretic or

1 evident cardiovascular signal.

2 As I read the question, the question is
3 specific for the doubt of theoretic risk. Does it
4 imply that the FDA already has firmed up its mind what
5 to do with drugs that do have a signal?

6 DR. COLMAN: That is Question 2.

7 DR. KAUL: But that's not a voting question,
8 is it?

9 DR. COLMAN: No, but it gets to the heart of
10 for a drug that does have a signal and needs a trial,
11 we want your input in terms of various design elements.

12 DR. KRAMER: A follow-up to that answer, so
13 that doesn't address the issue about doing a meta-
14 analysis, it's only the design elements of the
15 cardiovascular outcome trial. So does that mean that
16 FDA, in the case where there is a signal, does not
17 think there should be a combined approach in terms of
18 incorporating a meta- analysis with the cardiovascular
19 outcomes trial?

20 DR. COLMAN: You're correct. The voting
21 question does explicitly mention either a
22 cardiovascular outcomes trial or a meta-analysis or

1 both. The implication in 2 is, as an example,
2 dedicated cardiovascular outcomes trial.

3 DR. THOMAS: Dr. Kaul, a follow-up?

4 DR. KAUL: I'm sorry to bring it up again. I
5 mean, if I read the statement, I'm still not sure if
6 the FDA has firmed up its mind. I can read the
7 statement to assume that you already have firmed up
8 your mind. It should be assumed that the sponsors
9 would be required to rule out.

10 DR. THOMAS: Can I just make a comment? That
11 would be the case already in one of the agents that has
12 come up for review where there is a question about
13 uropathy; right? And the company was forced to do
14 studies to look at renal disease during the development
15 process. Would that be what's being asked for?

16 DR. ROSEBRAUGH: So can you repeat your
17 question again, Sanjay? What is the question you have?

18 DR. KAUL: Well, the discussion item number 2
19 leaves me to assume that the FDA has already firmed up
20 its mind what to do with drugs that have some signal of
21 cardiovascular risk, whether that be heart rate or
22 blood pressure. I'm less concerned about the valve

1 issue because I think for sure, but I'm not quite sure
2 how to read this. I mean, especially in light of
3 question number 3, which is specifically without a
4 theoretic risk. So that's why I need some
5 clarification. I will feel a lot more comfortable
6 answering Question Number 3 if I knew what the FDA's
7 position is on the statement regarding discussion item
8 number 2.

9 DR. ROSEBRAUGH: Well, I'm going to preface
10 this by saying I'm fully loaded on antihistamines right
11 now --

12 (Laughter.)

13 DR. ROSEBRAUGH: -- so I may not be reading
14 number 2 the same way you're reading number 2, but I
15 don't have a suspicious mind right at the moment, and
16 so I'm reading number 2 to say if we think there's a
17 signal, we're going to ask them to do an outcomes
18 study. Is that what you wanted? I think you should
19 feel reassured that if there is a signal, we're going
20 to make them do an outcomes study.

21 DR. TEMPLE: But also the goal is not to
22 discuss today what constitutes a signal, so that

1 requires a certain amount of trust on your part, and
2 maybe you don't have it.

3 (Laughter.)

4 DR. TEMPLE: But this says if there is a
5 signal, and then Question 3 is, if there is no signal,
6 should you do something anyway? So 2 is about what the
7 nature of the study design should be, how do you like
8 various enrichment things? what do you do with the
9 people who drop out? you know, those kinds of
10 questions, assuming there has got to be a trial.

11 DR. KAUL: Thank you. My anxiety is
12 alleviated.

13 (Laughter.)

14 DR. THOMAS: So it's not "The X-Files,"
15 right?

16 Dr. Proschan?

17 DR. PROSCHAN: Yeah, I wanted to ask a
18 question. It sounds like it's not related to our
19 discussion, but it actually is, and that was something
20 Dr. Bray said yesterday about the fact that these diet
21 studies used to use crossover designs back in the '70s.
22 They don't do that anymore, and, Dr. Bray, you said you

1 agreed with that. I'm just wondering why you agree
2 with that. Is it because of the high dropout rate?
3 And might that be a way to get the dropout rate
4 lowered, if the people who initially went on a placebo
5 knew that they were going to get the drug afterwards?

6 And this actually is related to even trials
7 with a hard outcome, like cardiovascular events, even
8 though the conventional wisdom is that you don't do a
9 crossover trial in that kind of situation. But I'm
10 just wondering, for the reasons that you believe that
11 they don't do crossover trials anymore.

12 DR. THOMAS: Dr. Bray?

13 DR. BRAY: I still remember the discussion we
14 had in the DASH-Sodium study about crossover designs,
15 and the challenge was, how do you assess the initial
16 value of the second or third arms of that trial? And
17 with weight loss, where you get a lot of effect on
18 cardiovascular outcomes -- blood pressure, lipids,
19 glucose, insulin -- in that early weight loss phase,
20 when you cross over you've already got most of that
21 effect and you don't see it the next time around
22 because you've already come closer to the plateau, and

1 so whatever you do second is difficult to assess at the
2 beginning.

3 So that was the problem, and it was one of
4 the problems that the trials that have done a run-in
5 get into as well, but the crossover makes it even worse
6 because by the time you've crossed over 6 months or 3
7 months later you've already got much of the weight loss
8 that you'll get. So they really sort of faded out.
9 There are lots of them in earlier literature, and Eric
10 Colman I'm sure has read the same papers I have, there
11 are just lots of them, but they all stopped sometime in
12 the late '70s or even earlier than that, Eric, is that
13 right? Very few after that. I think that's my view of
14 why.

15 DR. THOMAS: Thank you.

16 Dr. Seely?

17 DR. SEELY: I wanted to get back to a
18 question about signal that I think might help all of us
19 who are having trouble with that not being part of
20 today's discussion. So one part of the question is in
21 the FDA's decision about what is a signal, why is there
22 a decision being made not to include the Advisory

1 Committee input into the signal? Because the Advisory
2 Committee will then be reviewing drugs where the
3 question of how we view the signal is going to be
4 important in terms of how we in the future review drugs
5 that come up.

6 And then the other is, is the FDA going to
7 make very clear to sponsors what you define as signals
8 so the sponsors can design their studies accordingly?
9 Because what signal you expect to see none of is going
10 to be very important in terms of how the entire study
11 is designed.

12 DR. HIATT: Can I jump in on the signal
13 question? I really think we have to trust the FDA's
14 judgment here because --

15 DR. THOMAS: Well, can you let Dr. Colman and
16 then --

17 DR. HIATT: Okay.

18 DR. COLMAN: Yeah, that's a tricky issue.
19 The emergence of a potential signal can come anywhere
20 from the animal studies that companies do before they
21 even send in the drug to FDA to the later stages of a
22 phase 3 program when they're about ready to submit

1 their NDA. So ideally, if there is a real signal of
2 concern, you want to identify it certainly by the end
3 of phase 2 meeting before they develop their phase 3
4 program.

5 So, you know, for them, we may see a blood
6 pressure effect in their phase 2 trials and say, look,
7 that's enough of a concern, we think that this may
8 require an outcomes trial. So we would like to
9 identify the signals prior to the initiation of the
10 phase 3 program because obviously companies don't want
11 to go through a full phase 3 program and then send in
12 their NDA and then be told, "Oh, by the way, you have
13 to do an outcomes trial."

14 DR. SEELY: I'm still not sure how that will
15 let sponsors know how to design -- whether starting
16 from the animal to the clinical, wherever they are
17 designing it, unless you make clear what signals you're
18 going to count, how are they going to design the
19 studies to be able to pick up those signals?

20 DR. COLMAN: Well, as it stands now, we look
21 at the traditional risk factors; in other words, we
22 would look at blood pressure, we would look at pulse,

1 we would look at all the various lipid parameters,
2 glucose/insulin sensitivity, and we would have that
3 data by the end of the phase 2 studies. So, you know,
4 we have a group of factors that we look at, and that
5 would allow us to get some sense of whether or not we
6 needed to have a discussion with the company along the
7 lines of this may require future study in an outcomes
8 trial.

9 DR. THOMAS: Dr. Temple?

10 DR. TEMPLE: I think what's making everybody
11 nervous is that we don't always know what the right
12 signal is. So that's why the questions are arranged
13 this way. Number 2 is about there's a signal, in our
14 wisdom, we think there's a signal, the heart rate is up
15 or whatever those things are, it's like what we've seen
16 before. Question 3 is about maybe you're not smart
17 enough to know what a signal is; maybe you should
18 always do this. That's sort of the position Dr. Wolfe
19 took based on past experience, and that's the question
20 that's being posed.

21 You're right to worry about what's a signal
22 here. I mean, I'm not sure we know what did SCOUT in.

1 Is it the 1 to 3 millimeter mercury of blood pressure
2 that did it or is it something else? I don't think we
3 know. We frequently don't know until later what a
4 proper signal is, but this says if something that makes
5 you nervous that looks sympathomimetic or does one of
6 these things, what's the best kind of study? That's
7 what Question 2 is.

8 And Question 3 is, suppose that I don't see
9 any of those, but I'm aware that I don't always know
10 what the right answer is, should there be a study
11 anyway? I mean, in diabetes we said there's a study
12 whether there's a signal or not because it's a high-
13 risk population, things have gone bad, we've had
14 trouble, we should always get it. That's the position
15 taken there, and that's what these questions are
16 getting at. But, I mean, you're right to be nervous
17 about what a signal is; it's very hard to know.

18 DR. THOMAS: Dr. Hiatt?

19 DR. HIATT: Well, this may seem redundant,
20 but actually I'm not agonizing about that too much
21 because I don't think people on these committees have
22 the purview of looking at an NDA or end of phase 2

1 materials like you do, and we have to trust your
2 judgment, and we can't always know. It would be
3 astounding if a new drug that looked like sibutramine
4 didn't raise a signal for people because that has an
5 outcomes trial that clearly identifies that as a
6 problem. But there may be a constellation of other
7 things, and I don't think, as a Committee member, we're
8 really in a position to understand that unless the FDA
9 brings that forward to us in a way that we can help
10 interpret it. But I'm not going to agonize too much
11 about it. There may be shades of gray, but it's hard
12 for us, unless we have that same kind of experience, to
13 make that judgment.

14 DR. THOMAS: Dr. Savage?

15 DR. SAVAGE: I have a question about the
16 implementation of the diabetes guidelines in the sense
17 that it may provide a model for some of the things
18 related to obesity studies. Prior to the development
19 of those guidelines, one of the problems was that if
20 something was identified, you would go back and look at
21 the older data and find all sorts of gaps and little
22 bits and pieces of signals that hadn't triggered as

1 something, but then if there was a decision to go ahead
2 and have a study conducted, there was another gap that
3 could be a year or two while the company negotiated,
4 appeared to negotiate, with the FDA to actually design
5 a study and then get it implemented and so forth, so
6 that for rosiglitazone, for example, in the last
7 meeting we had, if I recall correctly, it was going to
8 be 2016 or '17 before they would have the results of
9 the study that was being conducted.

10 Have you been successful in being able to
11 shorten the time, so that if you decide that there is a
12 need for a post-marketing survey, that you get started
13 right at the time of the approval or as close as
14 possible and so that there is a reasonably short time
15 period before additional data are available?

16 DR. PARKS: So I think what you're alluding
17 to here are FDA's authorities under the Food and Drug
18 Administration Amendments Act, FDAAA. With these
19 trials -- well, before that, you're right, we didn't
20 have the regulatory authority to make them do these
21 studies and actually hold their feet to the fire there.
22 You might want to say that they were more voluntary; if

1 they didn't do it, there really wasn't much in terms of
2 regulatory teeth that we could go after them.

3 Under FDAAA, these are required studies, and
4 we also set timelines in which their final protocol
5 must be submitted to us. I can't remember the second
6 timeline, but the third one is when the study actually
7 has to come in. Our experience to date with the
8 diabetes PMRs, post-marketing required trials, in
9 general, it is about 5 years from the time that we
10 approve the application with the PMR to the time that
11 the study has to be submitted to us for review.

12 To answer your question on whether or not
13 we've seen success, well, as you heard yesterday, we
14 haven't had a program to meet the 1.3 yet, so I can't
15 say whether we've met success in that area with respect
16 to success in getting them to meet the initial
17 timelines. Yes, most of the companies recognize that
18 to be able to do this in that timeline, they'll
19 probably have to initiate the trial even before the NDA
20 or BOA has come in. Dr. Alexander is nodding over
21 there. I don't know if he's worked with some of these
22 companies. And certainly getting them to submit the

1 protocol, there may be some delays or there are
2 difficulties in enrollment, or event rate is a little
3 bit lower, but I think for the most part the companies
4 have actually been adhering to that.

5 DR. THOMAS: We will now take a 15-minute
6 break. Panel members, please remember that there should
7 be no discussion of the meeting topic during the break
8 amongst yourselves or of any member of the audience.
9 We'll resume at 10:15 a.m. Thank you.

10 (Break.)

11 DR. THOMAS: We will now continue the panel
12 discussion portion of the meeting. Although this
13 portion is open to public observers, public attendees
14 may not participate except at the specific request of
15 the panel.

16 Dr. Parks, you had some comments for the
17 panel?

18 DR. PARKS: Yes. So I wanted to provide some
19 clarification on these two discussion points and then
20 the final voting question.

21 For discussion point one, what we're asking
22 the panel members here is that -- and you've already

1 heard there is going to be a lot of testing, extensive
2 testing, pre-clinical phase 1 studies to help define
3 the safety profile of the drug, not only cardiovascular
4 signals. But beyond that, now we're asking the panel,
5 into their phase 2 and 3 program, to help enhance the
6 detection for a cardiovascular safety signal, should
7 these phase 2 and 3 programs be designed in such a way
8 that we can enrich them -- and you have an example here
9 of individuals at higher risk for CV events, and also,
10 very importantly, to have some sort of a prospective
11 assessment of these cardiovascular events, and put
12 together in a meta- analysis? I'm not talking about
13 any sort of risk margins, so we're not asking you to
14 discuss about 1.8, 2.0, or whatever, but whether or not
15 the phase 2 and 3 programs essentially will be designed
16 just like the diabetes phase 2 and 3 programs
17 currently. So that's discussion point number one.

18 Discussion point number 2 is assuming that we
19 hear from you from the phase 2 and 3 program how to
20 identify this cardiovascular signal -- and we have
21 already identified it -- you've heard that they will be
22 required to do a pre-marketing cardiovascular outcomes

1 trial -- is for you to now discuss, provide us some
2 guidance as to the design of the trial, the patient
3 population, the analysis population, et cetera.

4 And then Question Number 3, which is a voting
5 question, now that we know how to define signal, we've
6 ruled it out, so you have a drug that doesn't have a
7 theoretical risk, do these products here also have to
8 do some sort of assessment here? There's a CVOT or a
9 meta- analysis of phase 2 and 3 trials.

10 Just to remind the panel here -- and some of
11 you were at the Diabetes Advisory Committee in July
12 2008 -- that that similar question was raised, and a
13 lot of the diabetes products to date do not have a
14 theoretical risk, but many felt at the time, because of
15 the patient population in which diabetes drugs are
16 being used are at high risk for cardiovascular disease,
17 that you agreed that it should be done. Now, take that
18 into consideration as you weigh into voting Question
19 Number 3.

20 Does that clear things up for the panel
21 members?

22 Yes.

1 DR. THOMAS: Thank you, Dr. Parks.

2 If we can have the -- there's an FDA backup
3 slide, and I think, Dr. Soukup, you are going to
4 present that?

5 DR. SOUKUP: Yes. Yesterday there was some
6 question in relation to the point estimate and how it
7 relates to the margin, and should we be considering the
8 point estimate? And Dr. Zalroot (ph) had addressed
9 this in his conversation, and this I think is just a
10 little bit more of the illustration of the words he
11 used, is when we power these trials, we can power it
12 for a specific relative risk margin, as is presented
13 here on your X axis. But we also know when we power
14 these trials what the maximum value of the point
15 estimate can be in order to meet that risk margin, and
16 that we're showing on the Y axis. And also at the top
17 of the slide you'll these are the number of events to
18 actually get to that relative risk margin or rule that
19 out.

20 So, for example, if you really want your
21 relative risk margin, the point estimate, to be below
22 1.1, in essence you're requiring that the trial rule

1 out a relative risk margin of 1.1, and that's going to
2 require 4,600 events. So if you're really making
3 restrictions on what you want that point estimate to
4 be, your trials are going to become very large very
5 quick, and if you want it to be around 1.

6 So here you can also see is if you're looking
7 at ruling out 1.8, the maximum value that point
8 estimate can be is around 1.25, it's not really
9 specifically shown there, but that's what you're -- we
10 know when we power these trials.

11 DR. THOMAS: Thank you.

12 Dr. Hiatt?

13 DR. HIATT: So a question on that actually,
14 and this is more, I guess, a clinical question, but
15 there are two perspectives on the point estimate part
16 of the discussion, which I think was challenging a
17 little bit yesterday because we focused on the upper
18 boundary, but if we're simply here today to rule out
19 risk, then I'm assuming that the real point estimate is
20 1.000, if you studied enough patients, and simply then
21 it's a matter of how many patients with events you
22 acquire to bound the upper boundary, if we're assuming

1 that there is really zero risk.

2 If there is actually a 5-percent increase in
3 risk, that that's the real point estimate, we might
4 rule out that upper boundary easily with enough events,
5 but we might actually have a drug that might have a
6 slight amount of actual risk. But the current guidance
7 says that the risk should be reduced, and so it says
8 that the weight loss should be associated with
9 reductions in -- I think the quote is cardiovascular
10 morbidity and mortality -- in which case I'm assuming
11 the actual hazard ratio is a little less than 1, maybe
12 .9 or .95, not enough less necessarily to warrant
13 looking for a claim for cardiovascular protection
14 because I know that would be extremely hard from a
15 numbers game.

16 But I guess, from an operating point of view
17 here, are we really framing the question as the drug is
18 entirely neutral? Because if it is, then we'll rule
19 out a certain amount of risk and feel good about that,
20 but then you can't take that drug because you assume
21 that there's a cardiovascular benefit to taking that
22 drug, you have to lose weight on that drug and achieve

1 some other benefit, which might be better mobility or
2 less sleep apnea or things like that, but it certainly
3 wouldn't be that that drug is somehow achieving a
4 cardiovascular benefit as we presume could happen with
5 dramatic weight loss such as bariatric surgery.

6 So I think the point estimate matters a lot.
7 In my mind, I really wouldn't want an obesity drug to
8 have a point estimate above 1. I think if it's neutral
9 on 1 and there are other benefits that are clinically
10 appreciated, then knowing that it doesn't cause harm is
11 really what we're here to talk about, but ideally the
12 drug, if you lose weight effectively, there should be
13 some cardiovascular benefit to weight loss, in which
14 case the real point estimate should be somewhere below
15 1. And I guess the current guidance says benefit on
16 cardiovascular morbidity and mortality. Is that the
17 perspective we should have? Is that where the point
18 estimate really should lie? Or are we okay if it's
19 just at 1 and then there is other evidence from the
20 development program that beyond just losing 5 or 10
21 percent, that there is some other clinical benefit to
22 weight loss besides just losing the weight?

1 DR. COLMAN: Yeah, the guidance talks about
2 the improvements in the cardiovascular biomarkers for
3 the weight loss, and that's how the 5-percent reduction
4 came about, because in 5- to 10-percent weight loss,
5 depending on the drug, you do see favorable changes in
6 lipids, in blood pressure, and glycemia. Now, granted,
7 with the weight loss that we've seen over the years
8 with the drugs that we've had, those changes are
9 relatively small. So on an individual level, it would
10 probably do very, very little in terms of lowering
11 their actual risk for an event. Population-wide, you
12 would assume it would have a benefit.

13 So we didn't write the guidance and use those
14 words to assume that if the drug is approved and it
15 shows favorable changes in these biomarkers, that that
16 is going to reduce your risk for heart disease. Again,
17 it would be a degree of weight loss, the degree of
18 change in the biomarker, is the key aspect there.

19 DR. HIATT: So that's an important
20 clarification. So your assumption at the time you
21 wrote that was that these drugs wouldn't necessarily
22 provide cardiovascular benefit, that really what we're

1 thinking about is excluding cardiovascular harm;
2 correct?

3 DR. COLMAN: Well, again, if there were
4 modest reductions in all of the biomarkers, and you did
5 a study that was large enough and long enough, then you
6 would expect to see benefit.

7 DR. HIATT: Okay, and if you did, of course,
8 and you're still bound by an upper boundary if the
9 point estimate is less than 1, then that will help drag
10 down the upper boundary and you'll need fewer events to
11 get there, which would be a good thing numerically.
12 But I guess in trying to answer these questions today,
13 I would be comforted to think that weight loss provides
14 clinical benefit, not just weight benefit, and I think
15 that cardiovascular benefit should be considered
16 strongly as a beneficial attribute of a pharmacologic
17 therapy for weight loss.

18 I realize that it's hard to demonstrate that,
19 and, therefore, if the point estimate doesn't
20 demonstrate some evidence of bio-creep, that it's sort
21 of we're letting drugs on the market that raise the
22 risks 5 percent, 8 percent, but certainly well within

1 the boundary that we're worried about excluding. That
2 creates and poses a different situation, whereas if the
3 true hazard ratio is 1.000, then we've excluded
4 cardiovascular harm and we've excluded cardiovascular
5 benefit, and now I think that the challenge to
6 approving that drug is what other clinical benefit is
7 achieved in the absence of cardiovascular benefit.

8 So I think the point estimate matters a lot
9 in terms of being bad if it's bio-creep and you're kind
10 of getting one drug on and then you have a non-
11 inferiority design someplace down the line, and now
12 your drug looks just like that drug, but maybe they're
13 all causing harm, versus the idea that with effective
14 weight loss, there really should be benefit.

15 DR. THOMAS: Dr. Temple, is it possible, I'm
16 just going to ask a question to add on to that?

17 DR. TEMPLE: I didn't hear --

18 DR. THOMAS: Some of these benefits from
19 weight loss may be seen many years after a trial is
20 completed, so is it necessary to see the benefit during
21 the course of the trial as long as doctors are going --

22 DR. TEMPLE: Well, I think that's a good

1 point and it's part of what I was going to say. I
2 mean, it's worth remembering that nobody has shown that
3 control of diabetes better has these benefits. I think
4 one of the main problems is that you're not operating
5 in a vacuum. If the people in this trial have a notably
6 elevated blood pressure, it's going to get treated. If
7 their lipids are very abnormal, those are going to be
8 treated. Their diabetes is probably going to be
9 treated. So you're trying to show improvement when
10 everybody is trying to do the right thing for all the
11 patients, which makes it very tricky. And, you know, I
12 don't know why nobody has ever shown a benefit from
13 better control of diabetes, but I think the main reason
14 is you're comparing a hemoglobin A1C of 7 with 6.5, not
15 10 versus 6, maybe that would show a difference, but no
16 one will let you do that trial, quite appropriately.

17 So if you just look at the point -- I mean,
18 it's worth noting that if the point estimate, if the
19 true point estimate, is 1, half them in your trial it's
20 going to be above 1 and half the time it's going to be
21 below 1, and Dr. Proschan can get into that more. So
22 if you really insisted on that, then you would

1 obliterate half the drugs that have no adverse effect
2 at all, which is why we work with confidence intervals
3 and stuff like that, but you're right, it could be
4 making it slightly worse when you rule at an upper
5 bound.

6 And the other thing that's always been part
7 of my worries, we don't know how long these things
8 take. I mean, we know that treating, lowering, blood
9 pressure works very fast, you know, within a year you
10 see a benefit, and oddly enough, that's true for
11 lipids, too, but it certainly hasn't been true for
12 blood sugar control, and who knows why? So we have not
13 said you have to be beneficial, so far.

14 DR. THOMAS: Dr. Proschan?

15 DR. PROSCHAN: Yeah, I mean, related to that
16 point, I think since you would expect long term,
17 anyway, benefit on cardiovascular events, if you had
18 proof that the point estimate was above 1, then that
19 should be the end of the story, that should be game
20 over, and so I think you don't want to just look at the
21 upper confidence interval. If the lower confidence
22 interval is above 1, then I think that's game over.

1 Now, the FDA has addressed that by talking
2 about a reassuring point estimate, which there was some
3 discussion about what that really means. I guess it's
4 sort of like pornography: you know it when you see,
5 but --

6 (Off-mike comment.)

7 (Laughter.)

8 DR. PROSCHAN: Jazz? Okay.

9 (Laughter.)

10 DR. PROSCHAN: But, so I do think that should
11 be part of the criteria for passing, is certainly the
12 lower confidence limit should not be above 1.

13 DR. THOMAS: Dr. Hendricks?

14 DR. HENDRICKS: I agree with Dr. Hiatt, that
15 an ideal obesity drug would provide cardiovascular
16 benefit for the patients that need it. So a lot of
17 these patients that come into a clinic, if you look at
18 my clinic population, only about 15 percent of the
19 patients that come in have normal blood pressure. Over
20 half of them have pre-hypertension, and about a third
21 of them have hypertension.

22 If you recall the QNEXA trials, when they

1 looked at the whole group of patients in the trial,
2 they got some small decrease in systolic blood
3 pressure, but when they segregated out the
4 hypertensives, they got a striking decrease in blood
5 pressure, and we found the same thing in our patients,
6 that if we segregated the patients by initial blood
7 pressure, by initial JNC-7 category, that the
8 hypertensive patients that lost weight had really
9 significant declines in blood pressure, and those
10 persisted for a long time. The pre-hypertensive
11 patients had less of a decline, and the normal blood
12 pressure patients didn't have any decline. So when
13 you're looking at cardiovascular benefit, I think you
14 have to segregate the patients and the ones that are at
15 risk and the ones that are not necessarily at risk.

16 And that brings me to Question 3. Because
17 Question 3 bothers me a little bit, I would make it
18 into two questions. I mean, I would say, do you
19 believe obesity drugs that have no signal need to have
20 a cardiovascular outcome trial? And then do you
21 believe that drugs that have a positive signal, in
22 other words, that show, like QNEXA did, a positive

1 benefit? Now, QNEXA was complicated because there was
2 a heart rate issue, too, but let's suppose you had a
3 drug that you were able to demonstrate in phase 2
4 trials that the hypertensive patients had a decline in
5 blood pressure and there were no other signals, I would
6 say that type of drug probably doesn't need to have a
7 cardiovascular outcome trial.

8 So I'm going to have a hard time voting on
9 number 3. I mean, at the moment, I would probably say
10 no because my hypothesis is that when we get a good
11 drug, we're going to find that the relative risk ratio
12 is less than 1.

13 DR. THOMAS: Thank you.

14 Dr. Brittain?

15 DR. BRITTAIN: Yeah, I guess I just wanted to
16 make sure, I guess maybe I'm a little confused. The
17 relative risk that you can rule out with these 3,000
18 population study is nowhere like what we're talking
19 about here. And maybe I can get the statistician to
20 verify this, I think it's like 5 or something,
21 depending on what the event rate is, of course, but I
22 think it would really be helpful, this talks about in

1 terms of events, it's a little hard to see what the
2 sample size would be, the person-years would be, but
3 say you wanted to rule out the 1.8 that we've heard
4 about, that would take far, far more person-years than
5 the 3,000 unless you had a much, much elevated event
6 rate. But I think, if I understood correctly, like if
7 you had the current event rate of 05, for example, it
8 would only rule out about a relative risk of 5, and
9 even if it was an 015, it would only go down to about -
10 - be able to rule out a relative risk of 2.5. So I
11 think we should have a clear understanding of what you
12 can get with the current study size of 3,015 -- I mean,
13 of 1,500, and what you would need if you wanted to rule
14 out 1.8, assuming different event rates.

15 DR. SOUKUP: Right. You are correct that the
16 current guidance, as it says for sample size, you are
17 not going to get anywhere near some of these numbers
18 here. And also the calculations I think you were doing,
19 you maybe assume there is one-year follow-up for the
20 4,500 total subjects, and then we know that's much less
21 because dropout we're expecting to be around 50
22 percent. So even the patient-years you're seeing is

1 going to be smaller, so I think it's even a little more
2 dismal than the scenario you're presenting, and that's
3 the task that we're trying to figure out.

4 DR. BRITTAIN: And I want to clarify, I mean,
5 to add to what we talked about yesterday, 50-percent
6 dropout is not acceptable. I mean, it doesn't just
7 affect the sample size and the power, it affects the
8 validity of the results.

9 DR. THOMAS: Dr. Soukup, can you just
10 identify yourself for the record?

11 DR. SOUKUP: Oh, Matt Soukup.

12 DR. THOMAS: Dr. Temple?

13 DR. TEMPLE: Matt, if they did enrich the
14 population with people at higher risk, my assumption is
15 that 3,000, 1,500, might very well be able to rule out
16 a hazard ratio of 2 or something in that neighborhood.
17 Isn't that what we think?

18 DR. SOUKUP: I think if we get the follow-up
19 we need and the patient-years, I think we could get
20 there with that number, but, again, we'd have to work
21 with some of it and figure out dropout rates and what
22 the planned event rate is, but --

1 DR. TEMPLE: Right, it's true, but, I mean,
2 one of the hopes is that you'll be able to keep people
3 on the drug for longer than now. I mean, maybe we can
4 have a law that says they have to stay in the trial.

5 (Laughter.)

6 DR. TEMPLE: No, no, that wouldn't pass.

7 DR. BRITTAIN: If I could follow-up.

8 DR. THOMAS: Yeah, you can follow up.

9 That would probably have to go to the Supreme
10 Court to see if it was okay.

11 (Laughter.)

12 DR. BRITTAIN: Just to follow up, is there
13 any possibility that you would be able to construct a
14 slide over lunch -- I don't know if it's possible --
15 that just presents some of these varied just nitty-
16 gritty questions -- I mean, answers that we want, like
17 with the 3,000 and 1,500, what relative risks you can
18 rule out under different event rates? And it doesn't
19 have to be extremely complicated, but for a few options
20 and also again assuming -- you can assume -- when you
21 assume there is a benefit, you can really drop that
22 sample size down, and so that might be a way to also

1 think about it.

2 DR. THOMAS: So would the table that was
3 included with the corrections be sufficient to answer
4 that, the ones that we got in our briefing documents?

5 DR. SOUKUP: Yeah. I don't know if that will
6 specifically get into the 4,500 patient-years
7 specifically, but I can try to put something together
8 over lunch and run these through and display where
9 you're at with about the 4,500 with assumptions on what
10 the dropout rate would be and what the event rates
11 would be, and I can present that.

12 DR. BRITTAIN: Thank you.

13 DR. THOMAS: Dr. Konstam?

14 DR. KONSTAM: Yeah, a couple of comments.
15 First just maybe as we go on with this discussion make
16 clear what we're talking about, whether we're talking
17 about study drug discontinuation or we're talking about
18 lost to follow-up and just maybe use terms that are
19 really clear about that so we know what we're talking
20 about. And I would say that just on that point, I
21 mean, what I understand is that obesity is a chronic
22 disease, that if you stop taking the drug, generally

1 there has been a loss of the benefit.

2 And so I'm not clear why -- I mean, it just
3 seems clear to me that we absolutely need to have
4 sponsors assure that patients remain on the drugs
5 through a substantial duration of the period of
6 investigation, particularly if we're asking about
7 safety issues. So I think to me that's a given.

8 DR. BRITTAIN: Can I -- I don't know if you
9 were responding to my question.

10 DR. KONSTAM: Well, I had other -- why don't
11 you -- well, go ahead. I mean, I had another point I
12 wanted to make, but go ahead.

13 DR. BRITTAIN: Yeah, just to make it clear, I
14 was referring to whether you have the outcome, when I'm
15 talking about follow-up, I'm talking about whether you
16 have the outcome. If you discontinue, that's fine; if
17 you discontinue your treatment, that's fine. I'm
18 saying when I talk about 50-percent follow-up, 50-
19 percent follow-up on the outcome is what would really
20 concern me.

21 DR. KONSTAM: Okay, yeah. I know you know
22 what you're talking about, I have no doubt about that,

1 it just would help us to really be clear which of those
2 we're talking about. But to that point, if we're
3 interested in safety, then we have to have patients on
4 the treatment. You know, if you assume that there is an
5 adverse safety effect and you allow patients to
6 discontinue study drug, and then say we're okay because
7 we've got their outcome out to a year, that's not
8 right, and I know you would agree with that. You
9 wouldn't agree with that. Okay. But that's the way I
10 feel about it. Okay. So that's one thing.

11 But I just wanted to just say, I think this
12 is a terrific slide, and I think it's really helpful to
13 me and probably the rest of the panel. You know, the
14 point that I was trying to make yesterday, and Michael
15 has been really a proponent that just looking at the
16 upper confidence boundary as having blinders on, you
17 really have to look at the entire data and the entire
18 set of information that that information is giving you.

19 One of the pieces of information is actually
20 the point estimate, and I guess I would just still come
21 back to that this slide nicely illustrates that you can
22 rule out, with 95 percent confidence, an upper boundary

1 of 1.8 with whatever it is, 140 or some events, and you
2 could get there with a point estimate of 1.2 or 1.25,
3 and I guess -- I'll just speak for myself -- for me, if
4 I was looking at an NDA that had an upper boundary of
5 1.75 but had a point estimate for excess mortality of
6 1.2, we're talking about safety like the drug kills you
7 if we're talking about mortality as the endpoint. I
8 would not recommend approving that drug. And I guess
9 that really was the point I was making. I think it
10 would harm the Committee's thinking to feel like if we
11 say an upper boundary of 1.8, we're saying that's an
12 automatic approval, and I know nobody is saying that,
13 but I think if people are thinking that, that would
14 keep us from accepting that high number.

15 One more point I was going to make, and I
16 know we're going to come back to this when we talk
17 about relative risk versus absolute risk, and we
18 haven't gotten into that yet, but what I would be
19 thinking when we get to that discussion is, okay, we
20 have a population that has a very low event rate, and,
21 therefore, a given excess relative risk is going to
22 translate presumably, assuming it applies to that whole

1 population, is going to translate into a very small
2 absolute excess rate, which may be something that we
3 would be willing to tolerate, and I guess the example
4 that comes to mind is oral contraceptive agents.

5 So there is a set of agents that I think we
6 all know increases the probability of thromboembolic
7 events, but it's used in a population that has such a
8 miniscule event rate that that translates into a
9 miniscule absolute excess risk. Now, of course, we
10 give warnings, if you smoke, if you have type 1
11 diabetes, et cetera, et cetera, you don't want to use
12 it.

13 So I think -- you know, I mean, I hope my
14 thinking is right -- that we could accept, if we go to
15 this high-risk population to enrich it, we could still
16 wind up saying, okay, that probably translates into an
17 acceptable upper absolute boundary in a very low-risk
18 population, and we will provide a limited, you know, a
19 restricted, approval for that population. At least
20 those are my thoughts. I don't know.

21 DR. THOMAS: Dr. Waters is going to be the
22 last question for this clarification, and then we'll

1 move on to Question 1.

2 Dr. Waters.

3 DR. WATERS: Thank you. I have a question
4 for Dr. Colman that originally developed when you
5 talked about CRESCENDO and SCOUT yesterday, and it sort
6 of involves the whole issue of cardiovascular outcome
7 trials, and they served us really well in cardiology,
8 they brought a lot of good data to get drugs approved,
9 but they also informed clinical practice, so a
10 physician could say, well, the patient in front of me
11 is like what was in the trial and therefore this drug
12 is useful, and medical practice sort of advanced. And
13 it's sort of like now the tool that we have isn't
14 working as well for the problem we have at hand. It
15 works quite well for chronic risk factors, like
16 hypertension and diabetes, and Dr. Parks has mentioned
17 now that the patients in diabetes trials are much more
18 like the patients in practice, so that's a good thing.

19 But going to obesity, first of all, you have
20 a problem with enrichment, and that's a problem for
21 pretty much all outcome trials now in cardiology, but
22 you have to really enrich a lot to get from below 1

1 percent up to the level where a trial is feasible. You
2 also have a drug that's often given short term, so
3 ideally you might want to do a trial with a very large
4 number of patients but just a 6-month or a year follow-
5 up, but then you've got benefits that might be long
6 term where the harm might be short term, you've got a
7 huge problem with dropouts in a lot of the studies that
8 have been done up to date, and I just wonder if you
9 acknowledge that the tool that we're using,
10 cardiovascular outcome trials, it may be the only tool
11 that we have, and I'm not suggesting there is something
12 better, but it really isn't optimal for the situation
13 that we're looking at. I was trying to think of an
14 analogy. It's sort of like we're trying to build a
15 house with a knife and a fork, it's not quite exactly
16 what we need.

17 DR. COLMAN: Yeah, I think those are good
18 points. Let me just go with a hypothetical and let's
19 say that the CRESCENDO trial ran to completion and it
20 met its original objective and it was actually shown to
21 reduce the risk for MACE and maybe even cardiovascular
22 death. I think if that were the scenario -- and the

1 target population in CRESCENDO were really middle aged
2 individuals who had abdominal obesity, really going
3 after people with metabolic syndrome, which is quite
4 prevalent. So I think if that trial had been successful
5 and it was shown to reduce the risk for MACE, you would
6 have seen the use of that drug grow among different
7 demographics.

8 So I think currently, with the current crop
9 of weight loss drugs that we have and that we've had in
10 the recent past, that has led to a fairly narrowed use,
11 on the one hand, and a fairly narrowed demographic, but
12 I think as we head in and we head towards approval of
13 drugs that cause more weight loss and that have
14 tolerable side effects so people just don't go on and
15 off, on and off, I think we will start to see longer
16 term use, and therefore we'll see people who may start
17 off at 48, but they're not going to be 48 forever, so
18 they're going to get older, and I think once a company
19 shows that a weight loss drug can reduce the risk for
20 cardiovascular disease, that will change the whole
21 landscape.

22 DR. WATERS: Yeah, I think that makes sense.

1 You're talking about a drug that's much different than
2 a lot of the drugs that you've dealt with in the past.

3 DR. COLMAN: Right.

4 DR. THOMAS: Thank you. We're going to now
5 move to Question 1. The current draft obesity drug
6 guidance document recommends that at least 3,000
7 patients be randomized to investigational drug therapy
8 and at least 1,500 to placebo in one-year phase 3
9 trials. To date, most of the patients enrolled in the
10 phase 2 and 3 clinical trials for investigational
11 obesity drugs have very low short-term risk for major
12 adverse cardiovascular events -- example, less than 5
13 percent per year. Discuss the potential strengths and
14 weaknesses of enriching the phase 2 and 3 clinical
15 trials of overweight and obese individuals at higher
16 risk for CV events -- example, history of myocardial
17 infarction, stroke, multiple risk factors -- and
18 performing a meta-analysis of prospectively adjudicated
19 MACE.

20 Dr. Weide?

21 DR. WEIDE: Yeah, thanks. These are the same
22 comments I was going to make earlier, so we would have

1 just got pushed over here.

2 A clarification on a comment that was made
3 earlier that diabetes trials don't show any protection.
4 That's not true. Both the EDIC and the long-term U.K.
5 PDS clearly show improved cardiovascular protection,
6 which is called metabolic memory or the legacy effect.
7 Also, these patients got treated early at the time of
8 diagnosis. All the other studies that don't show this
9 were people who got treated later. It also took 10, 15
10 years to see an effect. This may be something that is
11 also relevant to this same population of obesity.
12 We're looking at short-term things when the effects may
13 be long term.

14 Enriching the population for a study to
15 increase event rates so that we can get the numbers
16 that we're looking at in this situation being asked for
17 in Question 1 seems reasonable. Implying that any risk
18 in this population that's older does not apply to
19 younger patients I think is a little naive. The
20 triggers are going to be the same if we're treating
21 those patients. Younger people may tolerate it, it may
22 take a while to show up, but we're probably doing the

1 same bad things to them that we would be doing in
2 somebody who is older to start with and already has
3 some cardiovascular events. So I think it's perfectly
4 reasonable to do that.

5 My concern is about the length, and not just
6 talking about patient-years of exposure; that concerns
7 me. My cardiovascular colleagues here know this much
8 better than I do, but as I understand it, when you do a
9 treatment, you do something, we put people on a statin,
10 it takes 3 to 5 years to stabilize the plaques, things
11 happen, they may regress. That first year -- I mean,
12 these one-year studies on statins don't tell us a whole
13 lot. So if we're looking at a one-year study, maybe a
14 two-year extension with dropouts of 50 percent, are we
15 really going to get the information we want? Because
16 we may be doing good things with these things that are
17 not going to be demonstrated for 3 to 5 years, and
18 that's a major, major concern to me, and I'm not sure
19 how to address it.

20 I mean, if we look at what happened in the
21 diabetes drugs, it looks like it's taking those trials
22 6 or 7 years, so if we use that 6-, 7-year process that

1 was shown to us, you can do a 4-, 5-year study and try
2 and get to the heart of some of this stuff. Does that
3 delay things? Yes, but no more than we're doing with
4 the diabetes drugs. You can argue whether that's right
5 or wrong, I don't know that we want to go there, but I
6 think I'm really, really concerned that if we're just
7 looking at one year, we're going to be missing the
8 point and some of the benefits of some of these drugs.
9 So I would urge people to think about that. I
10 certainly have no problem with enriching the
11 population.

12 DR. THOMAS: Dr. Seely?

13 DR. SEELY: I also think it's reasonable to
14 enrich the population as long as we keep a couple of
15 factors in mind. So one is the point Dr. Konstam
16 brought up of not extrapolating the risks that we see
17 in older individuals to a potential target population.
18 And I don't think we can assume that what we see in the
19 older population is what we would see in the younger
20 population in terms of even estimating a magnitude, you
21 know, reduction of putting in a mathematical model of
22 how you would recalculate risk because when you treat

1 people who already have more progressive disease, you
2 may be doing something when you treat than treating
3 people with earlier disease in terms of what Dr. Weide
4 was mentioning, and I think estrogen has taught us a
5 good lesson at that.

6 So when you give estrogen to women who are 65
7 and older, you cause some issues, and we reached a
8 point where it was hard to give women who were 50 any
9 estrogen prescriptions where there may be benefit to
10 them because a large study showed that there was no
11 cardiovascular benefit or maybe even harm in women 65
12 or older, and I don't want us to get into the same
13 situation with obesity drugs.

14 DR. THOMAS: Dr. Brittain?

15 DR. BRITTAIN: Yeah. I guess, again, I'm a
16 little confused by this question. If it's talking
17 about setting a margin and if that's the implication of
18 enriching, there would be a margin set, and again I
19 guess I would kind of repeat what I said a little while
20 ago, that I want to have a really clear understanding,
21 or I think everyone should have a clear understanding,
22 of what you really can get with given sample sizes and

1 given follow-ups with the enrichment. I mean, if the
2 enrichment isn't really going to give you that much,
3 that needs to be understood. So I think it needs to be
4 thought of in terms of the actual ability to rule out a
5 particular relative risk.

6 DR. THOMAS: Dr. Yanovski?

7 DR. YANOVSKI: So I wanted to agree, of
8 course, with everybody that the only practical way to
9 get the event rates sufficiently high to detect signals
10 and a reasonable confidence interval is going to be to
11 enroll older and sicker patients. That's not a
12 question. I don't think that we can possibly reach a
13 different answer. That's the only the way to
14 practically do the studies that will allow, you know,
15 if we're going to require that because with the younger
16 and healthy group that's typically enrolled for phase 2
17 and 3 studies, we're not going to be able to see the
18 kind of event rates that will allow discrimination, the
19 confidence intervals will be unacceptably high.

20 But what I wanted to make a point about was
21 that it's not necessarily the case that with an
22 elevated hazard ratio for CV events that a drug would

1 necessarily not be approvable for obesity because we
2 have lots of conditions that we accept increased
3 relative risk. For instance, NSAIDs are used with
4 great prevalence for conditions where folks are
5 receiving functional benefit from the anti-inflammatory
6 effects, but we know that they increase CVD risk. So I
7 think we should think carefully that, yes, if it turned
8 out that a drug had a little bit of increased CVD risk,
9 it could still be considered highly approvable if it
10 had sufficient benefits elsewhere for patients in terms
11 of their function and perhaps other complications.
12 It's actually why I was trying, maybe very inelegantly,
13 yesterday to talk about, what if we didn't see any
14 benefits to these cardiovascular events at all and
15 would there be a possibility of a drug being approved
16 or thought of as worthwhile because it reduced weight?
17 I mean, people could answer as they want. My view is
18 that it's quite possible it could.

19 So I think that we need to look for
20 cardiovascular events because that's clearly something
21 important for us to rule out. As patients age, they're
22 going to be exposed to these drugs if they were

1 successful early, and since we all believe chronic
2 treatment requires continuous or maybe even
3 intermittent, according to Dr. Bray, but at least
4 repeated exposures to the drug throughout many decades
5 potentially, and certainly for the pediatric population
6 it's even longer number of decades, that we need to
7 know about cardiovascular risk, and this is the only
8 practical way to obtain that information.

9 DR. THOMAS: Dr. Alexander?

10 DR. ALEXANDER: Yeah, I agree with others,
11 that really the only way to assess the cardiovascular
12 risk of these drugs is to enroll patients in trials
13 with them that have higher than .5 percent a year risk.
14 I think there are two main things we've been talking
15 about that present challenges with that approach.

16 The one is in general lumping together
17 extrapolation. So in order to do this, you would have
18 to treat higher risk patients for a prolonged period of
19 time, and that's different both in terms of the
20 population from how these drugs are used in practice
21 and in terms of the duration of therapy to how these
22 drugs are used in practice. And so whether the safety

1 signals -- and we talked about both relative and, I
2 think more importantly, absolute terms that we would
3 see in a program that was enriched for risk like this
4 would translate to these lower risk, shorter duration
5 exposures is something we'll have to wrestle with. I
6 mean, I think it's a good question.

7 The other important thing that's related in
8 some ways is this balancing of risk and benefit, and
9 we've talked -- you know, we've had a number of people
10 who have opined on this issue that some amount of risk
11 might be worth it if there were benefits, and those
12 benefits might be cardiovascular or they might non-
13 cardiovascular, and they might vary in magnitude. And
14 so I think we really also have to struggle with, how do
15 we get adequate assessments of those benefits of a
16 weight loss drug? And we've talked about weight loss,
17 we've talked about improvements in cardiovascular risk
18 factors, and then we've seen in some of the data
19 presented over the very long term, I mean SOS is 4, 5
20 years before we started seeing reductions in cardiac
21 events from weight loss. So to get an accurate
22 assessment of the benefit-risk tradeoff of these drugs,

1 we would have to really enroll high-risk patients in
2 very long duration programs.

3 DR. THOMAS: Dr. Jensen?

4 DR. JENSEN: Two points. One is that I think
5 for pharmacologic management of obesity now we're sort
6 of where we were in the 1950s with management of
7 hypertension. We have one or two, depending upon how
8 you look at it, compounds, and subsequently because we
9 did have some compounds in the 1950s that weren't all
10 that effective, they had a lot of side effects --
11 hexamethonium, phenoxybenzamine, and diuretics -- but
12 eventually the companies were able to make better
13 compounds with experience and with the "evil" profits
14 that they made from doing that, and we've subsequently
15 now got a large number of very good drugs to treat
16 hypertension, and I would argue that the same thing for
17 diabetes, the same thing for lipids, is that at some
18 point you have to start someplace, and you will always
19 start with imperfect knowledge.

20 The second point is related to Question 1 in
21 terms of enriching the trials with patients at high
22 risk. Two concerns that I have about that is, are

1 people who have had myocardial infarctions, do they
2 actually benefit from weight loss? And if you do look
3 at some of the admittedly observational data, it does
4 not appear that people who have had a myocardial
5 infarction have a lower mortality if they lose weight;
6 if anything, they have a higher mortality if they lose
7 weight voluntarily.

8 The second issue is, is it always a good idea
9 to enrich populations of a drug with high risk? So if
10 we had demanded that the initial ACE inhibitor trials
11 enriched their populations with people with renal
12 insufficiency and we saw a lot of renal insufficiency
13 problems, would we ever have approved ACE inhibitors?
14 So I do think you need to be very cautious about
15 demanding enriching things without understanding what
16 the potential downsides are of that enrichment and
17 giving you false signals. So I think thinking very,
18 very carefully about this question, I don't think it's
19 a slam-dunk that we should just do this without
20 incredibly careful consideration of the implications.

21 DR. THOMAS: Dr. Bergman?

22 DR. BERGMAN: Yeah, let me first just say

1 that I agree that we have very little perception of the
2 benefit in this case, and it's very difficult to make
3 decisions when you don't really know what the benefit
4 is, first, because there are many benefits of weight
5 reduction, and we haven't calculated what the actual
6 numbers are going to be. And secondly, there are going
7 to be people who take these drugs for whom the benefit
8 won't exist because they don't have the risks.

9 The other thing is I'm concerned, following
10 up a little bit on what Mike Jensen said, a little bit
11 about the innovation problem, which I think is quite
12 different for this group of compounds than it is for
13 others because we've seen -- the first point, which was
14 made by one of the public commentators, is that these
15 drugs are being developed by small companies, and this
16 is quite different from what happened with the diabetes
17 drugs. It is true that the exenatide drugs were
18 developed by a smaller company, but most of the trials
19 in the development was done by bigger companies, and so
20 they had the wherewithal to spend \$100 million, as
21 we've already heard, to do the tests to develop the
22 drugs, but many of these smaller companies can't do it.

1 And therefore the question is: Where is the innovation
2 going to come from?

3 We all believe, I think, that a very good --
4 and to requote what Michael said -- a very good drug is
5 out there somewhere, it may take a long time to find
6 it, but if the innovation is stopped because of the
7 enormous cost to a small company developing these drugs
8 and the very high risk of even keeping the company
9 going I think is at least something we ought to take
10 into account because we need -- just like bariatric
11 surgery, which is such an extreme thing, has been very
12 popular because it works. We definitely need other
13 agents, and they're going to follow from the bariatric
14 surgery research, I believe, and we need the
15 wherewithal to have people out there in the market to
16 really be willing -- and, of course, I have no interest
17 in any of this, financial interest -- but to really be
18 willing to come forward and try and develop these
19 drugs.

20 And we've seen already that the large pharma
21 companies have, at least to my knowledge, dropped most
22 of these efforts, so we're stuck with little companies

1 in San Diego, and they don't have the resources to
2 continue to do this. So that's something we have to
3 keep in mind because of the enormous possible public
4 benefit of being able to reduce overall obesity and
5 overweight rates in this country.

6 DR. THOMAS: Thank you. And just a reminder
7 to make my job easier summarizing, which everyone has
8 been doing that, is focusing on the strengths and
9 weaknesses of this decision about enriching
10 populations, still focusing on Question 1.

11 Dr. Kramer?

12 DR. KRAMER: Some parts of what I want to say
13 have probably been covered by others, but specifically
14 to Question 1, it seems to me that the underlying
15 principle behind the formation of Question 1 is that I
16 think most of the general public is no longer willing
17 to approve drugs to treat obesity and not know whether
18 we're hurting people. I mean, I think we need to say
19 that, it's obvious, but I think generally most people
20 assume that.

21 Now, I understand that the question about
22 whether we should enrich derives completely from the

1 statistical dilemma that unless we enrich with an event
2 rate of 0.5 percent, it's really not feasible to answer
3 that question, whether we're hurting people. So I
4 understand that. But obviously one of the first
5 concerns comes from the fact that we would then be
6 testing the product in a population that is different
7 from the target population, which is the exact opposite
8 of what we've been pushing for in other areas because
9 at the end of the day, then a doctor is facing a
10 patient and trying to explain these are the data, this
11 is the evidence that we have, but they really can't
12 quite explain what the outcomes are likely to be in the
13 lower risk population. So that's problematic, and I
14 think that probably touches on what Dr. Alexander said
15 about I think you called -- I see that as a
16 generalizability issue.

17 So then I started to think about the patient
18 drive, and I read through the materials that we were
19 submitted in advance from the people who were going to
20 speak, and I think this issue about, well, what's the
21 alternative? the innovation question, the issue of,
22 well, there's no treatment, what's the implication of

1 that? is obviously of concern to all of us, even those
2 of us who want to make sure that we don't increase
3 risk.

4 And so I started thinking to myself, well, if
5 theoretically there were a new treatment that could be
6 used in this lower risk population, the current target
7 population, that would truly significantly and
8 dramatically affect obesity to the point where you
9 didn't get to that high-risk population of having the
10 cardiovascular risk factors, we wouldn't want to
11 squelch that. But then I looked at all the data that I
12 was presented, and I thought every drug, every time,
13 when we're looking, we're talking about a 5- to 10-
14 percent decrease in weight, and I don't think we're
15 saying that those patients, even those that reach the
16 target weight reduction, are going to be people that
17 don't have increased cardiovascular risk.

18 So I have to say that after considering all
19 of that, I ended up thinking I don't know how you get
20 around enriching the population because I do think we
21 really must know whether this is increasing risk, and I
22 think we need to find ways to do these trials where it

1 doesn't increase the trials by \$100 million, and I'm
2 spending my daytime working on that, on a group of
3 organizations that are trying to improve quality and
4 efficiency of trials, and I think that's one of the
5 things we have to consider. But I'm troubled by the
6 generalizability issue, but I just don't see any way
7 around it, so I guess I would end up after all that
8 dilemma saying I think we need to enrich.

9 DR. THOMAS: Dr. Proschan?

10 DR. PROSCHAN: Yeah, I mean, we've all been
11 talking about the fact that there is this very low
12 event rate, and it's true, we've seen a very low event
13 rate in all of these trials. That doesn't necessarily
14 mean that it's a very low event rate outside the
15 trials. I mean, we've seen over and over again that
16 the event rate in the clinical trial data is often much
17 lower than what we thought it would be. I mean, I've
18 done sample size for these, and I've never gotten it
19 right.

20 (Laughter.)

21 DR. PROSCHAN: I've tried very hard to get it
22 right, but the event rate always turns out to be lower

1 than what we thought. So just because the event rate
2 is low in these trials doesn't mean that the event rate
3 is low in the general population who would be using
4 these drugs.

5 Now, having said that, I think Dr. Brittain's
6 point about, "What can you really get with the event
7 rates that we've got?" is a good one. I mean, we need
8 to do multiple things. Enriching the population is
9 necessary but not sufficient. I mean, I think if we
10 don't do that, we're going to have so few events, we
11 might as well not even do a trial and look at events
12 because there is just not going to be enough
13 information, and it will be more misleading than
14 helpful.

15 But I think we have to do more than just
16 enrich the population. I think there are other things
17 that we need to consider. One thing -- I know Dr. Kaul
18 might not like this -- but enriching the outcome as
19 well, and we'll talk about that, it's another item up
20 there, but that's another way to increase the event
21 rate. Another way -- or, yeah, increase the total
22 number of events.

1 And another thing that I think we need to
2 consider is instead of doing this two-sided 95-percent
3 confidence interval, you know, you could just look at a
4 one-sided, make it -- it's essentially doing a .05 one-
5 tailed test instead of two-tailed, that will also help.

6 So I think there are some things that we can
7 do that if we put them all together, we actually might
8 have a chance at finding out whether there is increased
9 cardiovascular risk.

10 The other thing that is a possible solution -
11 - well, maybe I'm getting off track, so I'll stop
12 there.

13 DR. THOMAS: Thank you.

14 Dr. Hiatt?

15 DR. HIATT: So in terms of Question 1, my
16 perspective is that an event is an event, and that an
17 MI in a 40-year-old woman is the same as an MI in a
18 person with diabetes or someone who has had a prior MI
19 and has had another recurrent MI, in the context of
20 this safety discussion. And so I think any way you can
21 events is meaningful and that the signal in an enriched
22 population I think is meaningful to the healthy

1 intended use population, and we've all said that we
2 have to do that.

3 There are a couple of points to make about
4 how to get more events. In phase 2 and phase 3, if
5 they're short-duration trials, you can certainly extend
6 the duration of placebo control and acquire more events
7 that way. Secondly, you've said they should be
8 adjudicated. And it's really interesting, that if you
9 look back on the history of diabetes and obesity drugs,
10 they hadn't been adjudicated, they were all adverse
11 event reports where people were trying to figure out if
12 it was real MACE or something else. So it's cheap to
13 prospectively adjudicate and put these committees
14 together, and why not do that when you start your phase
15 2 program and then ensure as much follow-up as you
16 possibly can, because you get a few more events that
17 way?

18 And then I think with the enrichment, I'm not
19 agonizing too much that if I get more events in a
20 higher risk population that that somehow doesn't inform
21 me of what's going to happen in a younger healthier
22 person. I think the only way to understand that signal

1 is to acquire that, and then the burden of proof, if
2 there is a problem, would be to show that it doesn't
3 exist in the low-risk population, because I'm going to
4 assume it does until you showed me otherwise.

5 DR. THOMAS: Dr. Kaul?

6 DR. KAUL: Thank you. Reconciling
7 generalizability with feasibility is quite challenging,
8 as is quite evident from the conversations.

9 I think generalizability is more applicable
10 to the efficacy endpoint, which is the weight loss.
11 For ruling out unacceptable cardiovascular risk, I
12 think it is appropriate to do what Dr. Temple yesterday
13 alluded to, a worst case scenario analysis, and I think
14 only enrichment techniques are the practical solution
15 for improving the fidelity to do those worst case
16 scenario analyses. So in this case, I think
17 considerations of enrichment trump considerations of
18 generalizability unless the drug at hand has some
19 unique properties that it only increases risk in a low-
20 risk population and not in a high-risk population,
21 which is an unlikely scenario.

22 So I don't have any concerns about

1 enrichment, but I certainly would like to have a more
2 formal evaluation of the diabetes drug program and
3 convince ourselves whether enrichment techniques
4 consistently enhance the risk. I would like to see a
5 formal evaluation of that. I think increasing drug
6 exposure by at least acquiring 2 years of exposure
7 minimum ideally up to 3 or 4 is necessary. I think we
8 will be kidding ourselves if we ask for a shorter term
9 exposure. So enrichment is the only practical solution
10 and is in keeping with a good and efficient clinical
11 trial design for answering the specific question.

12 DR. THOMAS: Dr. Gregg?

13 DR. GREGG: Yeah. I think there are some
14 important limitations and some drawbacks to enriching
15 the sample. When we really look at the ultimate job,
16 which is basically to weigh risk versus benefit, and
17 the reason being that in this situation, it pushes the
18 actual sample away from the demographics of the
19 population that are going to be using the drug, and the
20 reason why this matters, I think it's one thing to say
21 that, okay, an older, sicker population is a good
22 bellwether for everybody else, but when we have a

1 different task, which is actually quantitatively
2 weighing risk and benefit, the answer to that might
3 actually be different, and the reason is that
4 cardiovascular disease has a very steep relationship
5 with age; other outcomes don't necessarily.

6 And I don't know how accurate this is when
7 I'm doing this, but I find myself, when we do these
8 reviews, in a situation of actually trying to weigh,
9 you know, per thousand, I'm scribbling this down, how
10 many events were either causing or saving in
11 cardiovascular disease? and trying to actually weigh
12 that against these other benefits that we're looking
13 at, whether it's diabetes incidence, mobility,
14 anxiety/depression/suicides, or even much more rare
15 things, and the problem is that trying to make those
16 calculations, as problematic as they are, that may be a
17 very different calculation in an older, sick population
18 than in a young risk factor group, or basically the
19 group that are using the drugs.

20 And I think along with that, when I recognize
21 -- I think I've done maybe five of these reviews, and I
22 think about the things that made them difficult -- and

1 every one of them is difficult -- but they were bladder
2 cancers one time, cleft palates, anxiety/depression
3 another, mammary tumors in rats, I can only think of
4 one of the five where actually it was cardiovascular
5 disease that we were really concerned about, and
6 ironically, when we look at the cardiovascular, the
7 times that it's been, it's either valvular heart
8 disease or hemorrhagic stroke, I'm not sure these
9 trials would actually tell us or confirm for us that
10 there is an excess risk of those.

11 So all of this makes me think that this sort
12 of enrichment, all around the idea of solving the
13 cardiovascular disease problem, might be leading us
14 away from a more appropriate broader look at the
15 complications of obesity and at the same time, keeping
16 us from really demanding rigorous looks at some of
17 those other outcomes.

18 So anyway, sorry that was so longwinded.

19 DR. THOMAS: That's fine.

20 Dr. Konstam?

21 DR. KONSTAM: Yeah, thanks. So I do support
22 enriching phase 2 and 3 clinical trials with overweight

1 and obese individuals at higher risk of CV events and
2 performing meta-analyses for adjudicated MACE. And I'm
3 going to try not to read too much into what the
4 question is asking. It's saying enrich the population
5 and analyze the data. And then probably at the tail
6 end of that, provide some guidance for how to interpret
7 the data, but there's going to be broad latitude to
8 what to do with those data.

9 And so for starters, you know, if you have an
10 overwhelming blockbuster efficacy for the first time
11 ever, that's going to weigh in, and I think certainly
12 you're going to tolerate more probability of risk under
13 that circumstance. You know, similarly, Ellen made
14 this point earlier, you could easily say, well, you
15 know, we believe this risk applies to the high-risk
16 population, we believe the absolute excess risk in the
17 larger population is probably in an acceptable range
18 given the level of efficacy. So I see this as provide
19 us with information.

20 Now, I very much resonate with the comments
21 that there may be enormous downstream benefit,
22 including cardiovascular benefit, if you can achieve a

1 sustained benefit in weight reduction -- which, by the
2 way, hasn't been shown with these drugs -- but if you
3 could, I very much resonate with that. But this is a -
4 - it's not a class of drugs, but the group of drugs
5 that have been looked at and/or approved for obesity
6 have a terrible safety track record, and I think
7 everybody would agree that before we approve such a
8 drug, we owe it to the patients to understand as best
9 we can that level of risk that either is causing us not
10 to approve the drug or at least to declare what that
11 level of risk is, and there is really no other way to
12 do that without gathering data in high-risk
13 populations, so that's why I support it.

14 DR. THOMAS: Ms. McAfee?

15 MS. MCAFEE: Yeah, what he said pretty much.

16 (Laughter.)

17 MS. MCAFEE: And I also -- I mean, certainly
18 I'm in favor of enriching, you cannot be when you're an
19 advocate and when you've spent nights talking to people
20 with primary pulmonary hypertension and all kinds of
21 problems from other drugs. This is a complicated issue
22 for me because I look at drugs now, as we mentioned,

1 have a terrible safety record, drugs in the future,
2 which are going to be much more targeted drugs, much
3 more personalized medicine kind of approach, and I
4 can't have the same feelings about both of them, the
5 same guidelines basically for both of them.

6 I've never known what to do with the
7 hypertension data from the Swedish obesity study, which
8 showed basically none. These are the few people that
9 maintained loss, and really bariatric surgery is the
10 only place we can get that data, and while they showed
11 initial improvement, they went back up to baseline even
12 with sustained weight loss. So while you can see some
13 benefit in the short term, are we going to see that
14 long term? I mean, and that's the problem I have with
15 all this stuff, you know, that we need long-term
16 things. And, granted, people now do take this short
17 term partly because of the cost, it's not paid for by
18 insurance in most cases, and partly because of the
19 safety issues, but I would hope that over time that
20 would be overcome and that people will begin to take
21 this long term because that is the only way not to get
22 into "yo-yo" dieting kind of situation.

1 So I find the whole thing really difficult
2 and confusing, but I think that we have to try our best
3 now, and I think our best now is to throw some more
4 people in the mix and see what happens. I really hope
5 that the drug companies start figuring out why this
6 happens, not just saying, "Oh, it happened," but giving
7 some thought prior to phase 3 into what are the
8 possible scenarios, that could be, "Let's look at how
9 the drug works, let's look at some of the basic biology
10 involved that would cause this," because maybe then we
11 change the indication so that certain subgroups of
12 population don't get the drug, but the rest of them do,
13 because that would be much better for me than just
14 throwing a drug out altogether, because then we end up
15 bearing the cost for that.

16 DR. THOMAS: Dr. Capuzzi?

17 DR. CAPUZZI: Thanks. Yeah, I have a couple
18 of comments, more than a couple.

19 First of all, it seems like everyone is kind
20 of in agreement that we should have a cardiovascular
21 outcome trial. In doing this, the patient selection
22 has to be very careful. There is a big difference

1 between, as ATP II and III showed, having two more risk
2 factors as opposed to having had a prior event. So I
3 would say initially that two or more risk factors are
4 important to do for safety reasons before taking in
5 people who have already had a heart attack or stroke or
6 angioplasty or bypass surgery. That's pretty obvious.

7 So of the risk factors that were taken in ATP
8 III is a family history of obesity, low HDL, a natural
9 event, hypertension, and we're talking about I think
10 they're all in play except for natural event, to do
11 earliest, that's the earliest thing to do.

12 Now, in terms of that, if we look at this
13 question of MACE effects, again I think two or more
14 events would not be a problem. In terms of the study
15 itself, we would not use initially bypass patients,
16 angioplasty patients, patients that have an MI, and I
17 think that's okay.

18 Now, in terms of the signal being determined,
19 and I don't think that that's reasonable. You might
20 miss a signal, you might misinterpret a signal, so
21 whether or not the signal is there I don't think should
22 have an effect, personally I don't think should have an

1 effect, on the design of the study.

2 And finally, in terms of the patient
3 recruitment itself, I think it could be staggered so
4 that patients at lowest -- if you look at the ATP risk
5 factors, well, a low HDL is not -- it's okay, but it's
6 not the same thing as having a prior myocardial event.
7 Family history would be okay initially, hypertension.
8 I think I go up from the least combination of risk,
9 least intense or predictive risk factors, and the event
10 itself, which obviously becomes secondary intervention.
11 So if those are chosen earliest, age and those others,
12 you could gradually go in there. The fact, I think
13 there should be an event trial before any new drug is
14 approved.

15 Now, one other thing, the course of the kinds
16 of patients you recruit earliest and later is also an
17 issue. I mean, having female gender supposedly is a
18 protective factor in ATP II, and I think by and large
19 it is. So initially we take younger people that
20 haven't had an event -- females, hypertension, the
21 softer risk factors -- and then go to the more
22 convincing ones where you're increasing the risk. If

1 you've already had an event, then you are much more at
2 risk obviously than having risk factors for an event.

3 So I think that this study should take those
4 factors into consideration and in the course of
5 recruitment, while we're going -- and this is done in
6 the drug industry all the time -- from those that are
7 least at risk for the worst event and go gradually
8 upward, and that's why I said female, younger, and
9 those who have not already had a heart attack or
10 stroke, and those shouldn't be all equivalent.

11 And that's all I have to say.

12 DR. THOMAS: Thank you.

13 Dr. Cooper?

14 DR. COOPER: A couple of comments. The first
15 is to echo Dr. Hiatt's comment about the advantages,
16 the strengths, of this approach, of the prospective
17 adjudication of the MACE events. As you noted, Dr.
18 Parks, the model that you've seen with the diabetes
19 drugs where there has been a lot of advantage to
20 knowing what these events are I think would be a really
21 important strength.

22 One of the weakness or at least a caveat, to

1 echo Dr. Seely and other comments, is sort of the
2 generalizability of these populations to other
3 populations. And if I wear my pediatrician hat for a
4 minute, to think about children and the increasing
5 prevalence of obesity in children and the increasing
6 use of surgical approaches to obesity in children, it's
7 likely that there will be children exposed to these
8 drugs at some point, and understanding both the
9 potential long- term effects of these medicines, if
10 there is either benefit or harm, I think would be
11 important. In a similar vein, with the prevalence of
12 obesity in women of child-bearing age, the importance
13 of the exposures of these drugs during pregnancy I
14 think would be another thing to keep in mind as we
15 begin to think about how we evaluate the risk moving
16 forward.

17 DR. THOMAS: Dr. Hendricks?

18 DR. HENDRICKS: I agree with enrichment. I
19 just want to talk for a second about what that means in
20 terms of what kind of patients should be included in
21 the trial. And Dr. Weide is right, some of the effects
22 of weight loss are going to be very long term, so I

1 would suggest that we include a fair number of
2 hypertensive patients, at least that gives you a signal
3 and it happens pretty early in the weight loss if their
4 blood pressure is high and it's going to go down, it
5 usually starts going down the first few weeks of any
6 medication or any weight loss. Having said all that, I
7 would suggest we move on to the next question.

8 (Laughter.)

9 DR. THOMAS: I think we've got a few more
10 people with questions.

11 Dr. Temple?

12 DR. TEMPLE: Well, I was curious about one
13 thing. One of my worries is that people with a nominal
14 history of hypertension or lipid abnormalities, if
15 entered into a trial, will be treated vigorously for
16 those things, and that won't fix them right away, but
17 the response to an antihypertensive occurs pretty
18 rapidly, within months actually probably.

19 So it struck me that the main enrichment
20 feature is probably going to be a past history of
21 something, and I just wondered what people thought
22 about. I mean, it's fine to get people with a history

1 of hypertension, and maybe they're at higher risk for a
2 little while, but I'm sure they'll be treated in a
3 trial like this, you're not going to let them sit
4 around with a systolic of 180.

5 DR. WEIDE: Could he repeat the last part?
6 Because we missed it. Primarily they're going to have
7 what? Did you say events, MIs, or were you pre-
8 hypertensive? We couldn't quite hear you, that's all.

9 DR. TEMPLE: Okay. I was just saying that
10 the risk factor that's likely to persist in the trial
11 and not go away is a past history of something, it
12 could be an MI, it could be need for bypass, or any of
13 those other things. Some of the other risk factors
14 that we talk about, like being hypertensive or having
15 high LDL, surely in a trial setting would be treated
16 vigorously, and those would no longer be as important
17 risk factors, at least after the first 6 or 7 months
18 they wouldn't be. So I just wondered what people
19 thought about that.

20 DR. THOMAS: I'll just make a comment and
21 then I'll let Dr. Alexander. I wanted to make a
22 comment on this.

1 Assuming that they were randomized equally
2 and they're treated appropriately, then that should
3 cancel out to some degree. It will lower your event
4 rate, but --

5 DR. TEMPLE: Well, yeah, but then they won't
6 have the events you're looking for.

7 DR. THOMAS: Yeah, you're already starting
8 with a lower risk population if they just have
9 hypertension than all the other factors.

10 Dr. Alexander?

11 DR. ALEXANDER: Yeah. I mean, I think we
12 know pretty well how to enrich this kind of a
13 population for patients who are going to have events,
14 and you're absolutely correct, that there are some risk
15 factors that will be stronger drivers of recurrent
16 events or first events than others.

17 I think the goal of doing this is if you
18 think back to that figure, the power calculations with
19 the hazard point estimates and confidence intervals, is
20 to get events, and so I think I would agree with you,
21 if you enriched only for a weak risk factor for
22 recurrent events and a worse one that was quickly

1 treated in the trial, then you wouldn't achieve the
2 outcome of interest, which is to get events. I think
3 the one other interesting piece of that which I find
4 much more complicated is whether all ways of enriching
5 are the same, not in terms of getting events, but in
6 terms of predicting the safety of these drugs. And
7 it's certainly true in the case that with
8 cardiovascular drugs there are some risk factors that
9 enrich the population that don't predict modifiable
10 risk as strongly as other risk factors, and I haven't
11 really thought about whether that might also be true
12 for safety, which is another issue.

13 DR. THOMAS: Dr. Savage?

14 DR. SAVAGE: I agree basically with many of
15 the things that have been said. I think, because of
16 the history with the obesity drugs, that it is
17 important to check on the risk of cardiovascular
18 disease, but on the other hand, you really will only be
19 able to estimate from an older, high-risk population
20 approximately what the risk may be in the population
21 that's actually using the drugs. But I wanted to
22 actually expand upon the comments that were made about

1 a relationship between obesity and type 2 diabetes and
2 the parallels that indicate that some of the data we
3 get from studies in this type of patient differ from
4 patients who are hyperlipidemic or hypertensive.

5 Probably the early clinical trials people
6 were fortunate that they got started in an area where
7 they got good results in lowering blood pressure pretty
8 quickly. It didn't take 10 years to see a positive
9 result, and so it generated a lot of enthusiasm and
10 extra funding and so forth that led to a lot of
11 progress in the field. Type 2 diabetes has been sort
12 of the opposite, that there have been many fewer trials
13 and that they in general have not been very impressive.
14 Now, there was the long-term follow-up of the U.K. PDS
15 study that was commented on. There were some
16 irregularities in the way that study was funded, and so
17 there are some uncertainties, but it is impressive that
18 that group of people, when followed out for the better
19 part of 20 years, who were new onset at the time their
20 treatment was initiated, did appear to have a reduction
21 in cardiovascular disease risk, whereas the three large
22 studies that were reported a few years ago in patients

1 that had longer duration of diabetes either had some
2 negative aspects, most prominently in ACCORD, but there
3 was an excess of deaths in the intensive treatment
4 group in the VA patient population, and no benefit in
5 the third one. And obesity, in a sense, has a
6 relationship to type 2 diabetes in this sense, that
7 glucose is probably not a major CVD risk factor in its
8 own right, the risk is partly because hyperglycemia is
9 associated with other well-known major CVD risk
10 factors, and so the diabetic population in general has
11 an excess risk, it isn't just because of the level of
12 the glucose.

13 Obesity is even earlier in terms of the
14 evolution of abnormalities, that someone can be obese
15 for several years before they have any major risk
16 factors. And so it's probably reasonable to think it's
17 going to take a long time to demonstrate a major effect
18 of reducing obesity on cardiovascular complications or
19 major heart endpoints.

20 One other comment I just wanted to make as an
21 example of something that Mike Proschan brought up
22 about the importance of how a trial is run versus

1 potentially what happens when the treatments are given
2 more in a regular clinical setting is that although
3 it's only a sentence or two in the main results of
4 ACCORD, the intensive intervention group in ACCORD had
5 a lot of treatment with rosiglitazone, and the event
6 rates in that group of patients were actually lower
7 than that of the control group, presumably because
8 there had been a lot of warnings about some of the
9 cautions in using TZDs and the dangers of congestive
10 heart failure and so forth, and so that the people who
11 were in that trial who had had a lot of warnings about
12 the potential danger of using that drug stopped it or
13 didn't use it selectively because it wasn't a
14 randomized drug, it was part of an overall strategy of
15 treatment. So it is important to realize that
16 something that is done in a formal, complex clinical
17 trial may actually not work out quite the same way in
18 the real world setting.

19 DR. THOMAS: Dr. Spruill?

20 DR. SPRUILL: I agree with most of the
21 comments about enriching the population, and so I won't
22 repeat a lot, but the question I have and the

1 clarification I need is that when we talk about trying
2 to enrich this population for phase 2 and phase 3
3 clinical trials, what I'm concerned about is the
4 definition of individuals at higher risk, and if
5 individuals at higher risk is the same thing as people
6 who bear the brunt of the disease, and if that means to
7 me -- because when I read this, I'm not quite sure if
8 it's the same thing. So I don't if FDA is saying -- if
9 this is the same thing, then, yes, I would say, yes, we
10 should enrich it with individuals at higher risk, but
11 if it does not, then I think it needs to include
12 individuals at higher risk for CV events and
13 individuals who bear the brunt of the disease in this
14 country.

15 DR. THOMAS: Any clarification from the FDA?

16 MS. PARKS: I'm sorry, Dr. Spruill, I'm not
17 really clear on your question here. Can you repeat it
18 or rephrase it?

19 DR. SPRUILL: Let me try to rephrase it for
20 you again. When I read the second paragraph, when it
21 says "individuals at risk for CV events," the question
22 is, does that include people who bear the burden of

1 obesity in this country?

2 DR. PARKS: Yes.

3 DR. THOMAS: So you would be using this in
4 obese patients with high risk, not just any
5 cardiovascular risk patient, even if they're not obese,
6 just to get your event rate higher where there would be
7 really no benefit.

8 DR. SPRUILL: Because you could be at risk
9 and not bear the burden of the disease is the point I
10 wanted to make, because, yes, because if you think
11 about the SCOUT trial that Dr. Colman talked about
12 earlier, even though it was 60 percent effective, over
13 80 percent of the participants were white women.

14 DR. THOMAS: Dr. Rasmussen?

15 DR. RASMUSSEN: So I would just like to add a
16 little bit of perspective on what "enrichment" in this
17 context probably will mean. I mean, I did a little bit
18 of "back-of-the-envelope" calculation, and maybe we'll
19 have that confirmed after lunch.

20 But, I mean, current programs, approximately
21 3,000 patient-years of exposure generate 15 MACE events
22 or so. Even if we were to double that patient-year

1 exposure with a population of a 3-percent annual event
2 rate coming to additional 60 events, we would still
3 only be able to exclude a doubling of the hazard ratio.
4 So, I mean, what we're talking about here about
5 enrichment is actually completely shifting the
6 population that we're going to study in obesity
7 programs to establish cardiovascular disease and not
8 necessarily the population that we know actually seek
9 treatment in the real world.

10 So I think that's worth keeping in mind, that
11 enrichment may sound appealing because it sounds like
12 we will add a fraction of sick patients, but in
13 reality, this will be a complete shift of the
14 population.

15 DR. THOMAS: Dr. Brittain?

16 DR. BRITTAIN: Yeah. Just a couple quick
17 comments. I just want to make sure when we're talking
18 about enrichment, we're still talking about there being
19 a pretty sizable cohort of the patients who are most
20 likely to get the treatment in the end, or are we not?
21 (Chuckling.) Are we talking about completely going to
22 the high risk or are we still talking about -- to me,

1 enrichment sounds like it's a mix of high risk and --
2 but I would hope that there would still be a cohort
3 that could be more like the typical user, so there will
4 be an important subgroup to get results in that cohort.

5 The second point I had was about whether it's
6 critical that patients stay on drug the whole time for
7 these maybe 2- and 3-year follow-up. And I'm not so
8 sure that that's necessarily what we do want. I mean,
9 maybe you want more the natural exposure lengths that
10 people are going to have, and then there is going to be
11 some lag in the effect of the drugs, and so it will
12 take several years of follow-up to see what the effect
13 is, but I don't know that if no one is going to stay on
14 the drugs for 2 years in the real world, if that's
15 necessarily what you would want to do in the study. I
16 would think you would want the longer follow-up to get
17 the events but not necessarily to force people to stay
18 on longer than they would.

19 DR. THOMAS: Dr. Parks?

20 DR. PARKS: I don't know if the panel members
21 feel this way, but I want to kind of dispel the notion
22 that the obesity population and diabetes populations

1 are mutually exclusive. There is overlap. And to
2 point that out, we do have companies developing their
3 drugs for treatment of type 2 diabetes that have a
4 weight loss effect, and they also have INDs to evaluate
5 that drug for an obesity indication. So clearly the
6 same drug is being considered for both indications.

7 Regarding your question in terms of does
8 enrichment necessarily mean that everybody is going to
9 have to be in a high risk, is that phase 2 and 3
10 program now all of a sudden just in a population that
11 is not going to be reflective of what you would expect
12 to see? Again, from our experience with the type 2
13 diabetes program, some of the concerns that we heard
14 from companies, like, you know, "But we're being asked
15 to study these drugs earlier in a sick patient
16 population, and we have concerns about assessing safety
17 in a sicker patient population," what we've seen so far
18 is that it actually is a hybrid, and we still see
19 placebo-controlled monotherapy trials, treatment-naive
20 patients, but we also see a mixture of dual-triple
21 combination add-on insulin early on plus the dedicated
22 trials. So it is a mixture where you don't lose out on

1 the information on efficacy and safety in a population
2 that would otherwise use it but is not at a high risk
3 for cardiovascular disease.

4 DR. THOMAS: Dr. Waters?

5 DR. WATERS: I didn't know I was on the list,
6 but I just had something I wanted to say really quickly
7 in reply to what Dr. Parks said. If I was designing a
8 trial, in reply to what Dr. Brittain said, what it
9 would look like is there would be 40 percent smokers,
10 that's a risk factor that hardly ever goes away. Dr.
11 Temple is right, hypertension and high LDL don't get
12 you anything because they're too easy to treat. You
13 want to have as many diabetics in it as possible, maybe
14 40 percent diabetics, and then 80 percent documented
15 vascular disease, trying to get people who have a low
16 GFR below 60, and make people have at least two or
17 three of those risk factors, and, I mean, that's how
18 you would get the event rate up. And for the event
19 trial, putting people in who are low risk is a waste
20 because they won't have an event. You still want to
21 study them to see the effect for weight loss, but not
22 for events, because they don't have any.

1 DR. THOMAS: Dr. Hiatt?

2 DR. HIATT: Well, I can't add much more. It
3 was relevant to Dr. Temple's comment earlier, and I
4 think it's the same thing you just said, that risk
5 factors alone won't get you there, and even a premium
6 risk of 20 percent is 2 percent per year, so it's going
7 to have to be people with established disease.

8 DR. THOMAS: Dr. Weide?

9 DR. WEIDE: Yeah, just a couple comments.
10 And I think there's been a lot, and it's getting to be
11 even more, concern about the enrichment. Remember,
12 enrichment is not replacement. We're not replacing the
13 study. I mean, we could, but I don't think that's the
14 plan; it's to enrich them with a population that has
15 higher risk, cardiovascular risk. By doing that, we
16 have a little older population, and there has been some
17 concern that population is a population that's not
18 going to be indicative of those on a drug. I would say
19 maybe it's not as different as we think. In the slides
20 that were shown, there were older people on the drug,
21 and, in fact, if you look at those populations, those
22 over 65 actually were the most compliant and lost the

1 most weight, so you could say, hey, they ought to
2 benefit the most of all the population even if they're
3 at higher risk. So if we still see a signal, then
4 there is clearly something wrong.

5 I have another concern, and that's trying to
6 figure out where this fits in, what to do about it, how
7 to make sure it doesn't occur during studies. There
8 are so many over-the-counter weight loss preparations,
9 most of which are either worthless or harmful, and it's
10 a major concern to me. Most of them are caffeine
11 driven, I've had patients go into A-fib on them, and,
12 you know, if I had my way, the law should be changed
13 and all of those compounds should be taken over by the
14 FDA as well as all the over-the-counter preparations.
15 The FDA should be monitoring this. It's the largest
16 industry in the U.S. that is just given to people, and
17 people don't even come into our offices and say, "I'm
18 on this stuff," because it's over-the-counter, it must
19 be safe, and it interferes with thyroid medicines, it
20 causes A-fib, it depends on which medication. This is
21 a major problem in the U.S., and I really firmly
22 believe that the law needs to be changed.

1 So there are some good things out there.
2 There is a lot of junk out there. It's difficult for
3 us to know what's good and what's bad, and it's nearly
4 impossible for our patients to know what's good and
5 bad, and I would urge you and urge the Congress, if
6 that's what it takes to change the law, to fix this
7 problem because that's probably one of the biggest
8 problems in the U.S. health care industry.

9 DR. THOMAS: Okay. Dr. Konstam, you'll be
10 the last question, and if you can keep it short so I
11 can summarize.

12 DR. KONSTAM: Well, thanks for that. I
13 actually am going to make a comment, a general comment,
14 about the discussion. I'm having a little bit of a
15 problem because we're going around the table and we're
16 not kind of focusing topic-by-topic, so there were a
17 couple of things that were said multiple speakers ago
18 that I thought were worth some focused discussion
19 about, and the way we're doing it is really not
20 conducive to that, so maybe we might want to think in
21 the afternoon about a little bit different way to do
22 this.

1 So I had a comment. So Dr. Temple asked a
2 question, and I wanted to give my answer. I think
3 that's right -- I think that --

4 UNIDENTIFIED PARTICIPANT: Which question?

5 DR. KONSTAM: Which one? I don't remember.

6 (Laughter.)

7 DR. KONSTAM: About what's the nature of the
8 enrichment, and I agree, I mean, it's certainly going
9 to include patients who have established disease, but I
10 think people with diabetes, their risk isn't going to
11 go away and there is nothing we know we can do for
12 that, so clearly there is going to be an interest in
13 including a substantial diabetic population, and then
14 the other things, the risks don't completely go away,
15 they obviously get better with treatment. So anyway, I
16 half agree with you, but I think it's a little bit more
17 than that.

18 But I think Dr. Brittain has brought this up
19 a couple of times, and I really think we ought to have
20 a focused dialogue on this discussion about whether
21 patients need to stay on the drugs for a substantial
22 period of time and exposure during these trials, and I

1 think this seems to me maybe this is a really important
2 point because, first off, nobody has told me any value
3 of a couple of months of using these drugs in terms of
4 the prospective benefit, long-term benefit, to that
5 patient; I can't imagine that there is much. So what's
6 the point if you can't demonstrate that the patient is
7 going to have an ability to remain on the drug for a
8 sustained period of time, on the efficacy side?

9 Now, on the safety side, if the drug kills
10 people by any of a gazillion possible mechanisms while
11 you're using it, including heart rate increase, blood
12 pressure increase, or a gazillion things that we don't
13 know anything about, then the easiest way to hit your
14 upper boundary is to not keep the patient on that drug.

15 So what we're talking about really here is
16 safety. The first thing is safety. I mean, that's
17 really to me why, the main reason why, we want to
18 enrich the trial, and I guess it seems really an
19 important point that if you're allowed to let a lot of
20 the patients stop the drug and not get that exposure,
21 it will be easy to hit the confidence boundary, and
22 you're not going to be asking the question, "Does the

1 drug kill you?" or, "Does the drug cause MACE events?"

2 DR. THOMAS: So I agree that's a very
3 important question, and that's 2(e), so we'll be
4 discussing that with the next question.

5 I'm going to summarize, and just one comment
6 based on Dr. Konstam's question about how we're
7 handling this. When we're looking at the people who
8 are about to speak, we do try and get people who have a
9 comment directly related to something that may have
10 been asked when possible, but as you notice, there are
11 at least, I think, 24 people around this table, and
12 it's also important that everyone gets a chance to
13 comment, and as a result, there are people who usually
14 do not get a chance to comment if I were to just follow
15 a strategy of following the line of questioning.

16 Second is sometimes a line of questioning, no
17 matter how interesting and important it is, is it's
18 deviating from the actual question we're asked to
19 comment on. So sometimes we have to restrict that to
20 refocus back to the question that the FDA wants us to
21 comment on.

22 So nothing personal or intentional, but we're

1 just trying to make sure everyone has the opportunity
2 to contribute to the question we're asked to address.

3 So this is a very hard task. When I first
4 started doing this chairing, I would do a summary
5 statement. Of course, this is like summarizing 24
6 different opinions, so I'll try and do my best.

7 I think the first thing, I just want to add a
8 quick comment that adds on to two of the panelists and
9 Ms. McAfee, which is the target population that we've
10 been talking about a lot is generally women in their
11 forties who are Caucasian, but if we had better agents,
12 we would use it in a more expanded population. You
13 know, someone who uses reserpine for blood pressure
14 control on occasion, my threshold, if that was the only
15 agent, would be much different than if I had other
16 alternatives because of the side effects, and I think
17 obesity is, as Dr. Jensen put it, very similar to the
18 blood pressure history back in the '50s where there
19 were few choices, and many of them had quite
20 devastating side effects, so your treatment threshold
21 for when you start an agent may be a lot different.

22 The risk in older patients may be there, and

1 at a higher risk, but that doesn't mean that the risk
2 isn't there in lower patients, and I think that's
3 important to remember. And one of the issues with
4 these types of studies is that we may be shifting
5 populations in phase 2 and phase 3 trials so that the
6 companies can actually get these studies done because
7 of the event rates needed, though it was clarified that
8 there would not be an anticipation that this would just
9 be studying high-risk patients, but there also should
10 be a study of the lower risk patients of obesity
11 because they may get a benefit from treatment because
12 they have an earlier stage of disease than patients who
13 have had longstanding disease or complications from
14 obesity. An analogy was brought up about the use of
15 estrogen. Studies suggested estrogen should not be
16 used in patients who are postmenopausal, however, the
17 risk in subgroup analysis seems to be greatest in those
18 who are the oldest as opposed to those who are just in
19 their early fifties, and as we've eliminated the usage
20 for the most part for women who may benefit short term
21 because we've pulled a variety of different ages and
22 complications.

1 The strengths of enriching the population
2 really are to try and get the event rate needed to do
3 the study and get the question about cardiovascular
4 safety. It would be very unlikely that the risk would
5 be higher in a low-risk population than a high-risk
6 population was brought up earlier, but there are
7 several disadvantages. So one is you may see
8 complications or events happening in a high-risk
9 population that you would never see in a low-risk
10 population, and ACE inhibitors was brought up as an
11 example. If you started to include people with renal
12 disease, you may see events that didn't occur in a low-
13 risk population without renal insufficiency. And so
14 then do you suddenly color the perception of the risk-
15 benefit equation by looking at people with high risk
16 for other events related to an agent which would never
17 have the exposure in a low-risk population we would not
18 be concerned with?

19 Cost is going to be an important factor, and
20 that was brought up because the ability to do these
21 trials, as Dr. Rasmussen suggested, may be \$100 million
22 more, and will this limit the innovation that's needed

1 for companies to bring more agents to market,
2 considering 35 percent of our population currently is
3 obese? And this was related also to the hypertension
4 issues. As better products come along, we have better
5 ways of treating hypertension, and older products that
6 were approved aren't used as much.

7 Phase 2 and phase 3 trials, there is
8 enrichment for population risks of having higher risk
9 people with events, but you can also enrich the
10 population by actually having a longer duration on
11 treatment, and so that could be by extending phase 2
12 and phase 3 trials during the development process, and
13 I would also add, and it was also supported by many
14 other panelists, extending the ability of patients to
15 complete the trial on treatment. So one of the things
16 that we have all talked about is the low completion
17 rate of 50 percent in most of these studies, and we
18 tend to accept that as that's what's always happened
19 before, but we can see from NIH trials, as was
20 presented yesterday, they can achieve higher retention
21 in the study.

22 So do we have to rethink how the

1 pharmaceutical companies are doing these trials and
2 have them be more proactive in terms of enhancing the
3 ability to retain subjects? It may be more costly to
4 do an individual trial, but it may be cheaper than
5 doing two or three trials with long retention rates.

6 Over time, we should see the impact of the
7 diabetes guidance in designing this trial process in
8 the future. Right now, we're looking at a snapshot in
9 time where we don't have all the information of how the
10 diabetes guidance has played a role, and that may be
11 helpful in future design of the parameters that
12 companies will have to do trials and have to work with
13 the FDA.

14 And then other factors are very important,
15 such as patient selection, and I think that's important
16 in terms of retention during the trial and taking
17 medication. And then factors that affect risk factors
18 and also populations that eventually may be treated,
19 such as gender. Most of the patients that are in these
20 trials are women, but if an appropriate age to study
21 men, that would actually be an increase of a risk
22 factor. And then populations that we don't think about

1 early on in terms of treatment, such as children.

2 And I think I'm going to stop at that point.

3 If there are any other comments or corrections that any
4 of the panel had?

5 (No audible response.)

6 DR. THOMAS: Okay. We'll now break for
7 lunch. We'll reconvene again in this room in one hour
8 at 1:05 p.m. Please take any personal belongings you
9 may want with you at this time. The ballroom will be
10 secured by FDA staff during the lunch break. Panel
11 members, please remember that there should be no
12 discussion of the meeting during lunch amongst
13 yourselves or with any member of the audience.

14 Thank you.

15 (Lunch break.)

16 DR. THOMAS: Okay, we're going to get
17 started, if everyone can take their seats.

18 Dr. Soukup, if we can have you present the
19 slide that we talked about earlier in the day. Thank
20 you.

21 DR. SOUKUP: I'll do my best here. And I
22 should actually have put a disclaimer here. When you

1 put these things together in about a half hour, I can't
2 guarantee the accuracy, but I'll do my best.

3 The question was asked, based upon the sample
4 size that we have today, and the guidance, really where
5 are we at in terms of cardiovascular assessment? So I
6 kind of took it and worked backwards from maybe the
7 slides I presented yesterday and started with this
8 fixed end. So we're going to say it's 4,500 in the
9 current guidance. I'm also going to make a couple
10 assumptions here. I'm going to assume the dropout rate
11 is 10 percent, 20 percent, 30, 40, or even 50 percent
12 just to kind of give you a flavor of where things can
13 end up. And I'm also going to make an assumption here,
14 for those that do drop out, they each are going to
15 contribute 6 months of data, so half of the 1-year
16 plan. I'm also going to assume everyone that remained
17 in the trial contributed 12 months of data. So, again,
18 these are assumptions, but just to give you a flare for
19 what could happen.

20 I'm also going to assume event rates. I'm
21 going to assume it's equal in both arms. And I'm going
22 to assume event rates could happen at 0.25 percent, .5

1 percent, 1 percent, 1.5 percent, and 2 percent. And
2 the tables that are going to follow here are basically
3 going to show the expected number of events under these
4 various scenarios, and then I'll go a little bit step
5 further there and say with that planned number of
6 events, what amount of risk could we rule out?

7 So the first scenario here is if we assume
8 4,500 patients, and this would be 3,000 to active,
9 1,500 to control, we would expect to see about 11
10 events if the event rate is .25 percent and the dropout
11 rate is 10 percent. And you can see if you go down and
12 you get to about 50-percent dropout rate, you're only
13 going to expect to see about 8 events in this
14 particular clinical trial database.

15 And as one would expect, as the event rate --
16 so if you start enriching a trial where there is a
17 higher expected event rate, you can see we can start
18 getting up to fairly high number of events here, and
19 the highest would be achieved is if there is a 10-
20 percent dropout rate and there is a 2-percent event
21 rate, and then we would expect to see about 86 events.

22 So now taking all this table planned number

1 of events, what amount of risk can we rule out? You
2 can see that even in the best case scenario, you would
3 get to an event rate of about 2-percent or be able to
4 rule out a relative risk of 2. Worst case scenario, I
5 didn't even put down if the dropout rate is 40-percent
6 or 50-percent rate and a .25 event rate because those
7 numbers are getting very high.

8 So this gives you an idea of what the current
9 database would look -- or the events would look like in
10 the current plan trial design development programs.

11 However, if we assume that there is a 50-percent
12 increase in the size, the next couple slides kind of
13 give you an idea of what you might be able to observe
14 in those trials. So you can start seeing again we have
15 more subjects, we're going to get more patient-years,
16 we now start seeing that the event rates are higher,
17 and we then can translate all these then into, how much
18 risk could we rule out? And you can see that if there
19 is a 15-percent increase in size and there's an event
20 rate of around 2 percent, and dropout rate even around
21 20 percent, you can actually rule out relative risk of
22 1.8 with the current sample size of 6,750.

1 So this is just kind of an idea of where
2 things lie. Again, there are a lot of different
3 scenarios you can play with here, but I think this will
4 give you a little bit of kind of a big picture idea of
5 where things are at.

6 DR. THOMAS: Thank you.

7 Dr. Brittain?

8 And just before Dr. Brittain starts, because
9 we want to get on to Question 2, we probably only have
10 about 5 to 10 minutes on this topic.

11 DR. BRITTAIN: I just want to understand, how
12 long is the follow-up here for each person?

13 DR. SOUKUP: I assumed it's one year for
14 everyone that stayed in the trial and 6 months for
15 those that drop out.

16 DR. BRITTAIN: So person-years -- oh, I see.
17 Okay. Thank you.

18 DR. THOMAS: Dr. Proschan?

19 DR. PROSCHAN: So is this based on 90-percent
20 power?

21 DR. SOUKUP: Oh, yes, correct. I'm sorry, I
22 forgot to mention that. And then a type 2 error rate

1 of .025 are one-sided.

2 DR. PROSCHAN: Okay.

3 DR. THOMAS: Dr. Cooper?

4 (No audible response.)

5 DR. THOMAS: Dr. Rasmussen?

6 DR. RASMUSSEN: So thank you for providing
7 the very nice data; I think it gives some perspective
8 to the discussion we're about to have. I just wanted
9 to return to one thing because it's very apparent that
10 this is extremely sensitive to dropout rate, but I
11 think it's important that we start to distinguish
12 between dropout rate and lost to follow-up. We have
13 numerous times touched upon the very impressive
14 academic studies that have provided follow-up rates of
15 more than 90 percent in their trials. I think it's
16 worth mentioning -- and I just looked this up in the
17 break -- that these run-in activities that they had in
18 those trials actually included or excluded 31 out of 32
19 participants actually involved in the trials. So they
20 screened 160,000 people for the DPP trial to get the
21 5,000 that were actually included, and that's simply
22 not feasible to multiply this number by 33 to find the

1 right individuals to attain a 90-percent retention
2 rate. So I think we have to operate with the
3 assumption that we are in the 30- to 40-percent dropout
4 range.

5 DR. THOMAS: Dr. Proschan?

6 DR. PROSCHAN: I mean, I think that should be
7 one of the criteria for acceptance. If you have, you
8 know, a 50-percent dropout rate, I think that should be
9 the end of the story, no approval, period, and you must
10 insist on no greater than a certain amount. Now, what
11 amount that is, I don't know, but to me, it's not
12 greater than 25 percent in one year. I mean, that's
13 ridiculous that Dr. Wing is able to get 94 percent of
14 the people to come back in 4 years, and all these
15 companies are saying, "Gee, we can't get more than 50
16 percent in one year." I think that should be the end
17 of the story if that's the case.

18 DR. THOMAS: Dr. Goldfine?

19 DR. PROSCHAN: And essentially you don't have
20 a randomized trial when you have half the people
21 dropping out. It's no longer a randomized trial.

22 DR. GOLDFINE: I just want to answer to Dr.

1 Rasmussen's mathematical. I think that the DPP was
2 looking for patients who had risk factors for diabetes
3 and screening them specifically looking for 2-hour
4 glucose that fit IGT criteria, which is something you
5 can't tell by screening medical records or inclusion in
6 another, and I think that led to the screen failure
7 rate that was disproportionate. So I think that that
8 is not exactly apropos if you're looking for a very
9 specific group that is based on a 2-hour post-glucose
10 value.

11 DR. THOMAS: I want to thank you for the
12 presentation.

13 We'll now move on to Question 2. For drugs
14 with a signal for potential CV harm, it should be
15 assumed that sponsors will be required to rule out a
16 certain degree of excess CV risk -- example, through
17 conduct of a dedicated CV outcomes trial prior to
18 market approval. Discuss the potential strengths and
19 weaknesses of the following design parameters of a CV
20 cardiovascular outcomes trial for an obesity drug. And
21 there are five subcomponents.

22 A, Ruling out a certain degree of excess CV

1 risk with a pre-approval analysis of a fraction of the
2 planned number of total events, followed by ruling out
3 a smaller excess CV risk with the post-approval final
4 analysis. This assumes that the pre-approval analysis
5 will be based largely on data obtained during the first
6 year of patient exposure, a period of fewer dropouts,
7 and maximal weight loss.

8 B, Setting non-inferiority margins for excess
9 CV risk on the basis of risk difference versus relative
10 risk.

11 C, Primary endpoint of strict MACE -- CV
12 death, nonfatal MI, nonfatal stroke -- versus MACE-Plus
13 -- for example, hospitalized unstable angina and
14 emergent coronary revascularization.

15 D, Primary analysis population that
16 incorporates on-treatment and off-treatment information
17 -- total time analysis population -- versus a
18 population that incorporates only on-drug information -
19 - on-drug analysis population.

20 E, Discontinuing from study drug patients who
21 do not achieve a certain degree of weight loss within
22 the first 3 to 6 months of the trial. Those withdrawn

1 from the study drug would continue to be followed.

2 And just because there were some comments
3 about the opportunity to speak, what we decided is we
4 really are going to go point-by-point A through E, and
5 we've actually set time limits so we can make sure that
6 we get through the discussion on time and get to the
7 voting question and have proper discussions. For
8 Question A, I really would ask all of you to restrict
9 to subpoint A. And actually if you are starting to
10 wander off, I will go on to the next person.

11 The second thing is we've allotted 30 minutes
12 for Question A.

13 So, Dr. Kaul?

14 DR. KAUL: In my opinion, I think a two-
15 tiered approach seems quite reasonable. I think we can
16 draw upon from experience with the diabetes programs.
17 But I would like to reemphasize that ruling out the
18 same degree of fixed cardiovascular harm for drugs that
19 provide varying degrees of efficacy is probably not the
20 way to go. It should be more flexible, allowing
21 tolerability for a greater degree of harm in return for
22 a greater degree of benefit. And so allowing a higher

1 margin for the first tier fits in with that philosophy.
2 So precisely why greater tolerance of risk is
3 justifiable in the first tier given that the maximal
4 efficacy is going to be evident during the first tier.
5 So I think it's quite a reasonable approach.

6 DR. THOMAS: Dr. Hiatt?

7 DR. HIATT: I completely agree. If the
8 requirement were all post-approval, then you guys could
9 get burned in trying to enforce that, or maybe not get
10 exactly the study you're looking for. If it's all pre-
11 approval, the sponsor loses because they may be delayed
12 multiple years to marketing. I think the staged
13 approach makes perfect sense.

14 I agree with Dr. Kaul, it might be nice to
15 not have fixed boundaries so that if one drug coming
16 out of phase 2 going into phase 3 seemed to give a
17 greater than 10-percent weight loss, that might be
18 perceived as more efficacy than 5, and that might
19 modify a little bit the boundaries.

20 The other thing I like about this is that if
21 withdrawal from drug occurs early in many of these
22 trials, then the maximal exposure to the agent is going

1 to be during the first interval, and therefore the most
2 potential harm would be revealed during the early
3 interval. The benefit from the maximal weight loss
4 occurring early may not translate much in terms of
5 benefit long term because it might take longer time,
6 but since what we really care about is risk, you really
7 would like to see as much risk as possible accrued
8 during drug exposure. It makes perfect sense, and I
9 think it's probably the most economical way to go.

10 DR. THOMAS: Dr. Kramer?

11 DR. KRAMER: I would like to ask the Chair,
12 is it possible to ask questions of each other as things
13 come up that would demand clarification?

14 DR. THOMAS: Yeah, I think that's fine just
15 as long as it's related to the specific question.

16 DR. KRAMER: It is. So I'll start out by
17 saying I also think the concept of a tiered approach is
18 appealing in terms of not delaying innovative
19 treatments becoming available as much as it would if
20 you required it all to be pre-approval and yet also not
21 leaving it all to a post-approval setting.

22 But I have a question for Dr. Kaul. So I was

1 trying to imagine how you would implement -- I
2 understand the concept of wanting to have a flexible
3 boundary depending on the benefit, but if this is your
4 phase 3 trial where you're really going to be defining
5 your benefit and if we're talking about a fixed sample
6 size in order to calculate a certain level -- assure
7 ourselves that we don't have a certain level of risk,
8 as we just went through, how do you do that if you
9 haven't determined the benefit before you started the
10 planning for the study?

11 DR. KAUL: With benefit, I mean evidence of
12 magnitude of weight loss during phase 2 studies. I
13 mean, you already will have an idea whether you have a
14 weight loss of 5 percent versus 10 percent versus
15 somewhere in between plus some additional
16 cardiometabolic benefits as well. So that's what I
17 mean by benefit. It's fixed for a specific drug --

18 DR. KRAMER: Right, for a specific drug.

19 DR. KAUL: -- but don't make it universally
20 fixed for all drugs. It has to be done on an
21 individual drug-by-drug basis.

22 DR. KRAMER: So then I would love to hear

1 from the endocrinologists and people experienced in
2 doing these obesity trials as to whether in phase 2 you
3 actually have a fairly accurate picture of the level of
4 the degree of weight loss that you could expect in
5 phase 3 in order to do the sample calculations, or if
6 it's something that's really only a guess early on,
7 including which other potential signals might exist.
8 It seems like phase 2 may not do that, but I'd love to
9 hear from the experts.

10 DR. THOMAS: Anyone on the panel care to
11 comment about that specific question?

12 Dr. Rasmussen?

13 DR. RASMUSSEN: Well, actually part of the
14 current guidance is that you should establish the full
15 dose response in the phase 2 study. So I think, I
16 mean, that you could, with some confidence, say what is
17 expected of weight loss in phase 3.

18 DR. THOMAS: Dr. Brittain?

19 DR. BRITTAIN: Like the others have said
20 before, I definitely like the idea of the two-stage
21 approach. And in terms of the concept of having some
22 flexibility about the upper bound of the relative risk,

1 and I think that's fine. At the same time, though,
2 there probably needs to be some general standards so
3 that people can power their studies and so that if the
4 results are about what you would expect them to be,
5 everyone knows what that acceptable margin is and also
6 understanding that there is some flexibility.

7 DR. THOMAS: Dr. Proschan?

8 DR. PROSCHAN: Yeah, I mean, I also would
9 favor this two-tier approach, but with respect to the
10 different upper boundaries, depending on how effective
11 it is, I think that's potentially going to be difficult
12 to implement because, how do you define effectiveness?
13 There is going to be a certain amount of arbitrariness,
14 and I think people are already complaining that there
15 is a certain amount of arbitrariness in this business
16 about whether there is a safety signal, and so I think
17 -- and plus I don't think you want to go much above 1.8
18 anyway, so to say, "Well, your drug has pretty good
19 weight loss, we'll allow you to go up to 2.2.," or
20 something, I don't think you want to go there. So as a
21 practical matter, even though on the face of it, it
22 sounds like a good idea, I wouldn't favor changing that

1 upper limit depending on whether there is other benefit
2 because I think that's hard to define.

3 DR. THOMAS: Dr. Rasmussen, I was just
4 wondering if you would want to comment. Is it easier
5 to plan the trial if you know what the fixed boundaries
6 are versus having flexibility on the boundaries?

7 DR. RASMUSSEN: But I think there are
8 different factors that could factor into negotiating
9 those, I mean, prior knowledge. What is the actual
10 concern or signal that is being discussed? So I think,
11 I mean, we would favor, or I would favor, a more
12 flexible approach, though, I mean, it would need to be
13 set, of course, at the end of phase 2 meeting.

14 DR. THOMAS: Dr. Kaul?

15 DR. KAUL: I appreciate the arbitrariness,
16 but when faced with a choice of rigidity versus
17 flexibility, I draw upon my clinician's role, and that
18 is, how we do tradeoffs in day-to-day clinical
19 decision-making. So it makes common sense and clinical
20 sense to do that, although I appreciate the numerical
21 arbitrariness about it.

22 DR. THOMAS: Dr. Konstam?

1 DR. KONSTAM: You know, I mean, I certainly
2 resonate with what you're saying, Sanjay, but, you
3 know, this is just a guidance, right? I mean, I think
4 that at the end of the day there is going to be the NDA
5 and there are going to be decisions made on a multitude
6 of information, and so if, for example, you wound up
7 seeing that the upper boundary was 1.7, but there is
8 almost no efficacy -- okay? -- or the efficacy is very
9 small, obviously that's going to play in. On the other
10 hand, if you have some blockbuster efficacy that you're
11 only going to know about after you've done your phase 3
12 study, maybe people will be a little looser about
13 interpreting it. I see it as a guidance and as a --
14 you know what I'm saying?

15 DR. KAUL: That is precisely what I was
16 trying to get at. If you have a borderline efficacy,
17 why would you even want to tolerate a 1.7? I would not
18 even tolerate 1.3, 1.4.

19 DR. KONSTAM: Well, that's why the 1.8 is not
20 sufficient. Okay? It's a piece of guidance. Right?
21 So I think we're saying the same thing.

22 DR. KAUL: On the other hand, if the sponsor

1 understands that they have less of a bar to overcome
2 because the efficacy is so much overwhelming, I think
3 we are incentivizing them. So it's a win-win that way.
4 So I think we have to strike a careful balance here. I
5 mean, there is clearly an unmet clinical need, and I
6 agree with you, we are essentially repackaging old
7 drugs for weight loss, and if you want to incentivize
8 them for innovation, I think this plays into that as
9 well.

10 DR. THOMAS: Dr. Alexander?

11 DR. ALEXANDER: Yeah, I just want to expand
12 on that a little bit. I think this idea of having
13 flexibility, in principle, is a good thing, and it may
14 lead to some logistical challenges in program planning
15 or investment decisions because of residual uncertainty
16 in development programs, but I think the idea that it
17 might also incentivize us to better understand the
18 efficacy of weight loss drugs, not just on weight loss
19 but on other metabolic parameters, on other disease
20 states, orthopedics, et cetera, really might help us
21 move the field forward in terms of really understanding
22 the risk- benefit tradeoff of obesity drugs.

1 DR. THOMAS: And I just had a question,
2 Sanjay, if you'd want to comment. So flexibility goes
3 both ways. So you would be not accepting of a drug that
4 has low benefit even with an upper limit of 1.4, so if
5 you had a drug that had a 30-percent weight loss, would
6 you increase the upper limit above 1.8?

7 DR. KAUL: Repeat the second half?

8 DR. THOMAS: So if it has very small
9 efficacy, your tolerance for the upper bound is much
10 lower, 1.8 would be too high for you.

11 DR. KAUL: 1.8 would be too high.

12 DR. THOMAS: But if you had a drug that had a
13 very high efficacy, let's say 30-percent weight loss,
14 would you necessarily increase the upper bound?

15 DR. KAUL: Yeah, I mean, that's where I would
16 ask for insights from statisticians. Mike mentioned
17 that he's unwilling to raise the boundary from 1.8. I
18 don't think I would be that rigid. There is already a
19 precedence here. We have a product which is doing a
20 pre- approval trial, and the boundaries there are
21 higher than 1.8, at least for the first tier. So I
22 think that could be negotiated on a case-by-base basis.

1 Where do we draw the upper ceiling? Yes, but I think
2 it's negotiable.

3 DR. THOMAS: Dr. Proschan?

4 DR. PROSCHAN: Actually you hit on my point
5 because I thought you were saying one thing before, and
6 then I thought you were implying that if it had greater
7 efficacy, you would require to show like 1.5 instead of
8 1.8. I thought that's what you had just said earlier.

9 DR. KAUL: No, no.

10 DR. PROSCHAN: Okay.

11 DR. KAUL: I mean, it is somewhat
12 counterintuitive; isn't it? I mean, you expect weight
13 loss to translate into cardiovascular benefits, and
14 greater weight loss should translate into greater
15 cardiovascular benefits; therefore, it's easier to
16 overcome a more stringent threshold. But that's not
17 the construct here; it's the opposite. So I can
18 understand the confusion.

19 DR. THOMAS: Any further comments?

20 Dr. Goldfine?

21 DR. GOLDFINE: I think I'm just going to make
22 one to whoever responded first to Dr. Kaul's comment,

1 and that was that -- I think it was actually Dr. Hiatt
2 -- that using the paradigm that since most patients
3 don't take these drugs for very long, we will have
4 revealed most of the risk in the situation. I think we
5 don't understand completely why patients are not taking
6 drugs for chronic diseases for extended periods of
7 time, as seen in the TZD data, where it looked like
8 they were taking it for 3 months, and there were
9 (indiscernible) data that we saw this morning, but I
10 think that when patients, if they actually have a drug
11 that is effective and tolerable, they can get on a
12 scale, and they will be taking it long term for weight
13 loss if they're actually seeing benefit, and I think
14 the potential for real chronic use is actually quite
15 different here, they can see it, they can feel it, they
16 are very aware of it. And I would just be a little
17 cautious.

18 So I do agree with the two-tiered approach,
19 but I don't think that we will really be revealing all
20 the risk in the short intervals of time, but I think
21 it's a very telling time period to look at.

22 DR. THOMAS: Dr. Felner?

1 DR. FELNER: Yeah. I had a question that I
2 think I tried to ask earlier. It might go to Dr. Bray,
3 or anybody that had given some information on the
4 previous obesity drug studies, but I know you said that
5 those that don't respond in the first 3 months or 3 to
6 6 months are likely not to respond at all, but did we
7 get a percentage of patients? What was the percentage
8 of patients that actually didn't respond in the first 3
9 months?

10 DR. THOMAS: Dr. Bray? I know that may not
11 be your --

12 DR. BRAY: I couldn't find it anywhere, so
13 it's --

14 DR. THOMAS: Yeah, I'm not sure that was your
15 presentation, but you're a PI on it.

16 DR. FELNER: Or if you know the answer.

17 DR. BRAY: I showed you the figure with part
18 of the data. There is actually more on that figure,
19 and I would need to get the reference for it. It was
20 the paper by Finer (ph) and Ryan, I think in 2006, I
21 can get it for you if you'd like. They actually did a
22 RAC analysis curve, a responder analysis curve, to look

1 at the optimum time point after initiation of therapy
2 to get the maximum long-term response. So it's a 3-
3 month response, 3-month evaluation, and a 12-month
4 follow-up to determine what it looked like. I showed
5 you just the normal people, there are also diabetic
6 patients in the same figure, which I left off for
7 simplicity yesterday. But it's Finer (ph) and Ryan.
8 If you want it, I'll get the exact papers.

9 DR. THOMAS: Any other comments?

10 (No audible response.)

11 DR. THOMAS: Okay. If there are no further
12 comments, I'll summarize the discussion. I believe
13 everyone who did speak suggested, when they spoke about
14 this approach, that a two-tiered approach seems the
15 most reasonable approach for a study design. There
16 needs to have some flexibility was the opinion of
17 several of the panel members in what the boundaries
18 should be for this tiered approach for the first tier,
19 where there may be some more flexibility in the first
20 tier, to allow a drug that has more efficacy to have a
21 little more tolerance for risk, and a drug that has
22 less efficacy have less tolerance for risk. The second

1 phase would, of course, have to answer the definitive
2 risk as part of that study.

3 There is a concern that if you don't do a
4 two- tiered approach, that there would be problems with
5 delaying these drugs to market, and there may be an
6 excessive amount of cost.

7 There is also a concern that changing
8 boundaries may be difficult to determine because there
9 is somewhat of an arbitrary nature of, what do you
10 decide is the relative efficacy of the drug? So in
11 some respects, having a fixed boundary makes it easier,
12 but in the opinion from our industry representative,
13 flexibility actually may be advantageous to industry as
14 well.

15 We do need to have some flexibility on the
16 boundaries, or at least have this two-tiered approach,
17 so we can understand what are the other risks and
18 benefits beyond cardiovascular risks and benefits of
19 these agents in obesity, such areas of I think sleep
20 apnea was mentioned, osteoarthritis, because we won't
21 get a good understanding of that if we don't have an
22 approach which allows those areas to be investigated as

1 well.

2 And we may not reveal all of the risks in the
3 first tier, and hopefully in the second tier that's
4 captured.

5 Dr. Kaul, you had a comment or a correction?

6 (No audible response.)

7 DR. THOMAS: Does that seem reasonable to
8 everyone, or is there something I should correct?

9 (No audible response.)

10 DR. THOMAS: Okay. We'll move on to the
11 second question, which is setting non-inferiority
12 margins for excess CV risk on the basis of risk
13 difference versus relative risk.

14 Dr. Weide?

15 DR. WEIDE: Yeah, I guess this is one of my
16 pet peeves all the time. You know, it's very clear
17 which one the TV uses, they use relative risk. You
18 know, if you have an absolute risk of one in a million
19 that goes to two in a million, that doesn't impress us
20 very much. That's not very -- clinically you go, "Geez,
21 I wonder," but it's 100-percent relative risk. On the
22 other hand, if it's 10 out 100 that goes to 20 out of

1 100, that's still only 100-percent risk, relative risk.
2 They have the same relative risk. But I think we would
3 all say that's absolutely unacceptable.

4 So I know that relative risk is what you hear
5 on TV, it's what flags all the journal articles, but
6 absolute risk is what we're really concerned with, with
7 our patient, and I would be strongly in favor of seeing
8 the absolute risks. I think that's a critical way to
9 look at this. Relative risk does not tell you what's
10 going to happen, you know, what the risk is to an
11 individual patient, and the numbers are inflated or
12 deflated, depending on what the absolute risk is for
13 your patients.

14 DR. THOMAS: Dr. Kaul?

15 DR. KAUL: I think both indices have
16 desirable attributes. People resonate with absolute
17 risk when you're communicating risk. In fact, somebody
18 said that absolute risk should be used for policy
19 decision-making and relative risk should only be for
20 research purposes, and I can appreciate the sensibility
21 there. Absolute risk may also have some advantage in
22 terms of making a sample size more feasible. The

1 critical advantage of relative risk in trial designs,
2 like such as these, non- inferiority or ruling out of
3 unacceptable harm, is that you expect an event rate in
4 the control arm, but the observed event rate may
5 actually be much lower than the expected one, and if
6 you fix the margin in terms of absolute risk, you're
7 willing to tolerate a greater degree of inferiority for
8 the same amount of absolute risk margin because your
9 comparatory event rate is low. So if I were given the
10 choice of just one index, relative risk would be my
11 preference for that reason because I have never seen
12 observed event rates be the same as the expected event
13 rate. We always inflate the expected event rate for
14 sample size estimation. So I think it's important to
15 fix your boundaries or margins in relative risk rather
16 than absolute risk.

17 DR. THOMAS: Dr. Kramer, did you have a
18 comment on that?

19 DR. KRAMER: When I first read this question,
20 I was thinking like the -- I'm sorry, Dr. Weide? -- in
21 terms of clinically risk difference has always meant
22 more to me, absolute risk has meant more to me, but

1 when you look at the way B is worded, it's talking
2 about for setting the non-inferiority margins, and I
3 think when you're thinking in those terms, the comment
4 that Dr. Kaul just made is critical because we're
5 actually trying to decide up front how many patients
6 should be studied to get a certain number of events,
7 and you really won't know what the absolute event rate
8 is. So I think that for this question, as it's worded,
9 for the sake of sample size calculations, I understand
10 that relative risk probably makes more sense. When you
11 get results and you're trying to interpret it, you want
12 to look also at absolute risk -- I mean, absolute
13 effects.

14 DR. THOMAS: Dr. Cooper?

15 DR. COOPER: I agree that both provide
16 helpful information. For me, as I think about it, it
17 also depends sort of on the expected incidence of the
18 events. So as Lamont noted, a really rare event, a
19 doubling of risk really might not mean that much in
20 terms of absolute risk. But also for me, when I think
21 about it in terms both from a research and a clinical
22 perspective, it also depends on the seriousness of the

1 event and the benefit of the therapy that we're
2 considering. So death in a therapy for a condition
3 that's not life-threatening, doubling of risk even in a
4 rare event might be really important.

5 So in this context, as I put all the
6 decisions through that rubric, I would think that
7 relative risk, if we had to choose one, would provide
8 probably the most important information for this safety
9 margin, but both really do help us understand what the
10 true risk might be.

11 DR. THOMAS: Dr. Konstam?

12 DR. KONSTAM: Yeah, I think you need both,
13 and I think that there is a fixed relationship among
14 relative risk, absolute risk, and baseline event rate
15 within that particular population. Now, there was a
16 brief discussion yesterday about the likelihood that a
17 relative risk would be constant across a population
18 with varied baseline event rates, and that's a critical
19 assumption. If that assumption breaks down, then the
20 whole ability to extrapolate from this high-risk
21 population to the broader population disappears. And
22 you can't really figure that out probably during the

1 course of the pre-approval investigation because you
2 just don't have enough studies and don't have enough
3 events in your low-risk population.

4 But going with the assumption that it's
5 constant -- and I think probably as a first
6 approximation, it probably is right -- then becomes
7 enormously valuable, because if you know the relative
8 risk, then a clinician can apply that relative risk to
9 the patient in front of him or her with a particular
10 baseline rate. Now, importantly, I think, what really
11 matters to the patient is the absolute risk, and so the
12 issue then becomes this, that you can determine that
13 there is a 1.8 upper boundary that is being driven by a
14 high-risk population, and that is going to translate
15 into a relatively greater absolute excess risk than it
16 will be in the lower risk population, and you may wind
17 up concluding that the drug is acceptable for approval
18 in a constrained low-risk population where the efficacy
19 is sustained and the absolute excess risk is very
20 small, and so that's really the way I would approach
21 it.

22 DR. THOMAS: Dr. Hiatt?

1 DR. HIATT: Well, this repeats a lot of
2 what's said, but the table was really helpful. If you
3 look at excluding a relative risk of 2, then you need
4 87 events, but if the event rate is .5, then you have
5 five excess events; if it's 1.5, you have 15. So the
6 question on setting the margin, if it's based on
7 relative, would be invariant, but if it's based on
8 absolute, as Sanjay said, the observed rate is less
9 than the anticipated. You would have to actually do
10 some kind of adjustment if that occurred. So I think
11 as far as setting the margin, you could probably make
12 either one of them work.

13 For interpreting the data, we would calculate
14 number needed to harm, and then you need an event rate
15 of .5, you know, you would have a much greater, larger,
16 population to expose to the drug to harm. But remember
17 -- one other comment -- these are irreversible harm
18 events; so MI, stroke, and death are things that in an
19 otherwise healthy population should not be tolerated.
20 So I think the irreversible harm nature of it is
21 compelling, and even if the absolute risk is extremely
22 low, it's an absolute risk of something that is

1 consequential for someone in that age group.

2 DR. THOMAS: Dr. Proschan?

3 DR. PROSCHAN: Yeah. I mean, people have
4 already said some of the things I was going to say. I
5 absolutely agree that you need to look at relative risk
6 as the primary driver, but one reason that people
7 haven't mentioned that I think is worth mentioning is
8 there has been a discussion about using a meta-analysis
9 to combine data from different sources, and one of the
10 assumptions in a meta-analysis is that these different
11 sources are combinable, and if you've got relative
12 risk, it's much more likely that they will be
13 combinable. If you take different data sources with
14 different absolute risks, then the benefit in terms of
15 absolute risk is likely to be quite different in those
16 different studies.

17 DR. THOMAS: Dr. Jensen?

18 DR. JENSEN: So I was thinking that to
19 determine your absolute risk you're willing to
20 tolerate, you need to have information on the benefit.
21 If we had a compound that was as good as the DPP that
22 reduced the incidence of new diabetes by two-thirds

1 over the course of 5 years, you might be willing to
2 accept a certain adverse event rate in a low population
3 that could be pretty low, but it might be a high
4 relative risk, depending upon that population.

5 So I think part of what I'm trying to
6 struggle with is if you know the benefit, you have a
7 better idea of what absolute risk you're willing to
8 take to achieve that benefit, and then knowing that
9 absolute risk helps you back into relative risk. And I
10 would appreciate any feedback from the statisticians if
11 that's a wrong way of thinking about how to approach
12 this.

13 DR. THOMAS: Dr. Brittain or Dr. Proschan?
14 Dr. Gregg.

15 DR. GREGG: I don't consider myself a
16 statistician, but I think you're absolutely right, I
17 don't think we can compare across outcomes if we're
18 using relative risk, and that to me is one of the most
19 important reasons to at least have absolute risk a
20 primary outcome for the interpretation. I think the
21 distinction here is what's used for the design, whereas
22 relative risk might be appropriate for the design, the

1 absolute risk is more important for the interpretation
2 so that we can compare across outcomes.

3 DR. THOMAS: Any specific comment on Dr.
4 Jensen's question about the impact of benefit in
5 looking at relative risk or absolute risk?

6 (No audible response.)

7 DR. THOMAS: Okay. Any other comments or
8 questions?

9 (No audible response.)

10 DR. THOMAS: Okay. If there are no further
11 questions or comments, I will summarize. Relative risk
12 is what tends to be publicized, what hits the
13 television, what's reported in papers; but absolute
14 risk is probably what's important.

15 Dr. Cooper?

16 (No audible response.)

17 DR. THOMAS: Absolute risk is probably what
18 is important for a patient and the physician to help
19 guide the patient in a decision. One of the
20 usefulnesses of using absolute risk is it's probably
21 quite helpful in estimating sample size to design a
22 trial. A relative risk is useful if the event rate is

1 lower than expected as opposed to the absolute rate of
2 risk, and in many trials, as we've seen, even ones
3 presented over the last 2 days, the risk estimation of
4 the event rate tends to be lower than expected, and so
5 it's not an unusual situation to see that.

6 One of the things that should be under
7 consideration when you use absolute versus relative
8 risk is what type of event is happening. For example,
9 an event that has a dire consequence, such as death,
10 should be taken in light of the condition that's being
11 treated and a condition where there may not be a fatal
12 event or what's considered a nonfatal disease. So the
13 event type is also important to consider in this
14 discussion of relative risk versus absolute risk.

15 In terms of meta-analysis -- because that is
16 one of the approaches that could be used as part of the
17 analysis for cardiovascular specifically related to
18 outcomes trial -- meta-analysis requires that the
19 different studies are combinable and to help in that,
20 relative risk is actually more useful, if you need to
21 combine studies, than absolute risk.

22 And I think the last part is that the

1 relative risk is better for that purpose, but the
2 absolute risk is probably better at informing the
3 patients and looking at how the outcomes translate into
4 the practice for a clinical patient, and benefit has to
5 be somehow assessed along with the risk to make it more
6 meaningful for interpretation.

7 Any other comments or corrections?

8 (No audible response.)

9 DR. THOMAS: Okay. We'll go on to Question
10 C. Primary endpoint of strict MACE -- CV death,
11 nonfatal MI, nonfatal stroke -- versus MACE-Plus --
12 example, hospitalized unstable angina, emergent
13 coronary revascularization.

14 And, Dr. Cooper?

15 DR. COOPER: Our focus earlier on Question 1
16 was on the notion of maximizing endpoints, and I think
17 we reached some consensus on the fact that adding the
18 broader populations does give us a chance to get more
19 endpoints and reach the desired sample size. And it
20 also includes carefully adjudicated endpoints with the
21 caveat that we can generalize.

22 For this particular type, this question, I'm

1 not so sure that the tradeoff by adding the additional
2 endpoints from MACE-Plus is worth it. We saw in the
3 background information that the update provided that in
4 fact, depending on the relationship of the safety risk,
5 misclassification or adding these Plus endpoints might
6 obscure things in a different direction, so it would be
7 really difficult to interpret what you'd find. And in
8 addition, an additional thing to think about is that
9 some of the additional endpoints in the MACE-Plus are
10 much less subjective. So someone who is very vocal
11 might be able to be hospitalized for angina. In
12 addition, it depends on access to care and the ability
13 to find health care providers and those kinds of
14 things. And so those are much more subjective and I
15 think would have difficulty, both in terms of
16 adjudication in what they might mean. So for those
17 reasons I would be much more in favor of sticking with
18 the original MACE and not adding the Plus part of it.

19 DR. THOMAS: Dr. Kaul?

20 DR. KAUL: I completely agree. I think
21 enrichment has some desirable attributes, but
22 minimizing or reducing bias is equally desirable, if

1 not more. And if you end endpoints that are somewhat
2 subjective and driven by local individual geographic
3 practice patterns, you are adding noise and thereby
4 biasing the results towards the null, which will
5 provide you with a false sense of reassurance about
6 ruling out cardiovascular risk.

7 So in principle, I agree with you, that
8 keeping it to MACE, which are less subject to
9 ascertainment and adjudication bias, is the way to go.
10 However, there are ways around it. If you are going to
11 expand the endpoint, you are better off using endpoints
12 that are less subjective, and so perhaps ischemia-
13 driven revascularization requires documentation of
14 ischemia, which is less subjective. So if you're going
15 to add that, I would recommend ischemia-driven
16 revascularization, more objective endpoints which can
17 be standardized, which can be adjudicated better,
18 therefore minimizing bias. But my ideal preference
19 would be to keep it pure strict MACE rather than
20 expanded MACE.

21 DR. THOMAS: Dr. Brittain?

22 DR. BRITTAIN: I agree with the last two

1 comments. The only thing I would add is if it was felt
2 necessary to expand the endpoint, that the original
3 MACE endpoint be an extremely important sensitivity
4 analysis.

5 DR. THOMAS: Dr. Konstam?

6 DR. KONSTAM: Yeah, no, I agree with what was
7 said, and I think Sanjay said it very eloquently, and
8 actually I just wanted to bring to mind the CAPRICORN
9 study, which was a post-MI low ejection fraction study
10 where the original endpoint was all-cause mortality,
11 and midway through, the investigators were concerned
12 about low event rate and so expanded the endpoint to
13 include other forms of cardiovascular hospitalization,
14 all of which did nothing but add noise, and at the end
15 of the day, they didn't hit their primary, but guess
16 what, they hit all-cause mortality with a P of .03, but
17 because they expanded the endpoint, they had reduced
18 the alpha assigned to that, so technically they had a
19 negative trial.

20 So you really get into trouble doing it, and
21 I think that's a good example of just what Sanjay was
22 talking about, of diluting it, and particularly of

1 concern when you're interested in safety. You know,
2 there's nothing easier to prove on what proves safety
3 than -- well, first, by taking the patient off the
4 drug, that's one way to do it, and the other way to do
5 it is by throwing in a lot of stuff in your endpoint
6 that don't count.

7 So I would really favor sticking to hard,
8 very clearly adjudicable endpoints. I don't believe
9 that ACS, per se, necessarily fits into that category.

10 The other thing I would say about this is I
11 don't know why you would use CV death and not all-cause
12 mortality. If you're interested in -- and usually the
13 reason we use CV mortality in efficacy trials, and
14 including in the MACE composite, is because we believe
15 that the drug has its impact on cardiovascular events,
16 and that's what we want to demonstrate. Here we're
17 looking at safety, and if the drug happens to reduce
18 mortality by preventing car accidents, that offsets
19 mortality from cardiovascular death, they ought to get
20 credit for that, you know, that's okay. The only thing
21 that really matters to the patient from a safety
22 perspective is all-cause death, I don't think it's

1 cardiovascular death.

2 DR. THOMAS: Dr. Temple?

3 DR. TEMPLE: Marv, the usual argument there
4 is if you get a population that has other causes of
5 death because the study is a several year study, you
6 will once again find a bias toward no difference if you
7 include those other things, or you might. That's the
8 argument for it, for sticking to cardiovascular death.
9 Also, there is a general view that if you try to
10 distinguish various kinds of cardiovascular death, it's
11 hopeless, you won't be able to do that, but that you
12 can often tell cardiovascular from other.

13 DR. KONSTAM: Yeah, well, you made the point
14 earlier that the reason we're focusing on
15 cardiovascular is we're good at spotting it, not
16 necessarily because we believe cardiovascular safety is
17 more important than any other kind of safety, and
18 despite the fact that I'm a cardiologist, I agree with
19 that. So I think one of the reasons we're focusing on
20 CV is because we can measure it, but if we could do
21 cancer, we would be interested in that, too.

22 So sort of my comments are -- so you

1 convinced me about that. And so I would say, I mean,
2 my reaction at this point is really the safety piece.
3 You know, I think all -- I don't know -- I'd be okay
4 with all-causes part of the composite myself. I'd be
5 interested in what other people think.

6 DR. THOMAS: Dr. Kaul?

7 DR. KAUL: Yeah, I think we have to be
8 careful about including all-cause mortality
9 particularly in this particular scenario because there
10 is weight loss, weight loss is associated with
11 reduction in cancer mortality, and that reduction in
12 cancer mortality will mask any increase in
13 cardiovascular risk by incorporating all- cause
14 mortality. So I would be somewhat reluctant to use
15 all-cause mortality in the composite endpoint.

16 DR. THOMAS: And just a comment is I think
17 that has been shown in the surgical trials. I don't
18 think, because of the duration, any of the medical
19 trials have ever shown that.

20 DR. KAUL: Agreed, and the duration of the
21 weight loss as well.

22 DR. KONSTAM: Can I just ask Dr. Kaul a

1 question?

2 DR. THOMAS: Sure.

3 DR. KONSTAM: If I told you that I had a drug
4 that might cause cardiac death but will prevent you
5 from dying from cancer, what would you say? You'd say,
6 "No, I don't want to take that drug because --

7 DR. KAUL: It depends on what age I am and
8 what condition I am in.

9 DR. THOMAS: Dr. Waters?

10 DR. WATERS: Yeah, I would like to make a
11 couple of points about specific endpoints, and I
12 basically agree with the thesis that we need endpoints
13 with objective evidence.

14 And the first point I would like to make is
15 to make a plea to include unstable angina as part of
16 the composite endpoint, and there is really one reason
17 not to and four reasons why it's a good endpoint to
18 include. The one reason not to is that on the surface
19 it's very subjective and capricious, but if you take
20 unstable angina and you require objective evidence of
21 worsening myocardial ischemia associated with urgent
22 hospitalization, this is an endpoint that seems to go

1 in the same direction and seems to be relatively noise-
2 free, in at least statin trials.

3 The four reasons why it's good to include it
4 as an endpoint, I think, is, first of all, the
5 pathophysiologic mechanism is exactly the same as
6 myocardial infarction, so you have a plaque rupture,
7 and whether or not you have myocardial damage really
8 depends upon the size of the thrombus.

9 The second reason is because it's a very
10 expensive endpoint, it results in hospitalization and
11 often myocardial revascularization, so it's a huge
12 economic burden.

13 The third reason is it's a big quality of
14 life issue for the patient.

15 And the fourth reason is because it will
16 increase your event rate by approximately a third. It
17 depends on the population that you're studying and how
18 strict you are with the criteria, but having one-third
19 extra endpoints is a really big deal and reduces the
20 size of your study and the costs.

21 The other endpoint I would like to just
22 briefly talk about is myocardial revascularization.

1 And I used to think that that probably was a pretty
2 good endpoint, it's pretty objective, you can tell
3 whether you've had your chest split open or a stint put
4 in your heart.

5 But for the past several years I've been head
6 of a Cardiovascular Endpoints Committee, and it sort of
7 really opened my eyes as to how vague and difficult it
8 is to classify some of these endpoints. Dr. Kaul
9 mentioned yesterday a patient hospitalized with angina,
10 and whether the patient got hospitalized is extremely
11 variable. Well, whether the patient has angina or not
12 is also a very difficult question. There are a lot of
13 patients that get hospitalized every day in this
14 country with chest pain that is called angina, but when
15 you read the description of it in the case record, it
16 certainly doesn't sound like angina. And whether
17 someone gets revascularized when they have chest pain
18 is extremely variable from one place to another across
19 the country and from one physician group to another.
20 It probably depends more on things like insurance than
21 it does on the quality of the chest pain.

22 So revascularization is an endpoint. I would

1 be a lot more skeptical about if you make it
2 revascularization with objective evidence of ischemia,
3 that makes it a little better, but you could get picked
4 up off the street with atypical chest pain and turn out
5 to have ischemia and get revascularized, I think that
6 happens a lot, too.

7 So unstable angina with objective evidence,
8 yes. Coronary revascularization maybe not so much.

9 DR. THOMAS: Can I ask just a quick question
10 related to that? Do you think that's true for both
11 CABG versus angioplasty, or do you think that that's
12 not consistent?

13 DR. WATERS: I think it's a bigger deal
14 getting a CABG, so there is more resistance to it, and
15 there is one step in the referral process, so that you
16 have a cardiologist or a doctor that sees you with
17 chest pain, you get hospitalized, the cardiologist does
18 an angiogram, and at the same time, he puts in a stint,
19 but if you're going for bypass surgery, it's a whole
20 other step, so it requires a little bit more
21 objectivity and that you've really got something to get
22 a CABG. So I think CABG is probably a little better

1 than PCI.

2 DR. THOMAS: Dr. Hiatt?

3 DR. HIATT: The only thing I would add to the
4 endpoint discussion is if the drug is sympathomimetic,
5 that mechanism may lead you to add in new-onset atrial
6 fibrillation or new-onset heart failure. If the drug
7 is arrhythmogenic, you might focus on sudden cardiac
8 death. If you're worried about atheroprogession, and
9 we've sort of talked about that. So in general I think
10 we should be cautious about diluting the MACE endpoint,
11 but because these drugs do things that you might expect
12 could cause certain cardiac outcomes, you could
13 conceive of that.

14 DR. THOMAS: Dr. Alexander?

15 DR. ALEXANDER: Yeah, so I agree with
16 everything people have said. I think when we think
17 about endpoints, you know, the one thing we haven't
18 talked about is -- and it's more challenging here when
19 we're talking about a safety event than an efficacy
20 event, and as Dr. Hiatt just alluded to, the thing
21 that's -- the fourth, I guess, critical element of a
22 good endpoint is that it's likely to be impacted by the

1 treatment that we're interested in studying. And the
2 nice thing about MACE and unstable angina, if it's
3 objectively defined, is that they all follow a similar
4 pathophysiologic mechanism.

5 And so we've been focused on MACE, and so I
6 think, as a general rule, I would stick to MACE as our
7 main endpoint, but if there are other endpoints that we
8 think might be impacted by the drug that we're studying
9 -- A-fib, heart failure, et cetera -- then it might
10 make sense to probably not add those to the MACE
11 endpoint as a big composite, but look at those in
12 addition.

13 And that brings me to my second comment,
14 which is really that this analysis is going to include
15 a sensitivity analysis. I think we're likely to look
16 at the components of MACE as well. I mean, a drug that
17 made it within the boundary for the triple composite
18 but that had a worrisome hazard ratio for CV death I
19 don't think would be reassuring even though the number
20 of events would be low and it might be below the
21 whatever cutoff upper confidence interval we had put.

22 DR. THOMAS: Dr. Proschan?

1 DR. PROSCHAN: Yeah, so one of the things
2 that I said yesterday, and I really believe, is that
3 this 1.8 margin is a procedure, but what's really
4 important is what its properties are. So I want to be
5 able to say we had good power, even if the relative
6 risk was 1.5, we still had good power to see that and
7 to see the increased risk, and to do that, you need
8 more events, you need a fair number of events, like at
9 least 200, and if -- if -- this is the big if, of
10 course -- if enriching the endpoint doesn't add noise,
11 if it is the same disease process, so there's no reason
12 to believe that it would be different than the story
13 for MI, for example, then I would say that we need to
14 do everything we can to increase the event rate, and
15 that's one thing that we can do to increase the event
16 rate.

17 Just a couple of other things. As I said, I
18 think we have to do multiple things to increase power,
19 one of which -- you know, probably the most
20 controversial -- switching from a two-tailed .05 to
21 one-tailed .05, but the other thing that one of the
22 public speakers mentioned was the idea of using a risk

1 equation, and I think this is probably a good idea as a
2 secondary analysis, to take into account the drug's
3 effects on multiple things and say, what is your 10-
4 year risk of a cardiovascular event? I think that might
5 be a useful additional thing to do. So for someone who
6 has the cardiovascular event, they're counted as having
7 100-percent probability of having the cardiovascular
8 event; for someone who doesn't, then you use the risk
9 equation, and so -- well, I guess I'll stop there.

10 DR. THOMAS: Dr. Weide?

11 (No audible response.)

12 DR. THOMAS: Dr. Yanovski?

13 (No audible response.)

14 DR. THOMAS: Any further questions or
15 comments?

16 Dr. Kaul?

17 DR. KAUL: If I may respond to Mike's
18 suggestion of using a risk score as an endpoint, I
19 think it's fraught with problems because it is a
20 probabilistic estimation of an event that may or may
21 not occur and relies on the risk score having the
22 discrimination to be able to predict quite reliably

1 whether the patient or subject will have an outcome.

2 So I am somewhat hesitant to use a risk equation or a
3 risk model.

4 And you know this better than anybody else,
5 the risk models are based on only point estimates, and
6 there is uncertainty around that, which we don't talk
7 about, but that's one of the reasons why these risk
8 models don't have the calibration or the discrimination
9 that we demand, because nobody sees those uncertainty
10 bounds. So I would stay away from using risk models as
11 an efficacy or a safety endpoint.

12 DR. THOMAS: Dr. Proschan?

13 DR. PROSCHAN: Yeah, I mean, I did say
14 secondary analysis.

15 (Laughter.)

16 DR. PROSCHAN: I would not use that as the
17 primary, but I think that could be, you know,
18 confirmatory. And we desperately need something,
19 something more than what we're going to get. We're not
20 going to get enough events to really be able to say
21 anything definitive, and with the risk equation, we're
22 still not going to be able to say anything definitive,

1 but if that also goes in the same direction, then I
2 think that's better than if it didn't.

3 DR. THOMAS: Dr. Brittain?

4 DR. BRITTAIN: I just want to say that I like
5 Dr. Proschan's idea.

6 DR. PROSCHAN: That's not my idea. That was
7 one of the speakers who brought that up.

8 DR. BRITTAIN: Okay. And I agree, definitely
9 not as a primary endpoint, which is not what you're
10 proposing, but as a sensitivity analysis or secondary
11 analysis, as a way of letting everybody contribute to
12 the analysis, with, you know, interpreting it
13 cautiously, but I think it could be helpful.

14 DR. THOMAS: And just to confirm the way it
15 would be used, you would have the expected rate from
16 the risk equation and you would see the decrease or
17 changes rather than re-analyzing the risk at the end of
18 the study with new risk factor values?

19 DR. PROSCHAN: I mean, what my interpretation
20 was is you could basically do a t-test where each
21 person that died has a 1, each person that doesn't die
22 has a probability of dying within 10 years, .2, .05,

1 and do like a -- you could do a nonparametric test to
2 see whether that's different in the two groups.

3 DR. THOMAS: Dr. Goldfine?

4 DR. GOLDFINE: All right. I'm going to
5 suggest an idea that I would like the statisticians to
6 comment on because it's a little nontraditional. I
7 think that when you're setting up your pre-approval,
8 you really want the wider safety net and the larger
9 number of observations of events to actually help
10 inform about potential risk, and I think that in the
11 pre-approval window, I would be more inclined to allow
12 documented ischemia or ischemia-driven
13 revascularization, yet when I look at all of the larger
14 trials -- Dr. Konstam noted one -- I would bring the
15 proactive up as another example where the noise then
16 ends up defeating the purpose and you end up with a
17 neutral trial where the standard MACE might have been
18 beneficial or in another direction. So I might
19 tolerate using these events in the pre-approval window,
20 but when I really get to the hard outcome or the later
21 considering at that point including only the harder
22 MACE, and I would like sort of an adaptive comment like

1 that from our statisticians.

2 DR. THOMAS: Dr. Brittain or Dr. Proschan?

3 DR. PROSCHAN: So if I understood you, you're
4 saying you would tolerate sort of a looser endpoint in
5 the pre-approval, but for the final trial, after it's
6 approved, you would want regular MACE, no --

7 DR. GOLDFINE: So, again, I think that the
8 plaque rupture and everything is along the same
9 pathophysiological route as the MI, you would end up
10 increasing the number of events, albeit with some
11 possibility of contamination by noise, the way in which
12 we admit these patients, the revascularization, the
13 changes that occur over time as studies come in and out
14 saying that we should use medical therapy or we should
15 use a surgical intervention.

16 So I think I would actually feel a little bit
17 inclined to allow them in the pre-approval window where
18 I would then be increasing the number of events,
19 feeling a little bit better that there isn't perhaps a
20 terrible safety signal by including them, but then
21 refine later, and that might actually help with the
22 sample sizes that would be necessary in the development

1 process.

2 DR. PROSCHAN: I mean, that makes perfect
3 sense to me. I would go along with that.

4 DR. THOMAS: Dr. Brittain?

5 DR. BRITTAIN: Right, I agree. It sounds
6 like a reasonable idea.

7 DR. THOMAS: And other further comments or
8 questions?

9 (No audible response.)

10 DR. THOMAS: If not, I'll summarize this one.
11 So just to start off, enrichment has desirable benefits
12 in terms of having an increased amount of events, but
13 we have to be careful that we don't increase bias,
14 which can minimize some of the risks that could be
15 seen.

16 Events have to be adjudicated. And MACE-Plus
17 unfortunately may be more subjective and can add noise
18 or hide information that could change risk evaluation
19 in terms of obscure what the real risk is but also can
20 obscure what the real benefit is.

21 But if you do expand MACE-Plus, it would be
22 better to use less subjective endpoints, and there was

1 some controversy over what less subjective endpoints
2 would be. One thought was a less subjective endpoint
3 would be ischemic revascularization; however, there are
4 concerns that in certain parts of the country and
5 certain practice patterns, that this is not as reliable
6 in terms of being quite subjective of what's
7 revascularized or not. Angioplasty probably is more
8 subjective than probably CABG because of additional
9 steps that have to be taken, but there is an advantage
10 to using unstable angina or hospitalization for
11 unstable angina is that the pathogenesis is actually
12 similar to the other events that you see in MACE.

13 Overall, most of the panel thought if we
14 could stick to MACE, that would be the best idea as
15 opposed to MACE-Plus but understanding there are some
16 important factors of using MACE-Plus, which would be
17 the increased event rate and using events that are
18 MACE-Plus or related to the pathogenesis of MACE.

19 Other things that are important is that there
20 should be some examination of MACE, if that is what is
21 used, not just about the composite, but each of the
22 components, because if there was something concerning

1 in the sensitivity analysis of the components, that
2 should be addressed in the course of the trials or the
3 drug development.

4 The last thing is the question of using other
5 methods in addition to MACE to help answer this
6 question either in a secondary sensitivity analysis.
7 What was brought up was potentially using risk score as
8 a way of assessing what the risk might be and then
9 seeing what the risk reduction is as a secondary or
10 sensitivity analysis, not as a primary endpoint.

11 And one suggestion that was brought up, that
12 one of the ways that you could consider using MACE or
13 MACE- Plus is in a tier-two strategy. The first tier,
14 for approval or decision about what trials to use as
15 you would go for drug development would have an
16 expanded MACE-Plus composite. And then for the final
17 tier approval, you would use actually a more
18 restrictive tier for the tier-two so that you would
19 have more restrictive MACE endpoint only as opposed to
20 MACE-Plus.

21 Any comments? changes?

22 (No audible response.)

1 DR. THOMAS: Okay. I think lunch has worn
2 everyone out.

3 (Laughter.)

4 DR. THOMAS: We're going to move on to number
5 D -- letter D. Primary analysis population that
6 incorporates on-treatment and off-treatment information
7 -- total time analysis population -- versus a
8 population that incorporates only on-drug information -
9 - on-drug analysis population.

10 Dr. Konstam?

11 DR. KONSTAM: Well, so -- and we started
12 getting into this a little bit earlier. You know, I
13 think if you're interested in safety, I actually think
14 that you have to keep the patients on the drug. If you
15 don't do so, before you talk about analysis populations
16 within your trial, I think your first point is, well,
17 what is your study drug discontinuation rate? And if
18 you have a substantial study drug discontinuation rate,
19 I think the ability to pick up a safety signal is going
20 to diminish. And in point of fact, there is no way of -
21 - I don't believe that there is a foolproof way of
22 analyzing your way out of that because the decision to

1 discontinue study drug is not an unbiased decision,
2 and, therefore, you would have all kinds of confounding
3 potentially entering into it.

4 I mean, the obvious answer is, well, then you
5 do an on-treatment analysis, which is a typical safety
6 analysis. And so I would say that I think you have to
7 do that, and I think an ITT analysis where most of the
8 patients have discontinued study drug is of almost no
9 value in assessing safety. So I think my first point
10 would be that patients have to remain on drug. And my
11 second point would be -- and to use an ITT -- but my
12 second point would be to get some handle around it, I
13 think you would have to do an on-treatment analysis,
14 but mostly keep the patient on the drug.

15 DR. THOMAS: Dr. Brittain?

16 DR. BRITTAIN: Okay, I have a somewhat
17 different perspective. I guess if in reality these
18 patients are not going to be on the drugs very long, it
19 seems like we want to get the risk of exposures that
20 they are going to have, and it's true, I think you
21 earlier raised the point, what if the only risk is
22 while they're on drug? That's one thing. But if the

1 risk comes 2 years down the road, if we don't include
2 their information after they've gone off drug, then
3 we're going to miss something important. And, again, I
4 think if people generally are only on these drugs for 8
5 months, that's the risk that patients are going to
6 have. So I do think the ITT analysis has value, and of
7 course it has the great characteristic that it
8 preserves randomization. I do think you do need to do
9 the on-drug analysis, but it's going to be really hard
10 to interpret it.

11 There's no easy answer here, I agree there's
12 no easy answer, but I would prefer the intent to treat
13 as primary, but that doesn't mean that you wouldn't do
14 lots of sensitivity analyses to try to understand
15 differences and the results of the different analyses.

16 DR. THOMAS: Dr. Kramer, a question. Did you
17 have a comment related to Dr. Konstam?

18 DR. KRAMER: Yeah, the same discussion that's
19 going on. So, first of all, I don't think anybody
20 thinks that we should encourage people to drop out of
21 studies, I don't think anyone is saying that, but
22 personally, I think there is a reality that it is

1 ultimately the patient's choice whether they continue
2 in a study or not, and there is only so much -- I mean,
3 we're not going to tie people down and stuff the tablet
4 down their throat. I mean, it really is up to the
5 patient.

6 Now, having said that, I think that you raise
7 a really important point in that we don't know that all
8 the risk is from the drug immediately, and so I think
9 that we need to follow everyone to get a better picture
10 of risk.

11 The other thing is that not only do we lose
12 the randomization benefit if we just looked at the on-
13 treatment population, I think we have enough evidence
14 in other trials that patients who are adherent are
15 somewhat different than patients who are not adherent,
16 and it's not always the drug that determines the
17 outcome that you're saying is the result of that
18 adherence. So I think, if I had to consider
19 everything, I would do an intent-to-treat analysis and
20 you're always going to do an on-treatment as-treated
21 analysis if you want to just know what happened while
22 on drug.

1 DR. THOMAS: Dr. Konstam?

2 DR. KONSTAM: Well, you know, I think we've
3 got to be really careful. I think for sure the safety
4 effects of a drug may not be limited to when you're on
5 the drug, that's entirely possible. And nobody is
6 saying that isn't, and, yes, you would like to know
7 that, and, yes, an ITT analysis is absolutely the most
8 rigorous thing to do and absolutely should be done and
9 probably is the primary analytic approach, but I just
10 want to emphasize that most -- the flip side, most
11 safety effects occur while you're on the drug, and the
12 problem is you don't want to miss those, and we're
13 talking about an upper confidence bound for the safety
14 hazard of the drug, and if you have a substantial study
15 drug discontinuation, I would first say there is really
16 no way of solving that problem. You know, the ITT
17 analysis certainly will wind up with a diluted effect
18 of the drug, and I'll say it again, it actually -- I
19 think companies would be -- I'm not saying they will do
20 this, but it would be to their advantage to have the
21 patients not continue the drug because that's when it
22 will regress to a non-effect.

1 And I think I really agree with the point
2 that Michael made earlier. I think if we're serious
3 about judging safety, then we have to tell companies,
4 come to us with a dataset where you have the level of
5 exposure that we expect and that patients stay on the
6 drug for a period of time that they expect. Now, maybe
7 you do a 2- year trial and it's okay to analyze it in a
8 year and you say that's it, but whatever the exposure
9 time that you'd like, you need it in the patients who
10 are discontinuing. You know, you will lose your
11 opportunity to have an approved drug.

12 DR. THOMAS: Dr. Kramer, just a quick
13 comment.

14 DR. KRAMER: I would just like to clarify.
15 So we're talking about the phase 3 pivotal trial, so
16 we're not just talking about a safety analysis, we are
17 talking about what is the primary analysis of the study
18 -- right? -- and that includes benefit?

19 DR. THOMAS: Well, this overall question is
20 related to the cardiovascular outcome trial, so it
21 would be in relation to that, and the FDA can clarify
22 whether it be a specific outcome trial or the meta-

1 analysis.

2 DR. KRAMER: This is an important
3 clarification because, I mean, I got the impression
4 that whereas we would require a cardiovascular outcome
5 trial, it's going to be large enough that it will also
6 be the main outcome trial where you're looking at both
7 benefit as well as risk. So are we saying that we are
8 going to do a different analysis for safety than we do
9 for efficacy and if we're --

10 DR. THOMAS: Actually, probably the best
11 thing is to have someone from the FDA clarify that
12 question of yours, Dr. Kramer.

13 DR. TEMPLE: This is not different from
14 issues that arise when you're talking about non-
15 inferiority trials, and our guidance addresses this,
16 and, in fact, it could be perfectly possible to use an
17 as-treated analysis for safety and an ITT for a claimed
18 effect, which is contemplated in that guidance. The
19 problem is that, for reasons Marv gave, most effects
20 diminish when you're off the drug, not all, but most,
21 and if you include all the people who aren't on the
22 drug, and they're half the population, you dilute the

1 adverse effects.

2 So it's a way to win on a non-inferiority
3 trial, which is why we were worried about it, and it's
4 a way to win on a trial attempting to rule out a hazard
5 ratio of whatever. So that makes us nervous. In our
6 guidance on non-inferiority, we say that in many of
7 these cases the primary analysis will be the as-
8 treated, but we should also look at the intent to
9 treat, that's because there are a lot of statisticians
10 helping write it, and they really love those.

11 But you have to worry about that. If there
12 is a substantial dropout -- and preventing that is not
13 known, I mean, we don't know how to prevent people from
14 leaving a trial -- you can obliterate the effect
15 because during the period when nobody is on anything
16 they are probably equal. So that's a longstanding
17 worry, and there is a whole guidance that addresses
18 that, mostly for non- inferiority studies, but it also
19 mentions that safety studies have the same properties.

20 DR. THOMAS: Thank you.

21 Dr. Seely?

22 DR. SEELY: I'm concerned about uncoupling

1 the studies that would look at cardiovascular outcome
2 versus weight loss efficacy. I think if you're going
3 to enroll a large population of high-risk individuals,
4 you want efficacy also to be an outcome in that study,
5 and I would favor using the same primary population for
6 both the efficacy and for the adverse outcomes and side
7 effects. I think you get into a lot of trouble when you
8 are using one population for one outcome and another
9 for another in terms of then seeing how they actually
10 interact.

11 So although I think that doing on-drug only
12 increases your chance of seeing these cardiovascular
13 adverse outcomes, I think it dilutes a lot of the other
14 advantages of having the primary analysis be the entire
15 population. And just even in terms of safety, we know
16 that in the real world people go off and on medications
17 all the time, and I don't think we can assume that for
18 all these drugs it's going to be the worst
19 cardiovascular outcomes in those who take their
20 medication every day. So it may be the worst
21 cardiovascular outcomes are in the people who are on
22 the medication for several weeks, off it for several

1 weeks, and back on it for several weeks. So unless we
2 know really the pathway of the drug to the cause of the
3 adverse cardiovascular outcome, I don't think we can
4 divide up which time we need to look at, so I would
5 favor looking at the entire intention to treat.

6 DR. THOMAS: Dr. Proschan?

7 Dr. Bergman, if you have a question, we'll
8 add you to the list.

9 DR. PROSCHAN: So there was a comment made
10 about it's an advantage from a safety standpoint to
11 discontinue the drug, from the company's standpoint,
12 but, of course, that would also probably hurt them as
13 far as showing the weight loss. So, I mean, there is a
14 natural punishment for trying to do that.

15 Something just occurred to me that is a
16 little troubling. When you say on-treatment, on-drug
17 analysis, I mean, exactly how is that defined? Because
18 you certainly don't want to say, well, you must have
19 been on the drug for 80 percent of the days that you
20 were in the trial or whatever, because you could have
21 an event, and that's why you went off the drug, and
22 clearly that should count, you were on when you had the

1 event. I'm sure they do it the right way, but --
2 (laughing).

3 DR. THOMAS: We just have actually a few more
4 minutes for this one, so just to focus again on the on-
5 treatment or off-treatment analysis.

6 Dr. Goldfine?

7 DR. GOLDFINE: Given that we have limited
8 time, I'll let somebody else do it because I think that
9 my comments have been made.

10 DR. THOMAS: Dr. Weide?

11 DR. WEIDE: I think the answer is yes. You
12 know, some of this stuff has been -- I know that was a
13 little cynical, but if everybody stays on the drug,
14 then nobody has an issue, and that's just not reality
15 of what we see. The problem is if we knew that it was
16 only related to time on drug, it would be easier to
17 figure what to do, but we don't know that taking a drug
18 can't have a long-term effect even if you're off of it,
19 and that's our problem. And when you say, "How do we
20 deal with that?" Well, if it's only when you're on the
21 drug, and you do an intention to treat and everybody on
22 the drug who is no longer on the drug is included, then

1 you dilute the effect of the people who stayed on the
2 drug. So that's a bad thing; I mean, it makes it look
3 less than it is. But if there is an effect downstream
4 that we don't pick up, then we have also missed harm.

5 So I think the reality is that you have to
6 look at it both ways, you just do, because we don't
7 know what the effect is; otherwise, we wouldn't need to
8 do the study. And I just don't see a way of getting
9 around doing an analysis in both ways, both in
10 intention to treat as well as those on. And I would
11 view somebody who had an event on the drug who is no
12 longer on it, they're on it, they got the -- you know,
13 if they had the event on it, they got it, and that
14 counts, that's a click. So I think that's the only
15 reasonable way to try and accomplish a goal to protect
16 patients from that unforeseen downstream effect as well
17 as the acute effects and try and deal with this issue.

18 DR. THOMAS: Dr. Seely?

19 DR. SEELY: So would you have those as co-
20 primary analyses?

21 DR. WEIDE: Yeah, I think you'd have to,
22 otherwise, you're not going to be able to get the

1 information that you need. I know it's a pain in the
2 butt, but our job is to try and protect the patients
3 from whatever adverse effects there are.

4 DR. THOMAS: Dr. Brittain, did you want to
5 chime in on that?

6 DR. BRITTAIN: Yeah. I just agree. I think
7 that oftentimes in a non-inferiority setting, which
8 basically this is what we're in, that's the point of
9 view, is that they're co-primary.

10 DR. THOMAS: Dr. Jensen?

11 DR. JENSEN: So I was looking at this from
12 our obesity treatment perspective, and one of the
13 shocking things that came to us was when we heard about
14 the SCOUT trial being designed, as everybody said, this
15 is crazy, you're taking a high-risk population who
16 wouldn't use this compound normally anyway, and you're
17 leaving them on the drug even if they don't have the
18 benefit that we would use it for, and that's been my
19 concern about some of the designs of some of the risk
20 trials, is exposing people to a risk that you know
21 there is a signal here and forcing people on it, to
22 stay on it, even if they're not having the anticipated

1 benefit.

2 And that's why I think they wanted to look
3 at, what about the effects of weight loss? And,
4 admittedly, this is all retrospective things that it's
5 hard to determine, but in terms of looking at risk in
6 high-risk populations, I would think that if you knew
7 there was a signal there, you wouldn't want to keep
8 people on it if they weren't having the anticipated
9 weight loss because in real life they wouldn't stay on
10 it.

11 DR. THOMAS: Dr. Goldfine?

12 DR. GOLDFINE: Okay, so, again, I think this
13 is going to come up in D&E sort of together, and that's
14 that they're really two completely separate questions.
15 In an ideal world, everybody is going to be given the
16 drug in the ideal trial world, and they will stay on it
17 for the duration of the study, and therefore the
18 intention to treat in the protocol population are
19 identical, and the question is moot. Let's say,
20 though, that you have a drug that is exceedingly
21 effective and well tolerated but in a smaller
22 proportion of the patients, in which case you can have

1 patients dropping off because they weren't seeing
2 benefit for a variety of biased and nonbiased reasons,
3 and in that case, if you have a very small number of
4 people and you look at the entire population, you may
5 not see the adverse consequences because they would be
6 diluted.

7 So I think you can't separate and ask this
8 question without knowing the percentage of patients who
9 actually stay on the drug throughout the trial, and I
10 think that it goes back to what Lamont said about you
11 really have to look at both and you have to look at the
12 percentage of people on and try to figure out if you
13 can, as best you can, why there are a proportion of
14 people who are leaving the trial. I think one of the
15 reasons why the lifestyle studies are so effective on
16 keeping people in the trials longer despite whether
17 they're being randomized to nothing or not that's
18 challenging when you're doing a study that uses an
19 investigational drug product is patients are told there
20 may be a variety of different side effects that they
21 might experience with the drug, and every single time
22 they have an adverse side effect, whether it's related

1 or not, they will attribute it to the drug and are much
2 more likely to be concerned about staying on a
3 medication. So even if it's a gastroenteritis that
4 might have been viral in nature, that people will drop
5 from drugs much more commonly, especially if they're
6 not seeing benefit.

7 And so I think that it's a complicated
8 question, and I think it has to do with how -- is
9 everybody responding to the drug equally, or are you
10 having subpopulations where you can identify who they
11 are or not, who are responders and non-responders? But
12 I think absolutely, as that number gets smaller, you
13 certainly want to look at the adverse events in those
14 who are using the drug, because I agree with Marvin on
15 that point, that that's really where you're likely to
16 be enriching for those that are truly drug effect, and
17 I think it will come up again when we get into Question
18 E.

19 DR. THOMAS: Dr. Hiatt?

20 DR. HIATT: No further comments.

21 DR. THOMAS: Dr. Bergman?

22 DR. BERGMAN: I was just wondering, I mean, I

1 don't do this stuff, but it seems like compliance data
2 would be important here because obviously there will be
3 a lot of people who don't do what they're supposed to
4 be doing, and there are ways to measure compliance
5 besides looking at prescriptions or people getting
6 things in the mail, and I think that might be an
7 important thing to think about because if you're
8 talking about real exposure, then some information
9 about compliance would be important. This may be
10 obvious to everybody, but I think that often people
11 ignore the fact that noncompliance is very common in
12 these kind of trials, and building in something -- and
13 one can think of many things where compliance can be
14 measured -- would be important.

15 DR. THOMAS: Dr. Rasmussen?

16 DR. RASMUSSEN: I just want to remind
17 everyone that this is going to be taken in the context
18 of an NDA, where it will be benefit and risk that will
19 be evaluated at the same time, and all of the benefit
20 evaluations will be superiority trials. And as we've
21 seen -- I mean, and I think that's been documented
22 numerous times, the statistical approach or the primary

1 analysis where you use ITT and last observation carried
2 forward is not always to the company's or the sponsor's
3 benefit, they're often more conservative or regress
4 towards the mean. So that's not always the case, I
5 mean, and I think in all likelihood, this will be
6 executed or operationalized like we do for the diabetes
7 programs where there will be specific efficacy trials
8 for the population, for the different subpopulations,
9 and a dedicated cardiovascular outcome trial to assess
10 the cardiovascular risk.

11 DR. THOMAS: Dr. Temple?

12 DR. TEMPLE: I just wanted to mention, we
13 rarely, rarely, very rarely, count compliance in as a
14 factor in trials because it's well-known, as Dr.
15 Proschan said earlier, to be related to events in ways
16 that are mysterious and not necessarily related to the
17 drug. The Coronary Drug Project found that compliance
18 in the placebo group was the best possible predictor of
19 favorable outcome. So it would be very, very unusual
20 to make that a factor because it's not a baseline
21 characteristic and we would rarely --

22 DR. WOLFE: It sounds like you're arguing to

1 measure it rather than to not measure it.

2 DR. TEMPLE: You know, people can measure
3 anything they want, and maybe they get hints of what
4 further studies to do, but I'm just saying it would be
5 an unusual thing for us to agree to.

6 DR. THOMAS: Adherence to treatment has that,
7 but there are things you could do to adherence as
8 you're taking the medication, such as pill counts or
9 adherence to protocol, which would be different than
10 that.

11 DR. TEMPLE: And it's common to try to
12 stimulate adherence using those data, but I'm just
13 talking about using it as a subset analysis, good
14 compliers, poor compliers, that would be very, very
15 unusual.

16 DR. THOMAS: We have the last two questions,
17 and then I'll summarize this point.

18 Ms. McAfee?

19 (No audible response.)

20 DR. THOMAS: Okay. Dr. Yanovski?

21 DR. YANOVSKI: I think what we've been
22 talking about in part is that we would like to see

1 enough months and years, hopefully, of medication
2 exposure where we think people have truly taken the
3 medicine, and it sounds to me that that should be part
4 of FDA's trial design, that, yes, there will be
5 dropouts, and they're going to happen, and you need to
6 analyze both protocol and intent, I mean, all the
7 various versions, but there also needs to be an
8 agreement on how many months of exposure and how many
9 continuous months of exposure will be considered
10 adequate, that it would be beneficial for the drug
11 companies to know up front, we want so many people who
12 have taken drug for a year, so many people who have
13 taken drug for 6 months, and then the rest could be
14 smaller amounts. I think that would be very
15 beneficial, and that could inform perhaps the
16 calculations, too, of event rates that might be
17 studied.

18 DR. THOMAS: The last question on this topic.

19 Dr. Seely?

20 DR. SEELY: So in relation to the issue about
21 on drug, I think determining how you measure whether
22 someone is on drug is incredibly important. Otherwise,

1 what you're doing is excluding those people who admit
2 they're not on drug and including those people who say
3 that they are on drug but aren't on drug, and I don't
4 know that that gives you a clearer population than
5 taking everyone. So we know with studies that have been
6 done that do a lot of detail -- pill counts, tracking
7 when people take medication -- that if you have a
8 marker that you can measure in their blood, that a huge
9 percentage of those people are noncompliant.

10 DR. THOMAS: So I'll summarize Question D.
11 For safety signals I think in general the panel agrees
12 you have to be on the drug to have an understanding of
13 what the safety is. However, if the drug is
14 discontinued, there still may be events related to
15 safety that occur after treatment has been stopped. So
16 it is important to follow people, if you can, even if
17 they're off drug. Probably is little value in terms of
18 a safety analysis for some of the panel members to use
19 an ITT to understand that; however, for efficacy, ITT
20 might be very appropriate. There was a question about
21 sometimes ITT may overestimate the benefit to the
22 advantage of the pharmaceutical company, but that may

1 not be true in all trials, so an editorial comment is a
2 weight loss trial that tends to be the case as opposed
3 to potentially other areas.

4 If people are not taking the drug, is there a
5 potential in their taking it intermittently, is that
6 the same as someone who is taking it continuously? We
7 know that from multiple trials, and actually including
8 the ACCORD trial, that those who are not adherent to
9 the protocol tend to do worse than those who are
10 adherent to the protocol independent of which treatment
11 arm they seem to be in.

12 There should be some way of trying to figure
13 out an impact beyond adherence, and two suggestions
14 that were brought up were things like pill counts and
15 other parameters of compliance to protocol; however,
16 those are not necessarily as reliable because people
17 can tell you they're taking a pill and they're not, so
18 if you had some type of biochemical marker that you
19 could use, that would help in terms of seeing who is on
20 drug.

21 Finally, you probably want to do this trial
22 for both efficacy and outcomes in the same trial rather

1 than having separate trials with different populations,
2 but you may need to do different analysis, ITT, for the
3 efficacy, and on-time with the drug for the side
4 effects or risk, and those would be important
5 parameters.

6 I think, as an editorial comment, the main
7 problem is the dropout rate, so if we could have a
8 better design to encourage people to stay on the trial,
9 then a lot of these questions and issues would be
10 eliminated, and one of them that I would just throw out
11 -- this is my own opinion -- is we're not looking at an
12 effectiveness trial, so in a way, having the population
13 be completely like the population that we have
14 retrieved is not appropriate if we run an efficacy and
15 safety trial, so you may want to do a run-in on placebo
16 with lifestyle intervention to see that these are
17 people who will follow a lifestyle intervention and
18 follow the parameters of a trial before you randomize.

19 If there are any other questions or
20 corrections or comments to what I said?

21 Yes? Dr. Spruill?

22 DR. SPRUILL: In terms of what you said, have

1 there ever been any studies conducted on why people do
2 not stay on the trials that you know of? Just out of
3 curiosity.

4 DR. THOMAS: Dr. Rasmussen, would you want to
5 comment?

6 DR. RASMUSSEN: Yeah. I think there's a nice
7 publication by Thomas Wadden, who has spent quite a bit
8 of time looking at these kinds of factors, and, I mean,
9 to me, at least, a very striking element is that they
10 have asked participants in these clinical trials what
11 their expectations are coming into the trial, and the
12 average expectation for weight loss is in the area of
13 around 25 percent. So I think it's very likely that
14 with compounds that we have today and in the
15 foreseeable future, that we're not meeting those
16 expectations, even the ones who respond well above the
17 5 percent that's the current benchmark. And, of
18 course, then there is the element of side effects, and
19 you have to set off a lot of time to participate in
20 trials, but it is a concern.

21 DR. THOMAS: Dr. Proschan, do you want to
22 comment to that as well?

1 DR. PROSCHAN: Yeah. Just I think what's
2 left off from that summary is Dr. Weide -- and notice
3 the pronunciation is "WHY-dee" not "WEE-dee"; right?

4 DR. WEIDE: True.

5 (Laughter.)

6 DR. PROSCHAN: He's gotten tired of
7 correcting people, I know, but it is "WHY-dee."

8 (Laughter.)

9 DR. PROSCHAN: But Dr. Weide and Dr. Brittain
10 expressed the view that perhaps the on and off
11 treatment should be co-primary, and I think there was
12 some sentiment for that as well.

13 DR. THOMAS: I probably just didn't express
14 it clearly enough, so thank you for the addition.

15 We'll move on to Question E, which is:
16 Discontinuing from study drug patients who do not
17 achieve a certain degree of weight loss within the
18 first 3 to 6 months of the trial. Those withdrawn from
19 study drug would continue to be followed.

20 And I just want to advise everyone, we
21 probably have about 20, 25 minutes for discussion on
22 this, and before we start, I wanted to throw out one

1 comment. I've been thinking about this. I have
2 absolutely no idea how you could do this in a
3 randomized, placebo-controlled trial because you would
4 expect if the drug has any efficacy, that a lot of
5 people you would be throwing out would be on placebo.
6 So to start that off, I just don't know how it can be
7 done. If someone has some suggestions on how it could
8 be done, that would be helpful.

9 Dr. Weide?

10 DR. WEIDE: Thanks. I think you could look
11 at it two ways, and one of the ways is exactly how you
12 looked at it. You know, the placebo group loses on
13 average a couple kilos or maybe a couple percent,
14 depending on the study, whereas hopefully the drug
15 loses more than 5 or 10 percent, and compliance has to
16 do with that. The predictor for weight loss is clearly
17 weight loss in the first 3 to 6 months. So I guess
18 what you would say is those are the people who ought to
19 really stay on the drug, and if the others discontinue,
20 you're better off, but you are keeping people on the
21 drug, active drug, who are not going to benefit; right?
22 So in that case what you're doing is you're really

1 keeping them on drug in order to maintain the integrity
2 of the study and to look at final endpoints. And does
3 that maintain an ethical quality?

4 However, in order to take off people who
5 could be harmed without a benefit, you would have to
6 have somebody unblinded do that. That would be the
7 only way to do that. And then that gets extremely
8 complex because you wouldn't take anybody off the
9 placebo one even if they wouldn't lose weight -- right?
10 -- because you need those numbers, but you would only
11 take off people who were on drug who did not lose
12 weight, but it would have to be done by a separate
13 committee who was unblinded the result. That just
14 sounds too complex to do, so I think while there may be
15 some validity to the concept, the practicality of doing
16 this is not very good.

17 DR. THOMAS: Dr. Alexander?

18 DR. ALEXANDER: Yeah, I mean, this seems to
19 me that this only works -- and I haven't thought
20 through all the issues -- but this only potentially
21 works if the only outcome you care about is weight
22 loss. You're essentially censoring people who have met

1 their endpoint -- that is, weight loss -- but if you're
2 interested in safety for cardiovascular events, you
3 would have no ability to draw conclusions because you
4 would have thrown out a bunch of probably your control
5 group, and therefore you would have a nonrandomized
6 comparison.

7 And also if you're interested in other
8 potential benefits of the drug that may not be tied to
9 short-term weight loss, either longer term weight loss
10 or some other yet unknown benefit, you're also throwing
11 out your ability to detect that. So I think this kind
12 of a design, while one could think through it for a
13 short-term weight loss outcome, you couldn't answer
14 anything else from this kind of a trial.

15 DR. THOMAS: Dr. Temple?

16 DR. TEMPLE: Let's be clear what the question
17 was asking. This would be an intent-to-treat analysis.
18 Okay? Everybody would be followed, even if they left,
19 and I think the thought was --

20 PARTICIPANT: If they were off drug.

21 DR. TEMPLE: -- even if they were off drug or
22 off placebo, they would be followed. I think the

1 thought was that there might be a drug that had some
2 kind of modest adverse effect but that also had a
3 benefit, but that there was also a benefit from losing
4 all that weight, and if you only left on people who
5 were getting the benefit of losing weight, whatever
6 treatment they were on, you would give the drug a
7 chance to win by helping some people and you would get
8 rid of people it couldn't possibly help. I think that
9 was the thought. I mean, that's a fairly novel design,
10 so it's obvious that nobody has really seen anything
11 quite like this, but that was the thought.

12 DR. THOMAS: Dr. Proschan?

13 DR. PROSCHAN: Yeah, I don't think this would
14 require unblinding because, I mean, you could
15 discontinue the placebo, too, and people haven't lost
16 weight and you're not changing much; right? So I think
17 you could it, just if you haven't lost a certain amount
18 of weight, you take away whatever they're taking, which
19 is either a placebo or the active drug.

20 But I think the caveat is that if you do
21 this, and the person doesn't come back for follow-up
22 measurements, and they're in the drug group, which

1 you'll know at the end of the trial, I think you have
2 to apply a pretty big penalty because that person
3 clearly would have had a bad result if they had come
4 back. So I think you have to make sure that a strong
5 penalty is imposed for someone who does not come back.
6 I know the intention is to do this and have everyone
7 come back, but if it doesn't happen, I think you have
8 to apply a strong penalty, and that way the drug won't
9 win on the weight, and therefore there won't even be a
10 concern about safety because it will lose on weight
11 alone.

12 DR. THOMAS: And I assume some statistical
13 penalty; right? Yeah. Okay.

14 Dr. Seely?

15 DR. PROSCHAN: Those are my favorites.

16 (Laughter.)

17 DR. SEELY: So I see a big problem with this
18 in terms of what we're looking for, which is
19 innovation. So this uses the model that all the weight
20 loss studies that have been done so far see most of the
21 weight loss in 3 to 6 months and then regain, and what
22 we're looking for is loss in the first 3 to 6 months

1 and maintenance is one thing we're looking for, but
2 maybe there will be innovations of drugs that cause
3 weight loss later than 3 to 6 months, that cause it at
4 6 to 12 months, and maybe those will happen to be the
5 drugs that are associated with more maintainable weight
6 loss. So I don't know that we know the pattern of all
7 the agents and the lifestyle that have been available
8 today will definitely apply to drugs of the future.

9 And I just wanted to give one caveat, that
10 this pattern may be applicable to study populations
11 that have been included into prior studies, but it may
12 not be applicable to all studies. So, for example, we
13 study postpartum weight loss, and this does not appear
14 to be the pattern of effective weight loss in
15 postpartum women. So we may be ascribing a model that
16 has fit studies in the past and populations have been
17 studied in the past which may not be applicable to the
18 new drugs that become available and to wider, other
19 populations.

20 DR. THOMAS: Ms. McAfee?

21 MS. MCAFEE: It's interesting hearing this
22 discussion, and I agree that it would be very difficult

1 to do this, but I have to say that as a patient
2 representative, I don't care. I think it's unethical
3 to expose people in these trials to this drug certainly
4 not for 6 months, 3 months is questionable. If they
5 don't lose weight in 2 months, I say they're out. You
6 cannot expose them to this kind of risk.

7 And then the second thing I just want to
8 mention tangentially is I've heard the word
9 "compliance" bandied about a few times today, and there
10 is something important about compliance, and that is,
11 these drugs are meant to enhance compliance, these are
12 drugs that are supposed to make compliance possible,
13 and it's really important, to me, that the blame not
14 will be placed on the patient if there is perceived a
15 lack of compliance, that that is to a certain extent a
16 drug failure also.

17 And that's it.

18 DR. THOMAS: Dr. Konstam?

19 DR. KONSTAM: So as I keep thinking about
20 this, I just cannot see how you can do this in the
21 context of a randomized trial and retain the integrity
22 of the trial.

1 You're losing -- first off, I really listened
2 to Lynn a moment ago, and it sort of jolted me, so I'm
3 going to respect that. Now let's talk about trialism,
4 and so as far as I can tell, you completely lose,
5 substantially lose, the value of the randomization.
6 You're removing patients from the two groups in an
7 informative way, which is differently informative in
8 each group: in one case, based on response to drug; in
9 another case, based on something else -- right? -- in
10 the case of the placebo, you're removing them because
11 they don't lose weight, and there are a completely
12 different set of factors that are influencing why they
13 lost weight or they don't lose weight, and you're
14 losing the value of randomization.

15 DR. PROSCHAN: Nobody is saying remove the
16 patients.

17 PARTICIPANT: That's right.

18 DR. PROSCHAN: You're only removing the pill.
19 You're still counting their data. You follow all of
20 them.

21 DR. THOMAS: So one --

22 DR. KONSTAM: Well, you're still -- okay,

1 but, well, you're not removing -- well, you're removing
2 their exposure to drug, right? And you're performing
3 an intervention in both groups in an informative way
4 that's being influenced by different factors in the two
5 groups. I don't know. I'm really struggling with how
6 it -- you know, I'm just struggling with that. The
7 thing that I keep thinking -- and maybe it's doable and
8 maybe it's not, but I'm surprised nobody suggested it,
9 maybe because it's ridiculous -- is do an open label
10 period, and then randomize. So do an open label period
11 -- and the question to you guys is, how long would you
12 have to do that? -- identify responders to drug, and
13 then randomize, and that would solve your problem.
14 Then you wouldn't be exposing patients to the drug if
15 they didn't have an early response, and then you still
16 could have -- now, there are other issues that arise in
17 that situation, but I just throw that out to the group.

18 DR. THOMAS: Dr. Brittain, if you want to
19 comment on the --

20 DR. BRITTAIN: I don't know that I have much
21 to add over what Dr. Proschan said. It certainly
22 remains a valid randomized study as long as you're

1 continuing to follow people. That's always the key, if
2 you're continuing to follow everybody. I do think the
3 idea you just raised, though, however, is interesting,
4 about the run-in or whatever you want to call it,
5 although that would -- if you're worried about short-
6 term exposures perhaps causing harm, if everybody is on
7 drug for a while, then we wouldn't necessarily be able
8 to sort out that safety issue, although I thought the
9 other run-in idea we heard -- someone over here said
10 about the lifestyle run-in I thought was also a good
11 idea, to consider a lifestyle run-in to see about
12 compliance. But it does not get at drug response.

13 DR. THOMAS: Dr. Alexander?

14 DR. ALEXANDER: That's all right.

15 DR. THOMAS: Dr. Rasmussen?

16 DR. RASMUSSEN: I'm sorry, maybe I don't
17 quite get it, but I certainly appreciate the sentiment
18 of giving the sponsor an extra chance. But if the idea
19 here is to let people put -- I mean, not take their
20 medication, whether it be placebo or the study drug,
21 that would, in principle, I guess, unblind that person,
22 and we must assume that this will occur much, much more

1 frequently in the placebo group than in the active
2 treatment group. And I think that definitely
3 influences the outcome and I don't think is something
4 that we would be interested in.

5 And then I just wanted to comment also on the
6 idea of the run-in period, which we have tried on a
7 number in our trials, and it's really difficult to
8 remove the changes that occur during the run-in period
9 from then interpreting the actual post-randomization
10 period and is not something that we would recommend.

11 DR. THOMAS: Dr. Temple?

12 DR. TEMPLE: The person wouldn't be unblinded
13 as to what therapy they were on. Whatever therapy they
14 were on, it would be stopped. I guess you could
15 continue to give a placebo, but I don't think that
16 contemplates that. They would just know that they
17 didn't lose weight, which they sort of already would
18 know, and they would be off the treatment, and then you
19 would follow them for events. It's very important to
20 follow them for events, whether that can be done
21 properly is always a good question, but that's the
22 idea.

1 DR. RASMUSSEN: I'm sorry. If I can just
2 respond very briefly?

3 DR. THOMAS: Sure.

4 DR. RASMUSSEN: I just think that maintaining
5 patients in the study when you've removed their study
6 drug is exceptionally hard, and if it ends up skewing
7 how many of the placebo you lose to follow-up compared
8 to how many of your active treated you lose to follow-
9 up, that definitely impacts the final analysis and not
10 to our --

11 DR. TEMPLE: Everyone would agree that you
12 have to have good follow-up. Whether that can be done
13 is a good question.

14 DR. THOMAS: Dr. Colman?

15 DR. COLMAN: Yeah. I mean, there are pros
16 and cons to this, but one way to minimize the number of
17 people in both treatment groups who withdraw due to
18 lack of a certain amount of weight loss is make sure
19 you have a relatively intense lifestyle modification
20 program in both arms.

21 DR. THOMAS: Dr. Proschan, do you have a
22 comment on that?

1 DR. PROSCHAN: I just wonder if another
2 option -- I appreciate the point about the blinding
3 issue. One other option perhaps is to give them
4 placebo from that point on no matter what they were on
5 before and have that built into the protocol so that
6 they know that this could happen and they just won't
7 know whether it did happen.

8 DR. THOMAS: Dr. Felner?

9 DR. FELNER: I was just going to agree kind
10 of with Dr. Temple but also what Dr. Proschan said. I
11 mean, if you look at the orlistat data, both groups,
12 the placebo and the orlistat group, they lose weight at
13 3 months, and they lose it more than 4 kilos, and so if
14 you stop the drug, whether it be placebo or orlistat in
15 this case, the patients, they still should be followed
16 throughout the time, and I don't think you lose
17 anything as long as you keep them in, as we were
18 mentioning before, keeping them in the entire time, and
19 already it's been mentioned how hard it is for these
20 patients to stay in the study for a year anyway. So I
21 think this would be even more reason to do this,
22 because you're going really want to keep them in there

1 to monitor them after they've come off the medication
2 and not expose anybody to any of the harmful side
3 effects.

4 DR. THOMAS: Dr. Jensen?

5 DR. JENSEN: This trial design clearly isn't
6 an efficacy design because by definition you're only
7 keeping people in who succeed. So if it's a safety --
8 I mean, the long-term safety of it, this would have to
9 be complementary to the other types of study designs
10 we've seen. This could not be a standalone design but
11 would be one to design to assess the risk-benefit ratio
12 of people who lose weight, if there was some concern
13 about weight loss offsetting potential side effect of
14 the compound. But by definition, this couldn't be a
15 separate -- this couldn't be the only design that you
16 would have for a trial.

17 DR. THOMAS: Dr. Yanovski?

18 DR. YANOVSKI: Yeah. I just wanted to echo
19 what Dr. Proschan said about the possibility that
20 people could be -- if we really wanted to use this
21 design, they could be switched over to placebo, they
22 could even be put on a double dose of placebo so that

1 they think that they have a chance of doing better,
2 anything to improve adherence to the regimen. There
3 are all kinds of strategies that could be used and have
4 been done.

5 But I think we have to consider that this
6 kind of adaptive trial design, for the purpose of
7 finding a group who respond and maybe see if they have
8 any benefit, is the kind of thing that strikes me as a
9 very early kind of study that would be done for the
10 purpose of assessing, how good could it be to use this
11 drug, for benefit mostly, in terms of weight reduction
12 and maybe complications?

13 But that is a safety design, and it strikes
14 me as a really less than optimal design because of the
15 fact that it's going to reduce the months and years of
16 exposure unnecessarily, if you will. I mean, I
17 understand that some folks were being exposed to drug,
18 but when you are at the point of doing a big safety
19 assessment where you think you have efficacy, you want
20 to find out that fact before many people are exposed.

21 So I think you almost have to try to get as
22 many months of exposure as possible. And when one

1 joins a trial, one understands that there may not be
2 benefit, and there could be risk, so, I mean, I think
3 we're just making it harder to obtain the necessary
4 safety data that we want when we purposefully remove
5 patients from active treatment early. I think that's a
6 mistake.

7 DR. THOMAS: I just want to make one quick
8 comment, is that even though if you add the placebo
9 strategy when you switch them to the subject, the
10 investigator is no longer blinded because they'll know
11 from the protocol if you don't hit a certain weight
12 loss, you're going to be on placebo. So that may have
13 an impact on other parameters, like deciding lipid-
14 lowering agents, blood pressure agents, because you
15 know they're on a placebo at that point. So both sides
16 are not blinded even if you're blinding the subjects.
17 That's my opinion.

18 Dr. Proschan, did you have a comment?

19 DR. PROSCHAN: Well, with respect to that, I
20 think you could have someone else make that switch. So
21 I think there are still ways to keep the blind, but I'm
22 just wondering if this is the way it's done clinically.

1 I mean, if someone is put on a weight loss medication
2 and they don't lose weight -- I mean, it makes sense to
3 me, but I'm not a doctor -- to take them off, and if
4 that's what's usually done, almost always done, then in
5 a way you could say that this is answering the relevant
6 question.

7 DR. THOMAS: I think that's the way it should
8 be done in practice, and most probably for this it
9 does, but not for all medications. Some people stay on
10 medications that don't have efficacy.

11 Dr. Goldfine?

12 DR. GOLDFINE: I think I was going to make
13 the same suggestion that Dr. Konstam made about the
14 active run-in phase and then randomization after you've
15 reached that number. And I've been wrestling with this
16 quite a deal emotionally since the SCOUT trial, and I
17 think that this kind of design is very pragmatic in
18 that if you prescribe a medication to everybody in the
19 intention-to-treat analysis, you're saying in an
20 entire population, what's the magnitude of weight loss?

21 But let's step back and take away weight
22 loss, because we're all sort of charged for that at the

1 moment, and go to something like lipids. If I
2 prescribe a lipid- lowering medication and you take it
3 for a month and have myalgias and don't take it, I
4 don't anticipate that you will end up with a clinical
5 benefit as if you were continuing on the medication,
6 and, therefore, what's really different is for those
7 people who are on the drug, what is the magnitude of
8 benefit that you will see? And you can then extend
9 that to weight loss. So I think here we have a very
10 early biomarker, which we think is actually the
11 mechanism that's leading to a whole bunch of metabolic
12 improvements, whether it's through inflammation,
13 whether it's through their lipid-lowering, whether it's
14 blood pressure, all the different things that might be
15 happening metabolically, and you have this biomarker,
16 and then you continue those who look like they are
17 succeeding. The magnitude of weight loss will look
18 better because you pre-selected your responder
19 population, but you're also then targeting your adverse
20 events to those who are actually likely to be
21 responding and taking the drug. And it's really a
22 different question for those who are on the drug and

1 take the drug and have some evidence of responding to
2 the drug, what is their magnitude of risk and benefit
3 as opposed to if I tried it in everybody who met the
4 inclusion criteria, which is really what the intention-
5 to-treat analysis question asks. So one is a global
6 population health level question, and the other is
7 really a clinically focused question, and it's a
8 paradigm shift.

9 DR. THOMAS: Dr. Temple, did you have a
10 comment?

11 DR. TEMPLE: I was just going to say that if
12 it's true that people would presumably or could
13 conceivably know that the drug has been stopped, what
14 they wouldn't know is what the person was on during the
15 period before the cessation, and in many ways that's
16 the most important question here because that's the two
17 groups.

18 DR. THOMAS: Dr. Gregg?

19 DR. GREGG: I think it's worth pointing out
20 that this fourth option is actually conceptually what
21 the Look AHEAD study did. They didn't highlight it as
22 much yesterday, and the difference was that orlistat

1 was actually a secondary part of the intervention
2 there. The difference is that the control group is
3 basically an intention control, it's not a placebo per
4 se, and so the drug essentially is built on the
5 framework of an additional intervention, in that case,
6 education or counseling or whatever. So in theory, you
7 have the control is the counseling and then the
8 intervention is the drug plus the counseling, and in
9 that case, they ended up kind of phasing it out because
10 it was very much of a secondary part, but there is
11 precedent for doing it.

12 DR. THOMAS: Dr. Kramer, you had a comment?

13 DR. KRAMER: I actually have a question for
14 Dr. Goldfine, thinking about what you suggested. So if
15 you had everyone on a run-in period, and then at some
16 point you -- and you only randomized those people who
17 did respond, if most of these agents have only had a 5-
18 to 10-percent weight loss, if they have a significant
19 weight loss in that run-in period, then what are you
20 expecting for benefit in that next randomization
21 period? Does that compromise your ability to document
22 benefit in the official randomized phase?

1 DR. GOLDFINE: So I think then the bigger
2 question to me becomes, what's the baseline? and is the
3 baseline the initial evaluation before you actually
4 initiate the drug? So any adverse event that actually
5 occurs during the open label run-in may actually need
6 to be counted as an adverse event toward the drug
7 because you tried it in a group of people who met the
8 original inclusion criteria, and you continue it in
9 those who are the responders.

10 I think you absolutely need to have a second
11 baseline at the time of randomization, and I think that
12 there was some trial within the ACCORD where they did
13 lipids and didn't necessarily have the second baseline
14 evaluation, and I think one has to wrestle very
15 carefully about what you're considering the baseline
16 measurement in these individuals. It's not traditional
17 not to use the one right at the time of randomization,
18 but you've actually now documented a drug effect in
19 this group, and so I'm not positive I know the answer
20 to that question and in some ways lean to this
21 nontraditional when you first tried the drug in the
22 group in whom you're continuing it.

1 So then I think that what you would benefit
2 in those that you randomize off is I think that it
3 would be like the people who try it for a while, and
4 even though they had an effect, they now stopped the
5 drug and you get to see the washout and you would be
6 continuing to follow them over the period of time of
7 the duration of the study, and that would give you the
8 event rates in people who would have responded to the
9 drug but didn't take the drug or didn't stay on the
10 drug, and I believe that they would probably drift back
11 toward what their event rates would be if they had not
12 been on it if you're in an extended trial, and then you
13 would really see in the responders what's the event
14 rate. And my bet is that for those who were able to
15 demonstrate a benefit, they might be on the drug for a
16 more extended duration of time, but that's all
17 hypothetical.

18 DR. THOMAS: Because of time, we have to go
19 to the next -- take a break and the next question.

20 Dr. Weide, Weide, or Weide? You've got me
21 confused. I knew what it was before.

22 DR. WEIDE: Well, I just have two comments,

1 and I'm going to go way back and put my undergraduate
2 degree on for a second, if I barely remember that,
3 which was a double degree, but part of it was
4 psychology. And the act of being observed changes what
5 happens, and if you are going to say, "You didn't
6 respond, I'm changing what we're doing to you," then
7 the patients, in turn, are likely to change what they
8 do, and we have now altered the experiment. They know
9 whether they've gained or not gained weight, but if
10 you've done something else, then they go, "Okay, I'm
11 screwed, I give up, I'm not going to follow through
12 with the rest of this stuff."

13 I think there's a real bad series of things
14 that can happen with that because we've given a
15 negative reinforcement to the patients, regardless of
16 how you want to do it. Even if you double their pills,
17 we've told you, "Hey, you didn't do well enough, so
18 we're going to double your pills." You make it placebo
19 or maybe not -- and we know everybody is getting
20 placebo -- but you have altered the relationship of the
21 study, and you may alter the patients, what they do and
22 how they follow through, because you've reinforced them

1 negatively.

2 The second thing is the run-in. I think
3 there's a real problem with the run-in. We can look at
4 it a couple different ways. First of all, if you run
5 in and people lose weight and then you randomize them
6 and they don't lose weight, they know they got placebo,
7 and they don't like it, and they drop out. The other
8 problem you run into with a run-in is you're
9 eliminating the patients, so you don't know the true
10 negative effects of a drug.

11 For example, if you look at the acarbose
12 studies from way back, almost all of those had run-ins,
13 and they used a very low dose, and if you didn't
14 tolerate it, you didn't get in the study. And if you
15 look at all the studies, that's where you get all your
16 statistics of the side effects, et cetera. The fact of
17 the matter is that 50 percent of the people couldn't
18 make it through the run-in and were not allocated into
19 the randomization.

20 And so when you look at the percentage of
21 people who had side effects in the study, totally
22 distorted. When you get in the real world, the

1 percentage of people who have side effects is 75
2 percent even though it was only about 50 percent in the
3 study because you had 50 percent who got eliminated.

4 So there is a lot of negative things and
5 distortions that can occur with a run-in. So I think
6 we need to keep that in mind if we think about those
7 kind of things. And, again, the run-in, when you
8 exclude, then you're not looking at what happens in the
9 clinical world.

10 DR. THOMAS: Dr. Capuzzi, if you have a brief
11 comment, so I can summarize.

12 DR. CAPUZZI: This might be a silly question,
13 but in view of everything that's been said recently, is
14 the patient at least getting very good instruction by
15 nutritionists and filling out adherence issues? At
16 least that's one thing the patient gets, if nothing
17 else good comes of this. I may have missed it, but I
18 just wanted to ask.

19 DR. THOMAS: I believe from yesterday's
20 comments, the level of instruction or lifestyle
21 intervention varies from trial to trial and actually
22 varies from area of the world to area of the world.

1 Europe tends to have a different lifestyle intervention
2 and intensity than the United States.

3 So actually at this time I'm going to
4 summarize. If you discontinue the drug for a lack of
5 weight loss, then you may have a chance to unblind the
6 study. You could avoid unblinding the study if you
7 discontinue both subjects in placebo and active
8 treatment with the drug. However, the investigators may
9 be unblinded to the study. So there are potential
10 mechanisms for trying to work this out. There is a
11 precedent for doing this type of study that's been
12 used, and maybe that can be used as a model for trial
13 design. The assumption is that if you have early
14 weight loss, then you may see some benefits longer
15 term. However, that is true for the current
16 medications that have come along, but if we had a
17 medication in the future that weight loss occurred
18 later in the period of 6 to 12 months rather than the
19 first 6 months, then you would see a lack of efficacy
20 in that agent, and that agent may have appropriate
21 weight loss and maybe better weight maintenance, and we
22 would not be informed about the efficacy if we stopped

1 everyone on drug early who didn't have a weight loss.

2 It may be unacceptable to expose subjects to
3 risk if there is no benefit, so that would be really
4 the strongest consideration on a patient advocacy side
5 to not allowing patients to continue in a study if
6 they're getting drug and they're not losing weight.

7 There are some possibilities of trying to
8 avoid some of these issues. One would be considering
9 an active run-in, but an active run-in also does have
10 its problems with how do you analyze the data after the
11 active run-in period when you randomize at that point?
12 And also if you have an active run-in period, does that
13 eliminate a lot of subjects because of the side effects
14 that you wouldn't see if you had them go through the
15 trial?

16 Finally, I think one important consideration
17 is, will people stay in a trial if they know that they
18 didn't lose weight or figure that out somehow even if
19 they were kept in the trial, if they're not being
20 actively followed in the way that the trial
21 participants are and something is handled differently,
22 how they are treated, would they stay in the trial long

1 enough to be informative? If you do discontinue their
2 drug, they would have to be followed in the trial for
3 outcomes.

4 If there are any additions or corrections?

5 (No audible response.)

6 DR. THOMAS: Okay. Then what we would like
7 to do right now is take a break for 10 minutes. Panel
8 members, please remember there should be no discussion
9 of the meeting topic during the break amongst
10 yourselves or of any member of the audience. We will
11 resume at 3:25. Thank you.

12 (Break.)

13 DR. THOMAS: We'll be using electronic voting
14 system for this meeting. Once you begin the vote, the
15 buttons will start flashing and will continue to flash
16 even after you've entered your vote. Please press the
17 button firmly the response to your vote. If you're
18 unsure of your vote or you wish to change your vote,
19 you may press the corresponding button until the vote
20 is closed. After everyone has completed their vote,
21 the vote will be locked in. The vote will then be
22 displayed on the screen. I will read the vote from the

1 screen into the record.

2 Next, we will go around the room and each
3 individual who voted will state their name and vote
4 into the record. You can also state the reason why you
5 voted as you did if you want to. We will continue in
6 the same manner until all the questions have been
7 answered or discussed.

8 I'm going to read Question 3 to the
9 Committee, which is the voting question. Do you
10 believe that obesity drugs without a theoretic risk or
11 signal for CV harm should be required to rule out a
12 certain degree of excess CV risk with a cardiovascular
13 outcomes trial or an appropriately sized meta-analysis
14 of phase 2 and phase 3 MACE data? If you voted no,
15 please explain why you voted no. And if you voted yes,
16 please discuss how -- the cardiovascular outcome trial
17 or meta-analysis or both -- and when such data should
18 be obtained -- pre-approval, pre- and post-approval in
19 a two-staged approach with different non-inferiority
20 margins pre- and post-approval, or post-approval.

21 If there is no further discussion, we'll now
22 begin the voting process. Please press the button

1 three times on your microphone. Actually, is there any
2 question before we actually do the vote from anyone?

3 PARTICIPANT: Are we going to do these
4 sequentially or are we going to answer one and then go
5 around and do them?

6 DR. THOMAS: Actually, it's only one
7 question, and the response there would be no, why you
8 voted no, but if you voted yes, you would have to
9 explain where you would want the study done, pre-
10 approval, pre- and post-, or post-approval. So it's
11 actually only one voting question, yes or no.

12 Any other clarification or questions?

13 Dr. Kramer?

14 DR. KRAMER: Did you say press the button
15 three times?

16 DR. THOMAS: Yes. If you want to press it
17 more, you can, but --

18 (Laughter.)

19 PARTICIPANT: Do you have to use the same
20 button?

21 (Laughter.)

22 DR. THOMAS: If you press a different button,

1 it will record your vote until they lock you out.

2 DR. BERGMAN: So you're going to go around
3 and ask each person? Or I don't quite understand.

4 DR. THOMAS: Actually, the vote is done
5 electronically, Dr. Bergman, and after that's locked
6 in, they'll let us know that everyone has voted. And
7 then once the vote is released, I'll read the vote into
8 the record, and then we'll go around after everyone has
9 voted.

10 Okay. Go ahead, Dr. Bergman, one more
11 question?

12 DR. BERGMAN: No. I'm ready.

13 DR. THOMAS: Oh, okay, the finger is ready.

14 (Laughter.)

15 DR. TRAN: Please go ahead and make your
16 selection.

17 (Voting.)

18 DR. THOMAS: I will now read the voting
19 result into the record. Seventeen people voted yes for
20 Question 3, stating that there should be a
21 cardiovascular outcome trial or meta-analysis or both;
22 six people said no; there were no abstentions; and

1 there was no one who did not vote.

2 I will now read the votes into the record.

3 Dr. Alexander voted yes.

4 Dr. Bergman voted yes.

5 Dr. Brittain voted yes.

6 Dr. Capuzzi voted yes.

7 Dr. Cooper voted yes.

8 Dr. Felner voted no.

9 Dr. Goldfine voted yes.

10 Dr. Gregg voted yes.

11 Dr. Hendricks voted no.

12 Dr. Hiatt voted no.

13 Dr. Jensen voted no.

14 Dr. Kaul voted yes.

15 Dr. Konstam voted yes.

16 Dr. Kramer voted yes.

17 Ms. McAfee voted yes.

18 Dr. Proschan voted yes.

19 Dr. Savage voted yes.

20 Dr. Seely voted no.

21 Dr. Spruill voted yes.

22 Myself, Dr. Thomas, voted yes.

1 Dr. Waters voted yes.

2 And Dr. Weide voted yes.

3 Is Dr. Yanovski's vote lower? Because I'm
4 getting old, it's hard enough to read that as is, to
5 figure out your name.

6 (Laughter.)

7 DR. THOMAS: Okay. We're going to read this
8 all in a different format that has everyone on page.

9 Dr. Alexander, Dr. Capuzzi, Dr. Gregg, Dr.
10 Kramer, Dr. Savage, Dr. Waters, Dr. Bergman, Dr.
11 Cooper, Dr. Kaul, Ms. McAfee, Dr. Spruill, Dr. Weide,
12 Dr. Brittain, Dr. Goldfine, Dr. Konstam, Dr. Proschan,
13 and myself, Dr. Thomas, all voted yes.

14 Dr. Felner, Dr. Jensen, Dr. Hendricks, Dr.
15 Seely, Dr. Hiatt, and Dr. Yanovski all voted no on
16 Question 3.

17 We'll now go around the room, and if you
18 voted no or yes, please give your explanation. If you
19 voted no, just explain why you voted no. And if yes,
20 whether you would want the trial or meta-analysis done
21 pre- approval, as a two-staged approval process, or
22 post- approval.

1 Dr. Kaul.

2 DR. KAUL: My name is Sanjay Kaul. I voted
3 yes for requirement of a trial. And one of the main
4 challenges in drug approval, in my opinion, is an
5 asymmetry in the assessment of benefit and risk or
6 efficacy and safety, and I think benefit or efficacy is
7 evaluated in a very precise manner, and the quality of
8 evidence that informs our safety assessments is not as
9 robust. I think the drug approval process works best
10 if the efficacy is determined validly and the risks are
11 also detected prudently and both are done in a timely
12 and efficient manner. So I believe extra caution is
13 warranted because some risks are anticipated while
14 others are unanticipated, and given the checkered
15 history of weight loss drugs, I think it is better to
16 be prudent and err on the side of caution. I'm always
17 intrigued by our ability to explain away unanticipated
18 risks post facto. I think we need to be humble and
19 recognize that our ability to anticipate the risk a
20 priori is quite limited. So I think it is in the best
21 interest of the sponsor to plan ahead and assume that
22 they have to rule out unacceptable cardiovascular risks

1 and set on a path where they can design efficient
2 trials a priori whereby they can combine the phase 2
3 trials with phase 3 trials.

4 Just imagine a scenario where there is no
5 evident or theoretical risk, but they embark on a phase
6 2 trial where they find a signal and now they have to
7 redesign a program without being able to borrow
8 strength from the index phase 2 trials, and I think
9 that would be inefficient use of precious resources.
10 And for these reasons, I voted yes.

11 DR. KRAMER: Judith Kramer. I voted yes. I
12 think that whereas I understand the benefits, the
13 potential benefits, from weight loss are
14 multifactorial, not just the ultimate outcome of
15 improving cardiovascular risk or not, I still feel that
16 it's really unacceptable -- I guess Dr. Kaul expressed
17 it very well, that with all that we know about the
18 potential for cardiovascular risk, that we wouldn't
19 actually look carefully for this.

20 And so I voted yes, and I think the real
21 downside is if it prolongs development and increases
22 sample sizes to such an extent that it would inhibit

1 the development of new products, but I think that many
2 things have been suggested in the course of this
3 meeting that could ameliorate that negative effect.

4 So in terms of specifics, I think that there
5 should be a cardiovascular outcome trial as well as
6 meta- analysis across all the information that's
7 available, and I think that all the programs should
8 prospectively define endpoints at the beginning of the
9 development so that data can be combined across
10 multiple trials.

11 And I think that the idea of, as we talked
12 about earlier, the two-stage process of having pre- and
13 post- approval would avoid some of the negative
14 consequences requiring this extra effort even when
15 there's not a defined signal, but given the low rate of
16 events in the target population, I think we shouldn't
17 be inappropriately reassured by not having defined the
18 signal up front.

19 DR. THOMAS: Dr. Kaul, if you just want to
20 finish your comment. Then Dr. Parks.

21 Go ahead, Sanjay.

22 DR. KAUL: Well, I just wanted to add an

1 addendum that I think it's a good idea to harmonize the
2 obesity guidance with the diabetes guidance and adopt a
3 two-tiered approach, both the pre- and post-approval
4 approach, with just one difference, I think we need to
5 be flexible about the unacceptable cardiovascular risk
6 margins and base them on a totality of assessment of
7 the benefit-risk.

8 DR. THOMAS: Dr. Parks, did you have a
9 comment?

10 DR. PARKS: Actually, I was just going to ask
11 if Dr. Kaul would specify which one, pre-approval, and
12 he did.

13 DR. THOMAS: Dr. Konstam?

14 DR. KONSTAM: Yeah, I voted yes, and just to
15 concur with my colleagues here, I think the anti-
16 obesity drugs have a bad track record of cardiovascular
17 risk. I'm not confident that we can figure out what
18 outcome effects they'll have based on any signal that
19 is measured. I'm not convinced that doing this will be
20 excessively onerous to development of drugs in this
21 group, and I think it's certainly not sufficiently
22 onerous that we would want to let a drug escape to

1 market with an excessive risk to patients.

2 I also think that doing it and saying, well,
3 we'll look for a signal, I don't think we're really
4 doing companies a favor doing that because, first off,
5 I think you really want to initiate the program of
6 cardiovascular assessment in stage 2 and set that up.
7 And secondly, I think if you let the company go into
8 phase 3 and stand the risk, that you'll wind up with
9 the cardiovascular event rate looking in excess of 1
10 and then they'll have shot themselves in the foot and
11 be very difficult to go back.

12 So for all those reasons I support it, and I
13 would support the pre- and post-approval approach as
14 well, something analogous to what exists with the
15 diabetes drugs.

16 DR. THOMAS: Just a reminder to the panel,
17 when you speak, if you could remember to state your
18 name and your vote. Thank you.

19 DR. KONSTAM: That was Konstam.

20 DR. FELNER: Eric Felner. I voted no. I
21 think, you know, listening to obviously a lot of what
22 others had to say, and I think I focused a lot on what

1 Mike, Dr. Proschan, had to say as far as these studies
2 being done, not even considering the cardiovascular
3 effects, just trying to get patients to actually take
4 the drug and stay in the study for a year, and I am
5 much more concerned about even doing the initial
6 studies before worrying about the cardiovascular
7 effects until we can even get a year of data in because
8 I think if you make the sponsors do these studies, as
9 we're seeing with the diabetes studies, from the ruling
10 that I guess came out in 2008 from our meeting, you're
11 just not going to see any drugs getting out there.

12 And so at least if you can provide the
13 initial year's study, that you get the appropriate
14 number of patients to start and finish the study, then
15 I would think about the cardiovascular risk. But I
16 don't know if we're even going to get there, so I would
17 start really with just getting the patients to finish a
18 year-long study, and cardiovascular effects would think
19 about after that.

20 DR. CAPUZZI: David Capuzzi. I voted yes.
21 Basically these are high-risk patients with high risk
22 of cardiovascular disease. Obesity itself imparts that

1 risk, and a number of the other concomitant risk
2 factors that they would have in the ATP guidelines are
3 also present, and so they deserve this.

4 DR. WEIDE: Lamont Weide. I voted yes. And
5 I would favor the pre- and post-approval two-stage. I
6 think there is significant overlap in this population
7 and the diabetes population. One could argue that
8 obesity is pre-diabetes. I might be stretching it a
9 tiny bit, depending on how good your pancreas is, but I
10 think there is a lot to be said for that. In diabetes,
11 we clearly require the cardiovascular outcomes
12 regardless of any markers, so I'm not sure why we would
13 change the system.

14 And our ability to identify markers is I
15 think not great. We all look at blood pressure and
16 heart rate, but, I mean, we don't know other markers
17 that could be there, we're just using surrogates. So I
18 think the safest correct thing to do is to require
19 this, and, therefore, I voted yes, and the two-staged
20 approach.

21 DR. YANOVSKI: Jack Yanovski. I voted no. I
22 think it's always very easy to decide to increase

1 regulation and increase the cost of studies to pharma
2 because we will increase safety, and there is no doubt
3 that there's at least a theoretical possibility of
4 improving patient safety by having more subjects in a
5 big cardiovascular outcomes trial in every single
6 medication.

7 But I think we ought to allow there to be
8 flexibility for drug companies and the FDA in order to
9 consider -- actually for two reasons. First, I think
10 every pharma company at present who is thinking at all
11 recognizes the importance of establishing the
12 cardiovascular signals early on, so they're going to be
13 doing enough studies for us to find out if there is a
14 cardiovascular risk, or we'll have a theoretical reason
15 for being concerned. So that's a high burden already
16 that most of the drugs under consideration will be
17 required to do it because there is a theoretical or
18 actual signal.

19 And second, by making it less onerous for
20 drugs without a cardiovascular signal, we may actually
21 help foster the development of medications in whom
22 there is a greater probability of seeing benefit in the

1 cardiovascular domain because by removing this
2 increased requirement for drugs that don't have a
3 cardiovascular signal, it should maybe foster drugs
4 that would have much less cardiovascular signal, and,
5 therefore, more likely assessment of drugs where there
6 is a positive cardiovascular effect detected during the
7 early trials.

8 So that's my main reason, that I think that
9 we can imagine drugs that have effects that are
10 completely divorced from even internal systems, so they
11 work entirely in the gut, for instance, and those drugs
12 are not absorbed, and so plausibly it would be very
13 difficult to imagine the cardiovascular problem that
14 resulted from them. Anything is possible, of course,
15 but if they had no signal, I mean, why wouldn't you use
16 post-marketing surveillance to assess the risk of that
17 just like we do in all the other drugs that are
18 approved for many, many disorders?

19 DR. SPRUILL: My name is Ida Spruill, and I
20 voted yes. And I voted yes, and I agree with the
21 comments earlier. But I want to share something
22 different as well, and that is that as a nurse

1 educator, lots of times when I work with patients, I
2 often ask them or try to convince them to participate
3 in research, and they always -- 95 percent of the time
4 was a common theme, which was, "Nobody ever told me
5 about it," or, "My doctor didn't tell me about clinical
6 trials or try to encourage me to participate."

7 The point I'm making is this: we talked
8 earlier about enriching the population, and all I'm
9 saying is that as we look at the two-tiered approach,
10 and if drug companies can perhaps consider the models
11 from both the DPP program and the Look AHEAD, which was
12 able to recruit across ethnicity lines or racial ethnic
13 groups and able to keep people in, I think it's a good
14 model for the drug companies to try to learn from.
15 Additionally, I think perhaps it makes a difference
16 that based on where a person live and work and the
17 geographical differences, that they're going to respond
18 differently to practices and behaviors, and I think
19 that's important in terms of clinical trials as well.

20 And so I voted yes, and I was encouraged and
21 I'm beginning to trust FDA, and I was encouraged by the
22 guidance that they provided, particularly as they said

1 we think that there should be efforts made to recruit
2 people across all racial ethnic groups, and I applaud
3 them for that because sometimes it's difficult to sit
4 and listen at the presentations and look at the data,
5 and the data reflect a population that does not always
6 mirror the folks who are burdened by the disease.

7 Thank you.

8 DR. THOMAS: Dr. Spruill, could you just tell
9 us if you would suggest the trial be done pre-approval,
10 pre- and post-approval --

11 DR. SPRUILL: Yes.

12 DR. THOMAS: Just post-approval.

13 DR. SPRUILL: Oh, number two, pre and post.

14 DR. THOMAS: Thank you.

15 DR. BRITTAIN: Erica Brittain. I voted yes.
16 It was a close call because, you know, we don't usually
17 require safety studies when there is no signal, but
18 obesity drugs are going to be used by a very large
19 population, and there is a worrisome track record with
20 them. So the two-staged design seems like an efficient
21 approach. And wouldn't it be wonderful after someone
22 does one of these studies that they actually find out

1 there is benefit, cardiovascular benefit? And by
2 requiring this, we may find that.

3 And one final comment is, you know, as we
4 keep saying, these studies have to figure out a way to
5 keep people in the studies and to ascertain outcomes.

6 DR. THOMAS: My name is Abraham Thomas. I
7 voted yes. And I would favor a pre- and post-approval
8 mechanism for this question, if you're going to do a
9 cardiovascular outcome trial. A couple things that I
10 thought were important that many people have already
11 talked about, so I won't be too long. One is what
12 struck me is in the slide that was presented earlier
13 this afternoon by our FDA statistician, that if there
14 was only a 20-percent dropout rate, you could actually
15 probably hit the 1.8 upper limit based on the current
16 population in the study without actually enriching for
17 higher cardiovascular risk by previous events. So that
18 means we really have to do a better trial of keeping
19 people in the study, and it can be done. I think we
20 are just being very accepting of these are the low
21 rates because in many studies, even with medications,
22 as long as the sites are good at doing trials and are

1 motivated to keeping patients in trials, they should be
2 able to achieve 80 percent. And I think it's just
3 unacceptable to have such a low rate at this time. The
4 trials having run-in periods or other factors is
5 important, but I think this takes into account where
6 are you doing the trials? where in the world? who are
7 the investigators? who are you recruiting from? so that
8 people that you're recruiting will stay in trials.

9 The second thing is I think the reason to do
10 a pre- and post-approval is that you don't want to have
11 such restriction that people will not try and bring
12 products to market, and you don't want to be post-
13 approval because if there is a risk signal, you want to
14 try and address that early before approval.

15 And I will continue on. Dr. Seely?

16 DR. SEELY: Ellen Seely. I voted no, and I
17 voted no for three main reasons. So I think we need
18 drugs available to treat obesity, and I think a yes
19 vote will decrease the drugs that become available. My
20 considerations of voting no are we don't ask for
21 cardiovascular outcomes for all other drugs that don't
22 have signals. There is a lot in many fields that may

1 have way more cardiovascular risk than these drugs
2 we're talking about.

3 Second is related to what Dr. Yanovski said,
4 is that when the company is deciding where to spend
5 their money, and they have money, and they know they're
6 going to have to do a cardiovascular outcome trial,
7 that may take money away from earlier stage development
8 for developing drugs that may actually be designed for
9 cardiovascular benefit.

10 And the third is that I think it may give
11 actually a false assurance of safety because we don't
12 know that the side effects of these drugs are going to
13 be cardiovascular, and the money is going to go into a
14 cardiovascular trial. The side effects of these drugs
15 may be, as we've seen, related to mood, suicidal
16 ideation, it may be cancer risk, and we're dedicating
17 the company's funds now to looking at the
18 cardiovascular risks, which may not be the primary ones
19 and may falsely reassure us about the drug's safety.

20 MS. MCAFEE: Hi. I'm Lynn McAfee. I voted
21 yes. And I would vote for pre- and post-approval.
22 Although I have to say Dr. Seely made some excellent

1 points, some of which I agree with. I think for me the
2 primary determinant was really the number of people who
3 could be eligible to take this drug. We could be
4 talking about literally half of the population
5 theoretically. That brings to mind my days as an
6 insurance underwriter, and when you underwrite a risk -
7 - and that's really what we're doing -- is you
8 underwrite differently for a standard risk than you do
9 for a risk with catastrophic potential, and I think
10 these are drugs with catastrophic potential, and so we
11 need to require a little bit more.

12 Having said that, I am also concerned about,
13 as I mentioned earlier, cost or drug development time,
14 as you call it, and I really would like to see a lot of
15 the emphasis on post-approval. I don't think there is
16 enough in general in post-approval, and I would like to
17 see a lot more money spent on that.

18 And that's all.

19 DR. GREGG: I'm Ed Gregg. And I voted yes,
20 although primarily because I think that rigorous
21 evaluation of diverse morbidity is important. I think
22 it would send a bad message not to have an expectation

1 of trials by the sponsors. However, if there is no
2 signal, as the language states here, I would not demand
3 a pre- approval, and, in part, because I'm concerned
4 that the two-stage model that's being proposed is
5 actually going to not necessarily leave us with us with
6 an unambiguous situation, and I think that in terms of
7 guiding this Committee, it's not going to answer the
8 risk-benefit question necessarily.

9 So I would encourage guidance actually that
10 encourages into meta-analysis at the least and that
11 proposes a fairly standard set of diverse outcomes,
12 including cardiovascular disease.

13 DR. GOLDFINE: Allison Goldfine. I voted
14 yes. And I think the reasons that I think it's
15 necessary, again, as Lynn said, is the number of
16 patients exposed, and if we start with a very low-risk
17 population who are currently being treated, it's
18 important to recognize that obesity is occurring at
19 younger and younger ages, and we're beginning to see
20 the comorbid conditions at younger and younger ages,
21 and cardiovascular disease is a very important one.

22 In addition, both the physician and the

1 patient who have more advanced complications are going
2 to be asking, "How is this particular drug applicable
3 to me if it's studied in the earlier population?" and I
4 think we're going to actually have to have an answer,
5 which will then move us into whether or not this drug
6 is safe or whether this drug is beneficial in the
7 patients who have specific complications of obesity, of
8 which cardiovascular disease is a major complication.

9 I think there are unanticipated risks, and
10 when we come to one of the major causes of morbidity
11 and mortality in the population, understanding it in
12 that particular realm is important, and if other things
13 pop up, like mood and suicidality, then there will need
14 to be some attention focused on that, but I think to me
15 the harder problem was whether this should be a post-
16 approval only when you say there is without a
17 theoretical risk. Well, the question in the theoretical
18 risk is, what are you seeing as the point estimates and
19 event rates and compliance or adherence during the
20 trial as to whether or not it should be pre and post or
21 just post, and so interpreting that "without" that was
22 underlined was difficult for me, but I think I would

1 take the two-stage approach. You have to look at the
2 data that comes in as you got it from your enabling
3 trials and then move forward, and so that most of this
4 could be moved to post.

5 Thank you.

6 DR. WATERS: David Waters. And I voted yes.
7 And I would favor the two-stage approach. Without
8 recapitulating what a lot of people have said, just
9 adding what I think is different, I think it will be
10 very difficult to perform cardiovascular outcomes
11 trials in this population. It presents a lot of
12 specific difficult challenges that we discussed, and it
13 will be a lot more difficult than in patients with
14 diabetes, I believe.

15 However, on the other hand, we have the
16 expectation that weight loss should provide
17 cardiovascular benefit of some type at some point, so
18 that for the individual using a drug or for the
19 physician prescribing it, I think it's absolutely
20 imperative that we have some sort of a point estimate
21 of potential benefit or harm.

22 Thank you.

1 DR. THOMAS: Just one additional reminder,
2 part of the question is also if cardiovascular outcome
3 trial, meta-analysis, or both. I think most people
4 have actually answered that, but just remember as you
5 go through.

6 DR. WATERS: Just to add to that, Abraham --
7 David Waters again -- both, meta-analysis or outcome
8 trial.

9 DR. BERGMAN: This is Richard Bergman. I
10 voted yes. I'm voting for post-approval, number 3,
11 option number 3.

12 On the one hand, in the first place, of
13 course, obesity has great morbidity, and that's going
14 on all the time, so people are suffering from
15 overweight in many ways, we don't have to recapitulate
16 here. And when you think about the mechanisms of body
17 weight control, it's very likely that any new agents,
18 any new molecules, will have very different ways of
19 acting than the ones we've looked at before, and it's
20 very likely they won't be sympathomimetic, they could
21 very much work on energy utilization, they could work
22 on food intake, they could work on gastrointestinal

1 hormones. And so I think that the probability that
2 cardiovascular risk per se is only one of many
3 possibilities that will emerge as these new agents
4 become available.

5 Now, as I said before, I think that the
6 availability of these agents is very limited, the
7 innovation in this field is very limited, there has
8 been a lot of blowback against the large companies, and
9 the economic picture for the small companies isn't very
10 good, and given the need for such agents separate from
11 bariatric surgery, I think that there is an imbalance
12 and it requires to be very cognizant that we need to
13 have people to work on more mechanisms and learn more
14 about how body weight regulation happens and why some
15 people are obese and some people aren't.

16 So I think that it's not necessarily true
17 that cardiovascular risk is the primary risk that we're
18 going to see, and, of course, a good example is with
19 rimonabant where suicidal ideology -- that's not the
20 right word -- but suicidality turned out to be a risk,
21 which certainly wouldn't emerge from a trial like this
22 if that turned out to be what the risk was.

1 So I think that focusing on cardiovascular
2 risk a priori at the expense of all the other possible
3 risks is not really a good way for these companies to
4 expend their funds. And I believe that if we do a
5 post-approval evaluation, which will include
6 cardiovascular risk and other kinds of risk, then it's
7 a higher probability of getting some of these agents
8 into the market and helping the patients and the other
9 people who need to be able to reduce their adiposity
10 and then reduce cardiovascular risk as well as other
11 ones.

12 DR. COOPER: I'm Bill Cooper.

13 DR. THOMAS: Actually, Dr. Bergman,
14 preference as to the type of trial?

15 DR. BERGMAN: I said number 3. So do I have
16 to choose it for number 3?

17 DR. THOMAS: No. Cardiovascular outcomes,
18 meta- analysis, or both?

19 DR. BERGMAN: Oh, huh.

20 (Laughter.)

21 DR. BERGMAN: That's all fine. Any of those
22 is fine.

1 (Laughter.)

2 DR. COOPER: I am Bill Cooper. I voted yes
3 because of the past history of these drugs and in sort
4 of considering the information that's been presented
5 and discussed at this meeting. I particularly think
6 this gives us an opportunity to think, as Dr. Kaul
7 pointed out earlier, about the current imbalance in
8 information to guide benefit decisions and lots less
9 information to guide risk, and this would be a way to
10 move forward there.

11 I think that in balancing both the safety
12 assessment and the efficiency, the pre- and post-
13 approval approach, as discussed in item 2, I would be
14 comfortable with that, and I would favor both
15 cardiovascular outcomes trials as well as the meta-
16 analysis, as proposed.

17 DR. PROSCHAN: I'm Mike Proschan. I voted
18 yes. And I would favor a two-stage approach before and
19 after approval, but what I worry about there is if
20 there is a great incentive to suddenly have lagging
21 recruitment after the drug has been approved. So I
22 would want to make it clear that that approval will be

1 removed if the outcomes trial isn't done by a certain
2 time.

3 I also think that in an outcomes trial you
4 have to make it clear that you cannot have the kind of
5 dropout that is being seen in these studies. That's
6 just unacceptable, and that would not be deemed
7 sufficient evidence. And Dr. Kaul's point about not
8 being able to anticipate ahead of time what might cause
9 cardiovascular problems, it kind of reminds me of the
10 statistician who tells the M.D., "All of the results
11 are like this," and the M.D. says, "Oh, that makes
12 sense because platelets have this effect and that
13 effect," and then the statistician says, "Oh, I'm
14 sorry, I mixed up the groups, it actually goes the
15 other way," and the M.D. says, "Oh, that makes sense
16 because --

17 (Laughter.)

18 DR. PROSCHAN: You know, you can always --
19 everything makes sense in retrospect.

20 PARTICIPANT: It's geneticists that do that.

21 DR. PROSCHAN: (Laughing.) And I would be
22 okay with combining trials and meta-analysis.

1 DR. HIATT: William Hiatt. I voted no, with
2 two clear caveats. So let me first explain the no
3 vote. If you really want to impose this requirement on
4 a drug with no signals, then I think you ought to
5 impose it on all new drugs that are designed for
6 symptomatic indications. And so I'm just really
7 concerned that it's easy for us to sit here and say, of
8 course, it's weight loss, we don't want to harm the
9 public, and, of course, I'm very much in that camp, but
10 it makes no sense to me if there is absolutely no
11 signal why you would do this. So that's really my no
12 vote, and I think it would have to be extrapolated to
13 any other drug that's being developed for a symptomatic
14 indication, whether it's headaches or arthritis or GERD
15 or anything else. So I would really be cautious about
16 this blanket requirement.

17 Now, there are two key caveats. The first
18 one is my threshold for a signal would be quite low,
19 and so I would think that something that would indicate
20 concern would force you into option number 2, the thing
21 we talked about most of the afternoon.

22 And the second thing is that I think it's

1 very different to ask sponsors to gather data in their
2 planned phase 2 and phase 3 trials and adjudicate the
3 events. That's a low-cost item, which indeed may be
4 quite informative. I think it's very different to
5 require a cardiovascular outcome trial as a separate,
6 very large standalone trial.

7 So I would certainly pursue the phase 2/phase
8 3 meta-analysis of available data that could
9 potentially generate a signal which could then lead to
10 a late-stage decision to do a cardiovascular outcome
11 trial. So that to me -- the "or" could have allowed me
12 to vote yes, I just want to clarify that, because I
13 would have favored gather the data that were available,
14 but I was worried by voting yes that I would then say,
15 okay, every new drug that comes along should have a
16 cardiovascular outcome trial, and I was very
17 uncomfortable with that particular component.

18 DR. JENSEN: Mike Jensen. I also voted no,
19 along the same lines that Dr. Hiatt just mentioned.
20 I'm sure the FDA is very good at looking for signal in
21 the mechanism. If there's no signal in the mechanism,
22 it seems that the resources that you would need to look

1 for a CV signal in a CVOT trial could be better used
2 elsewhere. I'm sure if we had been asked to comment on
3 whether we should do psychiatric trials, neurology
4 trials, oncology trials, or GI trials and gather a
5 different group here, each would have come up and said,
6 yes, we should definitely be doing those trials
7 prospectively because we have to protect the patient.

8 But in point of fact, I think this will
9 inhibit development. We probably will have fewer
10 available compounds. And I don't see this as going to
11 really advance the field beyond the safety that's
12 already provided by the FDA.

13 DR. ALEXANDER: I'm John Alexander. I voted
14 yes, and I almost completely agree with Dr. Hiatt, who
15 voted no, and that's because of two important
16 vaguenesses in the way the question was worded. One is
17 no signal for harm -- I'm sorry -- no theoretical risk,
18 and the other is an excess risk should be excluded.

19 So my thinking is as follows. Overweight
20 patients are at increased CV risk, we know that. And I
21 also agree with others that there has been a track
22 record of risk with weight loss drugs. And there is

1 also, as people have commented on, a lack of a
2 consistent or well- understood mechanism of this
3 increased risk.

4 So I interpreted no theoretical risk to mean
5 no -- I'm sorry, no signal to mean no theoretical risk
6 and no worrisome effect on physiologic markers, and I
7 really do think we need some amount of clinical outcome
8 data on cardiovascular and non-cardiovascular outcomes
9 from phase 2 and 3 combined. These studies need to be
10 adequately designed with prospective collection and
11 adjudication of cardiovascular outcomes. I think pre-
12 and post-approval combination studies are fine.
13 However, I think how much should be post-approval would
14 really depend on the pre- approval signals. And I also
15 agree that post-approval studies need to be completed
16 in a reasonable degree of time.

17 The second part of uncertainty in the
18 question is, what degree of excess risk should be ruled
19 out? And I think the diabetes paradigm of something
20 around 1.3 or 1.8 is not unreasonable, but I also very
21 much liked what Dr. Kaul had commented on earlier, that
22 the certainty might depend on the potential benefits of

1 the drug, either on weight loss or on other outcomes.

2 And then, finally, I think we really do need
3 more research into how to obtain sustained weight loss,
4 maybe through better compliance in obese patients, both
5 through pharmacologic and non-pharmacologic measures.

6 And I'm fine with combined cardiovascular
7 outcome trials and meta-analyses.

8 DR. SAVAGE: I'm Peter Savage, and I voted
9 yes, again for many of the reasons that have already
10 been mentioned. I think that two things made me decide
11 to go to the yes side of the issue. One is the vast
12 size of the population that has the disorder, and
13 therefore tens of millions of people will be affected,
14 and we can't guarantee that the drugs will be used
15 exactly the way that the label authorizes their use.

16 And I also think that we're looking at
17 something that's happened in part because the
18 environment we now live in is so different from the
19 environment in which we genetically originated, and so
20 the attempts to reverse obesity are to some degree -- I
21 don't know if I want to use the word "poisoning," but
22 blocking key components of metabolism that we don't

1 fully understand.

2 So it seems to me that there is a deficit of
3 information in this area, and we just need to learn
4 more and we need to be cautious because of the
5 cardiovascular problems that have already been
6 identified.

7 That being said, I think that there is a wide
8 range of risk in obese patients ranging from, say, a
9 young obese person in their twenties or thirties with
10 no risk factor abnormalities, no family history of
11 cardiovascular disease, and so forth; now, that's a
12 very different person from an obese 60-year-old who has
13 hypertension, dyslipidemia, and type 2 diabetes. So
14 that I think the FDA has to use some discretion
15 deciding how much information or what type of study
16 they want done as a particular compound comes along
17 based upon its profile and the potential part of the
18 population it would be useful in.

19 So I would go along with the idea of a two-
20 stage process.

21 And I guess the last thing I would want to
22 say is again to reinforce the concept that we just

1 can't have as much missing data as seems to have been
2 revealed in the discussions that took place.

3 And also, the question I asked this morning
4 about how expeditiously we were able to make the
5 transition from the initial pre-approval process to
6 having some sort of a follow-up study, I agree with the
7 idea that that needs to take place quickly so that
8 there isn't a long delay of 6 or 8 or 10 years before
9 the results of that study come in, and I think that
10 it's clearly possible to shorten that time considerably
11 if there is some advanced planning. And I think the
12 FDA has to make sure that time tables are adhered to.

13 DR. HENDRICKS: I'm Ed Hendricks. I voted
14 no. I don't believe that we should require obesity
15 drugs to have a cardiovascular outcome trial if there
16 is no theoretical risk and no signal in the clinical
17 trials.

18 I would just like to echo something Dr.
19 Yanovski said, and that's if the FDA follows through
20 with this vote, we've just added another big
21 disincentive to the drug companies to come up with
22 obesity drugs, and we desperately need some drugs. We

1 have one drug that's approved for long-term use, which
2 leaves physicians like me in the situation of having to
3 use drugs off schedule to take care of my patients, and
4 that leaves many, many patients turning to over-the-
5 counter drugs, which are known to be not effective and
6 dangerous.

7 DR. THOMAS: Dr. Rasmussen, I know you're not
8 a voting member, but do you have comments? If you
9 don't, that's fine.

10 DR. RASMUSSEN: Thank you for the invitation.
11 I would like to comment and revert to the fact about
12 missing data. I mean, industry knows that missing data
13 cannot be accounted for by imputation. We put a lot of
14 money and effort into ensuring that in selecting sites,
15 in ensuring that there is adequate education of people
16 before they enter trials, and, I mean, we still end up
17 in a situation where people get on the scale as soon as
18 they enter the trial, get disappointed by us not
19 meeting their expectations, and it's just a very, very
20 difficult thing to overcome with however many good
21 intentions we put in there.

22 DR. THOMAS: Thank you.

1 And then, Dr. Capuzzi, you had some comment
2 that you forgot to mention?

3 DR. CAPUZZI: Yes, I did, when I heard the
4 other remarks, for saying this. Yes, in answer to the
5 trial to evaluate cardiovascular outcomes, I vote yes
6 for both for that trial.

7 And I just want to bring up one point because
8 a number of good points were made, in that one of the
9 first landmark studies, the Coronary Drug Project study
10 published in The Lancet in the mid or early 1980s,
11 shortly after the first Cholesterol Consensus
12 Conference recommended four drugs to be used for lipid
13 regulation and hopefully for reducing cardiovascular
14 risk. These were dextrothyroxine, Atromid-S, low-dose
15 estrogen, conjugated estrogens, and high-dose
16 conjugated estrogens, and a bile acid sequestrant, I
17 believe they used colestipol, and placebo. The placebo
18 group did the best of all those drugs, and each one of
19 the others were discontinued. So I don't think you can
20 -- d-thyroxine apparently does have some metabolic
21 effects but wasn't thought to be so. So I just put
22 that out as an example of what you can't presuppose.

1 DR. THOMAS: Thank you.

2 Any comments from the FDA or final words?

3 DR. COLMAN: Well, yeah, I would like to
4 thank everyone. I think this was a very interesting 2-
5 day meeting. I know it was a lot of work on your part.
6 And we appreciate all of your views. And I will see
7 some of you in May. So thanks again. We appreciate
8 it.

9 Adjournment

10 DR. THOMAS: I would like to thank all the
11 speakers, both external and from the FDA, and the panel
12 members for their questions and comments and spirited
13 discussion.

14 And this meeting is adjourned.

15 (Whereupon, at 4:27 p.m., the
16 Endocrinologic and Metabolic Drugs
17 Advisory Committee (EMDAC) Meeting was
18 adjourned.)

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1 CERTIFICATE OF NOTARY PUBLIC

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3 I, RICK SANBORN, the officer before whom the
4 foregoing proceeding was taken, do hereby certify that
5 the proceeding was recorded by me; that the proceeding
6 was thereafter reduced to typewriting under my
7 direction; that said transcript is a true and accurate
8 record of the proceeding; that I am neither counsel
9 for, related to, nor employed by any of the parties to
10 the proceeding; and, further, that I have no financial
11 interest in this proceeding.

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RICK SANBORN
Notary Public in and for the
State of Maryland

1 CERTIFICATE OF TRANSCRIPTION

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5 proceeding and that I have typed the transcript of this
6 proceeding using the Court Reporter's notes and
7 recordings. The foregoing/attached transcript is a
8 true, correct, and complete transcription of said
9 proceeding.

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April 10, 2012

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