1   FOOD AND DRUG ADMINISTRATION

2   CENTER FOR DRUG EVALUATION AND RESEARCH

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6   ENDOCRINOLOGIC AND METABOLIC DRUGS

7   ADVISORY COMMITTEE (EMDAC) MEETING

8

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11   Monday, December 14, 2015

12   8:01 a.m. to 4:54 p.m.

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18   FDA White Oak Campus

19   Building 31, The Great Room

20   White Oak Conference Center

21   Silver Spring, Maryland

22

1   **Meeting Roster**

2 **ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Stephanie L. Begansky, PharmD**

4 Division of Advisory Committee and

5 Consultant Management

6 Office of Executive Programs, CDER, FDA

7

8 **ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY**

9 **COMMITTEE MEMBERS (Voting)**

10 **Daniel Budnitz, MD, MPH**

11 CAPT, US Public Health Service

12 Director, Medication Safety Program

13 Division of Healthcare Quality Promotion

14 Centers for Disease Control and Prevention

15 Atlanta, Georgia

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17 **Brendan M. Everett, MD, MPH**

18 Assistant Professor of Medicine

19 Harvard Medical School

20 Director, General Cardiology Inpatient Service

21 Brigham and Women's Hospital

22 Boston, Massachusetts

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2   *(Consumer Representative)*

3   Visalia, California

4

5   **Susan R. Heckbert, MD, PhD**

6   Professor

7   Department of Epidemiology

8   University of Washington

9   Cardiovascular Health Research Unit

10   Seattle, Washington

11

12   **William R. Hiatt, MD, FACP, FAHA**

13   *(via telephone)*

14   Professor of Medicine/Cardiology

15   University of Colorado School of Medicine

16   President, CPC

17   Aurora, Colorado

18

19

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22

1 **Robert J. Smith, MD**

2 *(Chairperson)*

3 Professor of Medicine (Endocrinology)

4 Alpert Medical School of Brown University

5 Professor of Health Services, Policy and Practice

6 Brown School of Public Health

7 Research Staff, Ocean State Research Institute

8 Providence Veterans Administration (VA)

9 Medical Center

10 Providence, Rhode Island

11

12 **Peter W. F. Wilson, MD**

13 Director

14 Epidemiology and Genomic Medicine

15 Atlanta Veterans Administration Medical Center

16 Professor of Medicine and Public Health

17 Emory University

18 Emory Clinical Cardiovascular Research Institute

19 Atlanta, Georgia

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TEMPORARY MEMBERS (Voting)
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Sanjay Kaul, MD

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Milton Packer, MD

Distinguished Scholar in Cardiovascular Science

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4   Cardiovascular and Pulmonary Branch

5   NHLBI, NIH

6   Bethesda, Maryland

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9   Director, Heart Failure

10   Director, Echocardiography

11   San Francisco Veterans Affairs Medical Center

12   Professor of Medicine

13   School of Medicine

14   University of California San Francisco

15   San Francisco, California

16

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ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Reshma Kewalramani, MD

(Acting Industry Representative)

Vice President

US Medical Organization

Amgen

Thousand Oaks, California

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Director

Office of Drug Evaluation II (ODE II)

Office of New Drugs (OND), CDER, FDA

Jean-Marc Guettier, MD

Director

Division of Metabolism and Endocrinology Products

(DMEP), ODE II, OND, CDER, FDA

1   **James P. Smith, MD, MS**

2   Deputy Director

3   DMEP, ODE II, OND, CDER, FDA

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5   **Iffat Nasrin Chowdhury, MD**

6   Medical Officer

7   DMEP, ODE II, OND, CDER, FDA

8

9   **Jennifer Clark, PhD**

10   Mathematical Statistician

11   Division of Biometrics (DB) II

12   Office of Biostatistics (OB)

13   Office of Translational Sciences (OTS)

14   CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

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

2   (8:01 a.m.)

3   **Call to Order**

4   **Introduction of Committee**

5   DR. R. SMITH: Good morning to everyone.

6 Thanks for being here. I would first like to

7 remind everyone here to please silence your cell

8 phones, your smartphones, any other devices that

9 make noise, if you've not already done so. And I

10 would also like to identify the FDA press contact,

11 Andrea Fischer. Hand up in the back. Thank you.

12   My name is Robert Smith. I'm the

13 chairperson of the Endocrinologic and Metabolic

14 Drugs Advisory Committee, and I'll be chairing this

15 meeting. I will now officially call the

16 Endocrinologic and Metabolic Drugs Advisory

17 Committee meeting to order.

18   We'll start by going around the table and

19 introducing ourselves here on the panel. And we'll

20 start, I think, with the FDA over here on my left

21 and then go around the table.

22   DR. ROSEBRAUGH: Good morning. I'm Curt

Rosebraugh, director, Office of Drug Evaluation II.

DR. J. SMITH: Good morning. Jim Smith, deputy director, Division of Metabolism and Endocrinology Products.

DR. CHOWDHURY: Iffat Chowdhury, medical officer, DMEP.

DR. CLARK: Jennifer Clark, statistical reviewer.

DR. PACKER: Milton Packer, cardiologist, Baylor University Medical Center.

CAPT BUDNITZ: Dan Budnitz, lead, medication safety program, CDC.

DR. SHAMBUREK: Bob Shamburek, clinical scientist, the intramural NIH/NHLBI.

MS. HALLARE: Diana Hallare, consumer representative.

DR. R. SMITH: Dr. Hiatt, are you there?

DR. HIATT: Yes. William Hiatt, University of Colorado.

LCDR BEGANSKY: Stephanie Begansky, designated federal officer for today's meeting.

DR. R. SMITH: And I'm Robert Smith. I'm an

endocrinologist. I'm professor of medicine in

public health at Brown University.

DR. EVERETT: Brendan Everett. I'm a

cardiologist at the Brigham and Women's Hospital in

Boston and Harvard Medical School.

DR. HECKBERT: Susan Heckbert, Department of

Epidemiology, School of Public Health, University

of Washington, Seattle.

DR. WILSON: Peter Wilson, preventive

cardiology, endocrinology, public health, Emory

University.

DR. BLAHA: Good morning. Mike Blaha, Johns

Hopkins, cardiology/epidemiology, School of Public

Health and School of Medicine.

DR. FLEMING: Thomas Fleming, Department of

Biostatistics, University of Washington.

MS. MCCALL: Debra McCall, patient

representative, Healthy Heart Study.

DR. KAUL: Good morning. Sanjay Kaul,

cardiologist, Cedars Sinai, Los Angeles.

DR. PROSCHAN: I'm Michael Proschan,

statistician at the National Institute of Allergy

1   and Infectious Diseases.

2   DR. TEERLINK: John Teerlink, professor of

3   medicine at University of California San Francisco,

4   and cardiologist at the San Francisco VA Medical

5   Center.

6   DR. KEWALRAMANI: Reshma Kewalramani, the

7   industry representative, from Amgen.

8   DR. R. SMITH: Thank you. And back to the

9   other side of the table, Dr. Guettier.

10   DR. GUETTIER: Jean-Marc Guettier, division

11   director, Division of Metabolism and Endocrine

12   Products.

13   DR. R. SMITH: Thank you.

14   For topics such as those being discussed at

15   today's meeting, there are often a variety of

16   opinions, some of which are quite strongly held.

17   Our goal is that today's meeting will be a fair and

18   open forum for discussion of these issues, and that

19   individuals can express their views without

20   interruption. Thus, as a gentle reminder,

21   individuals will be allowed to speak into the

22   record only if recognized by the chairperson. We

1   look forward to a productive meeting.

2   In the spirit of the Federal Advisory

3   Committee Act and the Government in the Sunshine

4   Act, we ask that the advisory committee members

5   take care that their conversations about the topic

6   at hand take place in the open forum of the

7   meeting.

8   We are aware that members of the media are

9   anxious to speak with the FDA about these

10   proceedings. However, FDA will refrain from

11   discussing the details of this meeting with the

12   media until its conclusion. Also, the committee is

13   reminded to please refrain from discussing the

14   meeting topic during breaks or during lunch. Thank

15   you.

16   I'll pass the microphone to Lieutenant

17   Commander Stephanie Begansky, who will read the

18   Conflict of Interest Statement.

19   **Conflict of Interest Statement**

20   LCDR BEGANSKY: The Food and Drug

21   Administration is convening today's meeting of the

22   Endocrinologic and Metabolic Drugs Advisory

1   Committee under the authority of the Federal

2   Advisory Committee Act of 1972.

3   With the exception of the industry

4   representative, all members and temporary voting

5   members of the committee are special government

6   employees or regular federal employees from other

7   agencies and are subject to federal conflict of

8   interest laws and regulations.

9   The following information on the status of

10   this committee's compliance with federal ethics and

11   conflict of interest laws covered by, but not

12   limited to, those found at 18 USC Section 208 is

13   being provided to participants in today's meeting

14   and to the public.

15   FDA has determined that members and

16   temporary voting members of this committee are in

17   compliance with federal ethics and conflict of

18   interest laws. Under 18 USC Section 208, Congress

19   has authorized FDA to grant waivers to special

20   government employees and regular federal employees

21   who have potential financial conflicts when it is

22   determined that the agency's need for a particular

1   individual's services outweighs his or her

2   potential financial conflict of interest.

3   Related to the discussions of today's

4   meeting, members and temporary voting members of

5   this committee have been screened for potential

6   financial conflicts of interest of their own as

7   well as those imputed to them, including those of

8   their spouses or minor children and, for purposes

9   of 18 USC Section 208, their employers. These

10   interests may include investments, consulting,

11   expert witness testimony, contracts, grants,

12   CRADAs, teaching, speaking, writing, patents and

13   royalties, and primary employment.

14   Today's agenda involves the results of the

15   IMProved Reduction of Outcomes: Vytorin Efficiency

16   International Trial, IMPROVE-IT. IMPROVE-IT was a

17   clinical trial that studies the effect of ezetimibe

18   and simvastatin compared with simvastatin on the

19   occurrence of cardiovascular events in patients

20   with recent acute coronary syndrome.

21   The results from this trial have been

22   submitted to support supplemental new drug

1   applications 21445, Supplement 038, and 21687,

2   Supplement 054, Zetia, ezetimibe, and Vytorin,

3   ezetimibe/simvastatin tablets, respectively, by MSD

4   International GmbH.

5   The proposed indication for Zetia, in

6   combination with a statin, and Vytorin is to reduce

7   the risk of cardiovascular events in patients with

8   coronary heart disease. This is a particular

9   matters meeting during which specific matters

10 related to Merck's supplemental new drug

11 applications will be discussed.

12   Based on the agenda for today's meeting and

13 all financial interests reported by the committee

14 members and temporary voting members, no conflict

15 of interest waivers have been issued in connection

16 with this meeting.

17   To ensure transparency, we encourage all

18 standing committee members and temporary voting

19 members to disclose any public statements that they

20 may have made concerning the products at issue.

21   With respect to FDA's invited industry

22 representative, we would like to disclose that

1   Dr. Reshma Kewalramani is participating in this

2   meeting as a nonvoting industry representative,

3   acting on behalf of regulated industry.

4   Dr. Kewalramani's role at this meeting is to

5   represent industry in general and not any

6   particular company. Dr. Kewalramani is employed by

7   Amgen.

8   We would like to remind members and

9   temporary voting members that if the discussions

10   involve any other products or firms not already on

11   the agenda for which an FDA participant has a

12   personal or imputed financial interest, the

13   participants need to exclude themselves from such

14   involvement, and their exclusion will be noted for

15   the record.

16   FDA encourages all other participants to

17   advise the committee of any financial relationships

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

19   you.

20   DR. R. SMITH: Thank you. We'll now proceed

21   with the FDA's introductory remarks from Dr. James

22   Smith.

FDA Introductory Remarks

1

2   DR. J. SMITH: Good morning. Once again, my

3   name is Jim Smith, and I would just like to thank

4   you all for being here. I'm going to keep my

5   introductory remarks quite brief.

6   We've convened this committee to discuss the

7   results of the IMPROVE-IT trial, a cardiovascular

8   outcomes trial, as you know, that studied the

9   addition of ezetimibe to simvastatin among patients

10   with recent acute coronary syndrome.

11   Many of us have awaited this trial for a

12   long time, as I bet many of you. Zetia was

13   approved in 2002, Vytorin in 2004. And as you know

14   well, the lack of cardiovascular outcomes data for

15   Vytorin and Zetia has been quite controversial over

16   the years, especially after the publication of the

17   ENHANCE trial in 2008 and the SEAS trial about six

18   months later.

19   ENHANCE was a trial that used carotid intima

20   media thickness as a measurement of efficacy, and

21   the SEAS trial studied patients with asymptomatic

22   aortic stenosis. And as I'm sure you'll recall,

1   the SEAS trial also raised a concern that active

2   therapy was associated with cancer-related events,

3   and the safety of ezetimibe was questioned.

4   This committee met in November 2011 to

5   discuss the results of the SHARP trial, which

6   studied Vytorin against placebo among patients with

7   chronic kidney disease. And although the SHARP

8   trial demonstrated a reduction in major vascular

9   events with Vytorin, it was not designed to isolate

10 the effects of ezetimibe itself. So we continued

11 to look forward to the results of the IMPROVE-IT

12 trial.

13   One thing I'd like to say at the outset is

14 no matter where the discussion goes today, there is

15 absolutely no question that the IMPROVE-IT results

16 are the product of a remarkable effort by thousands

17 of investigators and other individuals.

18   This trial spanned 2005 to 2014. I'm sure

19 that data will be mined from it for years to come.

20 We are going to learn a lot from this trial. And

21 this trial enrolled more than 18,000 patients at

22 more than 1100 sites in 39 countries. So there is

1   no question that this trial is a remarkable

2   achievement just in its conduct.

3   Before turning to the agenda and discussion

4   points briefly, I also wanted to make one other

5   comment at the outset that I hope might liberate

6   you a little bit, and that's that we know that many

7   have looked at IMPROVE-IT as a test of the LDL

8   hypothesis, if you will.

9   That LDL hypothesis is not on trial today.

10   This discussion today is a discussion of the

11   results of this trial as they are relevant to the

12   claims and the indications that are being sought by

13   the applicant. And I think that's important. We

14   are not making decisions today about every other

15   drug that may be in development. We are focused on

16   this trial, this trial's results, and how they

17   relate to these products at issue.

18   With regard to the agenda, we are going to

19   begin, as we typically do, with the applicant's

20   presentations. Both the applicant and FDA are

21   going to try keep our presentations to an hour or

22   less to try to be succinct. I know there will be

1   some overlap, but we're going to attempt not to as

2   much as we can.

3   After the applicant's presentations, you

4   will have an opportunity for clarifying questions

5   directed to the applicant. And then we will have a

6   short break, let you process what you've heard,

7   perhaps, and then we will have the FDA

8   presentations.

9   From the FDA side, Dr. Chowdhury will give a

10 bit of an introduction, and then Dr. Clark, who is

11 the primary reviewer for biostatistics, will give a

12 presentation, and then Dr. Chowdhury will return

13 for a few more things about efficacy and then

14 safety.

15   Then you'll have an opportunity for

16 clarifying questions to FDA. I imagine that we

17 might even be running ahead of schedule, and so if

18 you have other questions for industry, Dr. Smith

19 will be able to facilitate that. Then we'll break

20 for lunch. We'll have the open public hearing.

21 And then we'll go into the afternoon of discussion

22 points, with breaks as needed.

1   If I can have the discussion points, I just

2   wanted to walk through those quickly. I won't read

3   them at this point; that can come later. I won't

4   read them verbatim, but I just wanted to set the

5   stage a little bit.

6   The first discussion point is really about

7   your interpretation of the overall efficacy results

8   from the trial. And we have listed some things to

9   get you started, for example, specifically

10   discussing the magnitude of the observed treatment

11   effect, the robustness of the result of the primary

12   composite endpoint.

13   As you know from the briefing materials, and

14   especially with a trial of this duration, the FDA

15   review focused largely about the potential impact

16   of missing data, and that gets at the robustness of

17   the result and what you think about that; then any

18   comments you may have regarding either observed

19   effects on the components or other secondary

20   endpoint measures, or really any other discussion

21   regarding the overall results of the trial.

22   Discussion point 2, as you know, multiple

1   subgroup analyses were performed, and there were a

2   couple that have been of interest internally, and I

3   know that some have been presented publicly. And

4   that relates to the presence or absence of diabetes

5   at baseline, and then age. So we're going to ask

6   you to provide some interpretation of the subgroup

7   findings and your thoughts about those.

8   Regarding discussion point 3, as you've

9   heard, the applicant has proposed that the results

10   from IMPROVE-IT, which can be extrapolated to other

11   clinical situations, weren't directly tested in a

12   trial, such as adding ezetimibe to any statin among

13   patients with stable coronary heart disease. And

14   we'd like you to discuss a little bit about to what

15   degree you believe the results from IMPROVE-IT can

16   be extrapolated to other clinical situations.

17   Fourth is rather straightforward, that we'd

18   like you to discuss the safety findings of the

19   IMPROVE-IT trial.

20   Then last, we have a voting question that

21   reads, "Do the efficacy and safety data from the

22   IMPROVE-IT trial provide substantial evidence to

1   support approval of a claim that adding ezetimibe

2   to statin therapy reduces the risk of

3   cardiovascular events?"

4   If yes, we're going to ask you to comment on

5   your rationale and incorporating all at the rest of

6   the discussion if there's any limits or comments

7   that you would want to make about such a claim or

8   indication. And then if no, we'd like to hear your

9   rationale for that and comment on what additional

10   data may be needed.

11   So with that, I would like to thank you

12   again for being here, and I will turn the

13   microphone back to Dr. Smith.

14   DR. R. SMITH: Thank you.

15   Both the Food and Drug Administration and

16   the public believe in a transparent process for

17   information-gathering and decision-making. To

18   ensure such transparency at the advisory committee

19   meeting, FDA believes that it is important to

20   understand the context of an individual's

21   presentation.

22   For this reason, FDA encourages all

1 participants, including the applicant's non-

2 employee presenters, to advise the committee of any

3 financial relationships that they may have with the

4 applicant, such as consulting fees, travel

5 expenses, honoraria, and interests in a sponsor,

6 including equity interests and those based upon the

7 outcome of the meeting.

8 Likewise, FDA encourages you at the

9 beginning of your presentation to advise the

10 committee if you do not have any such financial

11 relationships. If you choose not to address this

12 issue of financial relationships at the beginning

13 of your presentation, it will not preclude you from

14 speaking.

15 So we'll now proceed with the presentations

16 from Merck.

17 **Applicant Presentation – Andrew Tershakovec**

18 DR. TERSHAKOVEC: Good morning. I'm Andrew

19 Tershakovec from cardiovascular clinical

20 development, Merck Research Labs, and I'm very

21 pleased to be here with you today to discuss the

22 IMPROVE-IT trial, the first trial to show the add-

1   on LDL-lowering benefit in cardiovascular therapy.

2   I'll start by introducing those who are with

3   us today, and then provide a short overview of the

4   ezetimibe development program. I'll be followed

5   then by Dr. Christopher Cannon from the TIMI study

6   group, who will provide an overview of the IMPROVE-

7   IT results.

8   Dr. Cannon will be followed by Dr. Paul

9   DeLucca, a statistician at Merck and a member of

10   the IMPROVE-IT team, who will discuss data

11   completeness in the IMPROVE-IT trial. Dr. DeLucca

12   will then be followed by Dr. Eugene Braunwald, co-

13   chair of the IMPROVE-IT executive committee, who

14   will discuss the clinical implications of the

15   IMPROVE-IT trial.

16   IMPROVE-IT was jointly managed by the TIMI

17   study group, the Duke Clinical Research Institute,

18   and Merck. Dr. Michael Blazing from Duke, and one

19   of the study leaders, is also with us here today to

20   help discuss the results.

21   For the last of our introductions, we

22   invited some experts to be here to also address

1 your questions, Dr. Henry Ginsberg from Columbia

2 University, Professor Colin Baigent from Oxford

3 University, and Dr. Gary Koch from the University

4 of North Carolina.

5   We're here today to discuss the IMPROVE-IT

6 trial. IMPROVE-IT was designed to assess the

7 incremental benefit of adding ezetimibe, a

8 cholesterol absorption inhibitor, on background

9 statin therapy to decrease cardiovascular risk in

10 high-risk subjects. The IMPROVE-IT trial results

11 demonstrated that ezetimibe does offer incremental

12 benefit in a well-tolerated manner.

13   Therefore, the IMPROVE-IT results support

14 the proposed indications, specifically, for Vytorin

15 to reduce the risk of cardiovascular events in

16 patients with coronary heart disease, and with

17 Zetia, a similar indication, to decrease

18 cardiovascular events in patients with coronary

19 heart disease when used with a statin.

20   Let me transition to some background. We

21 know that coronary heart disease is a leading cause

22 of death in the United States and in many countries

1   around the world. Over 15 million adults in the

2   United States have coronary heart disease. And

3   despite recent treatment advances, the prevalence

4   of coronary heart disease is expected to increase

5   almost 20 percent by the year 2030.

6   LDL cholesterol is a major causal factor for

7   atherosclerotic vascular disease, and there's a

8   broad range of epidemiologic, preclinical,

9   clinical, and genetic studies supporting the

10   importance of LDL cholesterol and linking LDL

11   cholesterol to cardiovascular risk.

12   There have been many trials assessing lipid-

13   lowering therapies to try to decrease

14   cardiovascular risk. In 1994, a group of academic

15   trialists, led by Oxford University, formed the

16   Cholesterol Treatment Trialists collaboration, also

17   known as CTT, to assess the relationships between

18   LDL cholesterol lowering and cardiovascular risk

19   reduction.

20   CTT gathered individual patient-level data,

21   and using this combined database was able to assess

22   questions that were not able to be addressed in

1   single studies because of issues around power and

2   otherwise. The first CTT analyses were published

3   in 2005 and focused on the statin versus placebo

4   trials.

5   The second cycle of CTT, published in 2010,

6   added data from the high-dose, high-intensity

7   versus low-dose, low-intensity statin trials, and

8   included 26 clinical trials and 170,000 subjects.

9   Thus, CTT represents the broadest, most

10   comprehensive database that we have regarding LDL

11   cholesterol lowering and clinical benefit.

12   As shown in this figure, CTT has

13   demonstrated and found a consistent and strong

14   relationship between LDL cholesterol lowering and

15   cardiovascular risk reduction in the statin trials.

16   Specifically, the 2010 CTT meta-analysis described

17   a 22 percent risk reduction per millimole per liter

18   of LDL cholesterol lowering.

19   The CTT analyses also found and described

20   a consistent relationship across a range of

21   cardiovascular endpoints and also across a range of

22   subgroups, including those related to age, gender,

1   diabetes, and risk status. It is important to

2   understand the CTT analyses when considering the

3   IMPROVE-IT results and to help put the IMPROVE-IT

4   results into context.

5   Thus, clinical trials have demonstrated that

6   we can decrease risk with drug therapy. However,

7   residual risk remains a major unmet medical need,

8   as subjects continue to have cardiovascular events

9   even when aggressively treated.

10   There have been several trials trying to

11   address this potential residual risk, and it is

12   thought that potentially added lipid-lowering

13   therapy could be beneficial. These trials that

14   have occurred included fibrates, niacin, and the

15   CETP inhibitors. But to date, these trials have

16   been negative or were stopped prematurely because

17   of efficacy or safety considerations.

18   Other add-on therapies are also available,

19   namely, the bile acid sequestrants, mipomersen,

20   lomitapide, and the PCSK9 inhibitors. But to date,

21   we do not have outcomes data relating to their

22   cardiovascular benefit.

1   Ezetimibe was developed to try to address

2   this unmet medical need by offering additional LDL

3   cholesterol lowering when added to a statin. As

4   shown in this illustration, ezetimibe targets

5   NPC1L1, inhibiting cholesterol absorption in the

6   intestine. This leads to decreased cholesterol

7   delivery to the liver. The liver responds by

8   upregulating LDL receptors and decreasing

9   circulating LDL cholesterol levels.

10   Statins, on the other hand, target HMG-CoA

11   reductase. This decreases hepatic cholesterol

12   synthesis. The liver also responds by upregulating

13   LDL receptors. This also decreases LDL cholesterol

14   levels. So ezetimibe and statins both offer LDL

15   cholesterol lowering and together offer additive

16   and complimentary LDL cholesterol lowering.

17   The lipid lowering and LDL cholesterol

18   lowering of ezetimibe is also consistent in a broad

19   range of clinical situations. As shown in this

20   slide, ezetimibe offers approximately 20 percent

21   LDL cholesterol lowering when used with all doses

22   of atorvastatin, including the highest dose

1   atorvastatin, 80 milligrams.

2   The lipid-lowering effect of ezetimibe is

3   consistent when used with different statins, as

4   shown in this figure. I will also note that other

5   studies have shown a consistent effect with

6   ezetimibe when added to rosuvastatin. Therefore,

7   ezetimibe offers consistent LDL cholesterol

8   lowering when added to all statins, to all doses of

9   statins, and across a broad range of patient

10   populations.

11   Ezetimibe was approved in the United States

12   in 2002 and Vytorin soon afterwards in 2004.

13   Ezetimibe has a broad clinical experience,

14   including over 37,000 subjects in clinical trials

15   and over 36 million patient-years in postmarketing

16   experience.

17   Therefore, ezetimibe has a broad safety

18   database supporting that it is well-tolerated, with

19   limited added risk. In clinical trials, the

20   adverse event rates with ezetimibe administered

21   with a statin are similar to the adverse event

22   rates when statins are taken alone.

1   Three outcomes trials were planned and

2   completed as part of the ezetimibe development

3   program, SEAS, SHARP, and IMPROVE-IT, each

4   targeting an important scientific question about

5   the potential benefit of LDL cholesterol lowering.

6   The first two of these trials, SEAS and SHARP,

7   focused on ezetimibe/ simvastatin versus placebo.

8   SEAS assessed the question of whether LDL

9   cholesterol lowering could stem the progression of

10   aortic stenosis and could it offer benefit in

11   cardiovascular risk reduction in subjects with

12   aortic stenosis. SHARP, on the other hand,

13   assessed the question of whether

14   ezetimibe/simvastatin therapy could safely decrease

15   the cardiovascular risk in patients with chronic

16   kidney disease, a major unmet medical need.

17   Regarding the results of these trials, the

18   primary endpoint for SEAS, which was a composite of

19   aortic stenosis and ischemic cardiac event, was

20   negative, as LDL cholesterol lowering did not stem

21   the progression of aortic stenosis. However, the

22   secondary endpoint of ischemic cardiac events was

supportive of a cardiovascular risk reduction with

LDL cholesterol lowering.

SHARP showed that ezetimibe/simvastatin did

decrease the risk of major vascular events in a

well-tolerated manner, and today remains the only

lipid-lowering trial with proven benefit in

decreasing cardiovascular risk in chronic kidney

disease patients.

I will also note that the cardiovascular

risk reduction observed in SEAS and SHARP was

generally consistent with the risk reduction you

would expect with the LDL cholesterol lowering

supported by ezetimibe/simvastatin in these two

trials.

IMPROVE-IT, the third outcomes trial planned

and completed, assessed the incremental benefit of

ezetimibe and assessed some specific questions. Is

there an incremental benefit of adding ezetimibe

onto statins in coronary heart disease patients?

And related to that, is the benefit consistent with

what would be expected, given the LDL lowering

supported by ezetimibe and consistent with what

1 would be expected with a statin in a similar

2 clinical situation?

3 IMPROVE-IT also addressed whether lowering

4 LDL cholesterol below 70 milligrams per deciliter

5 is beneficial in patients with coronary heart

6 disease. And IMPROVE-IT also added important

7 additional safety information regarding ezetimibe.

8 In considering the IMPROVE-IT results, it is

9 also to consider recent genetic information.

10 Studies have shown that subjects who have genetic

11 variants that are associated with lower LDL

12 cholesterol levels have lower coronary heart

13 disease risk.

14 The coronary heart disease risk expressed in

15 those subjects is proportional to their lower LDL

16 cholesterol levels. This includes genetic variance

17 of NPC1L1, the target of ezetimibe, and the genetic

18 variance of HMG-CoA reductase, the target of

19 statins.

20 When you look at subjects who have generic

21 variants, both of these generic variants, the risk

22 reduction they express is the sum of the risk

1 reduction expressed by each of these variants

2 individually. This mimics the clinical situation

3 of taking ezetimibe and a statin together and

4 supports the observation that ezetimibe and statins

5 should have additive and do have additive benefit

6 in clinical outcomes.

7   Thus, we know that ezetimibe offers

8 consistent LDL cholesterol lowering when used with

9 all statins, different doses of statins, in a broad

10 range of patient populations. There's a broad

11 safety database for ezetimibe, supporting that it

12 has limited added risk.

13   IMPROVE-IT has shown that ezetimibe offers

14 added benefit and incremental benefit in decreasing

15 cardiovascular risk in a well-tolerated manner. So

16 therefore, when you take the IMPROVE-IT results

17 along with the broad safety database related to

18 ezetimibe, this supports a positive risk/benefit

19 assessment. I thank you, and I'm going to ask Dr.

20 Cannon to continue with our presentation.

21   **Applicant Presentation – Christopher Cannon**

22   DR. CANNON: Thank you. It's a privilege to

1 join the committee here to discuss the results of

2 the IMPROVE-IT trial.

3   As discussed, the IMPROVE-IT trial was

4 designed to test the hypothesis that the addition

5 of ezetimibe to statin therapy would lead to a

6 clinical benefit on cardiovascular outcomes

7 relative to use of statin alone in subjects who've

8 been stabilized following an acute coronary

9 syndrome.

10   The key issue, as noted, was that we knew of

11 the LDL lowering in all the different settings with

12 different background, but would the added LDL

13 lowering with a nonstatin agent, ezetimibe, lead to

14 a clinical benefit? We had all the data from the

15 CTT for statins, but the question really was a

16 yes/no question for ezetimibe.

17   As also noted, there were questions about

18 the safety of ezetimibe that came up during the

19 conduct of this trial, so this serves as a very

20 large and long-term database to add prospective

21 data on the safety of ezetimibe.

22   Now, as investigators and cardiologists, we

1   took this opportunity to also study another

2   question on whether pushing even lower on the LDL

3   range that we would aim for would be of benefit, so

4   many trials we had done in the past had targeted

5   lower and lower LDL levels or achieved lower and

6   lower LDL levels.

7   We asked the question, would even lower be

8   even better for cardiovascular events? We

9   estimated that with statin alone, we would have an

10   average LDL in the group of about 70, and that

11   would be about 55 in the combination therapy group.

12   I wanted to highlight a few of the critical

13   elements as we designed this study to help put it

14   in perspective. We began the study with a post-

15   acute coronary syndrome population who are known to

16   have a high event rate, and this was driven by

17   the need for the more than 5,000 endpoints to have

18   adequate power to detect the clinical benefit that

19   we would expect, on the basis of the LDL difference

20   that we would see in this population with already

21   very low LDL levels.

22   Now, at the same time, we also planned a

1 very long-term, and it ended up being even longer-

2 term, that we set a minimum in the design phase of

3 2.5 years. So we went well into the phase of

4 coronary disease that is more stabilized.

5   In the end, the last patient enrolled was

6 followed for a minimum of 4 years and a median of

7 6. The maximum was 8 and three-quarters years.

8 And so this was a very long-term trial that

9 transitioned into the chronic phase of coronary

10 disease for the majority of the time of the trial.

11   The third point is that we selected low LDL

12 entry criteria. So this is a little bit

13 interesting. We're studying people with LDLs, as

14 you'll see, between 50 and 125. Now, this was in

15 order for us to ensure in the control arm that all

16 the patients were treated to the then-goal of

17 achieving an LDL of 70.

18   So we wanted to ensure that the patients in

19 the control arm got the best possible therapy

20 according to the guidelines. Then we added on top

21 of that the experimental therapy of ezetimibe.

22   Finally, we used simvastatin as the single

1   background therapy for several reasons. First, it

2   has broad clinical experience. It was the first

3   one to have a mortality benefit demonstrated. It

4   has proven outcomes in multiple trials.

5   We also used the two highest doses, so the

6   40 milligram and 80 milligram dose of simvastatin,

7   both of which provide a very significant percentage

8   LDL lowering. And then finally, for the trial, we

9   wanted a standardized background therapy that we

10   could use to allow management of the LDL in both

11   groups in a blinded fashion by the trial setup.

12   So that allowed us to ensure that the

13   control arm would get to the target level, and also

14   with a standardized background therapy, would allow

15   us a better way to assess the safety of the

16   question at hand, the addition of ezetimibe. So

17   the statin is the background therapy, and we wanted

18   to look at the efficacy and safety of what was

19   being added, ezetimibe, and this would be

20   facilitated by a standardized background therapy.

21   The design is illustrated here. We studied

22   patients of age 50 or older who were stabilized

1   following an acute coronary syndrome and enrolled

2   them within 10 days of that event.

3   As I just alluded to, the LDL criteria

4   ranged from 50 to 125 milligrams per deciliter for

5   those who were not receiving prior lipid-lowering

6   therapy; or for those who were on lipid-lowering

7   therapy, it was between 50 and 100. And again,

8   this was designed so that the statin-alone group

9   would get to the controlled levels recommended by

10   guidelines.

11   Now, the patients, there were 18,144 who

12   were randomized, and they all received the standard

13   medical and interventional therapies for acute

14   coronary syndrome. We'll review some of those

15   briefly. Then patients were randomized in a

16   double-blind fashion to receive either simvastatin,

17   initially a 40 milligram dose, or

18   ezetimibe/simvastatin, the 10/40 milligram dose.

19   Again, in a blinded fashion, the LDLs were

20   monitored centrally. And if confirmed to be

21   greater than 79, the simvastatin dose in either

22   group was up-titrated to 80 milligrams to assist in

1   control of the LDL, and again, all that in a

2   blinded fashion.

3   Patients were followed every 4 months, again

4   with that minimum of 2 and a half years, to the

5   point where we had achieved at least 5,250 events.

6   The primary endpoint is listed here. It was

7   cardiovascular death, nonfatal MI, unstable angina

8   requiring hospitalization, coronary

9   revascularization conducted at least 30 days after

10 randomization, or nonfatal stroke.

11   We prespecified three secondary endpoints,

12 and the differences relative to the primary

13 endpoint are in bold. So the first of that

14 included death from any cause, or all-cause

15 mortality, as part of that composite.

16   The second one was a coronary-focused event,

17 that is, coronary heart disease death, nonfatal MI,

18 and urgent coronary revascularization. And then,

19 the final one was a broader endpoint that included

20 revascularization, both coronary and noncoronary.

21   With regard to safety, we had a

22 comprehensive safety analysis. And so this

1   included all adverse events, both serious and

2   nonserious. They were categorized as drug-related

3   or not. We looked at discontinuations due to

4   adverse events and discontinuations of study

5   medication related to drug-related adverse events.

6   Then we did prespecify several safety

7   endpoints of special interest relating to either

8   statin or ezetimibe therapy, notably, muscle-

9   related events, liver-related adverse events, gall

10   bladder-related adverse events.

11   Then, as we've noted during the trial,

12   different safety questions came up. With statins,

13   and indeed with high-dose statins as well, the risk

14   of new onset diabetes was identified over this past

15   decade, so we added an analysis of that into the

16   analysis plan.

17   Then finally, cancer was identified as a

18   possible adverse event, and so this was all

19   prospectively adjudicated by a special cancer

20   clinical events committee.

21   With regard to sample size and power, we

22   randomized over 18,000 patients and aimed to

1   continue until having at least 5,250 events, and

2   again, that minimum follow-up.

3   Now, the assumptions for this were that

4   looking at the range of LDLs, we thought that the

5   23 to 24 percent relative reduction in LDL in this

6   group would lead to about a 15 milligram per

7   deciliter absolute difference in LDL. And using a

8   meta-analysis to see what would that translate into

9   in terms of clinical benefit, we estimated that

10   would be a 9.375 percent reduction. We also

11   calculated in there information that became

12   available of a time lag of benefit of lipid-

13   lowering therapies identified in the CTT as well.

14   So this sample size would have 90 percent

15   power to detect the expected amount of clinical

16   benefit on the basis of the expected amount of LDL.

17   And because we were studying so low LDL levels in

18   the patients, the modest difference in LDL, we

19   fortunately could tell what benefit would we expect

20   and designed the trial and the power in order to

21   detect that expected difference. And the final

22   nominal alpha level for the analysis is .0394.

1   That accounts for three interim analyses done by

2   the DSMB during the trial.

3   The timeline is illustrated here. We

4   enrolled the first patient in October of 2005, and

5   the last patient was randomized in 2010. Then

6   follow-up continued, where the follow-up visits

7   began in May of 2014.

8   We concluded and had the last patient visit

9   in September of 2014 and locked the database a

10   month later, then we presented the primary results

11   at the American Heart Association meetings in

12   November of 2014. The final data were submitted to

13   the FDA in April, and the peer-reviewed publication

14   appeared in the New England Journal on June 3rd.

15   So the population, some of the key

16   characteristics of the patients enrolled, is

17   illustrated here. It's very representative of

18   patients with coronary disease and acute coronary

19   syndromes: an average age of 63 years, a quarter

20   of the patients were women, over a quarter had

21   diabetes. The acute coronary syndrome type was

22   distributed among the three types, and we enrolled

1   a median of five days after that event.

2   As I noted, these patients were managed

3   with medical and interventional therapies, so

4   88 percent of patients underwent cardiac

5   catheterization following that for the management

6   of that acute coronary syndrome, and 70 percent of

7   them underwent PCI. At the time they presented, a

8   third of patients were already receiving chronic

9   lipid-lowering therapy, and their mean LDL was

10   93.8.

11   Now, with regard to the study metrics, we

12   ended up with 5,314 primary endpoints. The patient

13   experience is very large for a single trial; it has

14   80,286 patient-years up through the time of the

15   patient achieving a primary endpoint. But the

16   total clinical follow-up, because we did follow

17   patients after a first event, was 97,822 patient-

18   years of follow-up.

19   Now, within the trial, as I noted, the

20   up-titration to the intensive dose, 80 milligrams,

21   occurred in both arms, and as expected, more

22   commonly in the simvastatin-alone group. So

1   27 percent were up-titrated. In the combination

2   group, it was just over 6 percent.

3   The median follow-up was again 6 years.

4   Study drug was discontinued prematurely in

5   42 percent of patients by the end of the trial.

6   But dividing that by the length of the trial,

7   that's about 7 percent per year, which is well

8   within or better than many of the prior trials that

9   we've done.

10   Now, in terms of follow-up and completeness,

11   we'll have a dedicated presentation. But the key

12   metrics are here, that the amount of follow-up, the

13   time in patient-years of follow-up, was 91 percent

14   for the primary endpoint, for the complete

15   ascertainment of the endpoint. And for survival,

16   so we could get a vital status, it was 97 and a

17   half percent. And most importantly is the bottom,

18   that this was balanced between the two treatment

19   groups.

20   This is what was achieved on the LDL. As I

21   noted, at the time that patients presented to the

22   hospital, it was 94 and a half, was their LDL. At

1 the time of randomization, it was just over 80.

2 And then in the two groups, you can see that the

3 time-weighted average of all of the on-treatment

4 LDLs was 69.5 milligrams per deciliter for the

5 simvastatin alone group and 53.7 for the

6 combination ezetimibe and simvastatin.

7 These are the data at one year, a time point

8 often used to measure the efficacy, so the LDL

9 there was 16.7 milligrams per liter, a difference

10 at one year. As you can see, there was also a

11 significant reduction in total cholesterol, a

12 reduction in triglycerides, a very modest increase

13 in HDL, but also a significant reduction in high

14 sensitivity C-reactive protein.

15 So the question that we had posed is, would

16 this further lowering of LDL translate into a

17 clinical benefit? And that we knew for statins,

18 but we really did not know for nonstatin agents

19 like this one, ezetimibe.

20 So we were very excited to see that in fact

21 the further lowering of LDL with ezetimibe did

22 translate into a significant reduction in

1   cardiovascular events. This is the primary

2   endpoint. As shown, the hazard ratio was 0.936 and

3   p-value of .016.

4   The curves are plotted out through 7 years;

5   again, the median duration of treatment and

6   follow-up was 6 years. At the end of the 7 years,

7   the event rates were 34.7 percent for the

8   simvastatin alone, and 32.7 for the combination

9   ezetimibe/simvastatin. And that translates into a

10   number needed to treat of 50 patients to achieve a

11   reduction in one event.

12   As also seen, these curves were largely

13   overlapping over the first year, but then began to

14   separate after a year and continue separating

15   during that more chronic phase of the patients'

16   course.

17   We plot here the primary endpoint as of

18   hazard ratio and confidence interval, as well as

19   the three secondary endpoints. The primary and all

20   three of the secondary endpoints all met the

21   prespecified statistical significance and were very

22   consistent with the relative benefit that was

1   observed.

2   These are the individual components of the

3   primary endpoint, beginning at the top with

4   all-cause mortality, which was actually not part of

5   the primary endpoint, but cardiovascular death,

6   which was. As shown, there was no reduction in

7   death; there hadn't been anticipated to be one as

8   well.

9   Unstable angina was less frequent and not

10   different; coronary revascularization next. But

11   then the difference, you can see, was in all MI and

12   stroke, and particularly nonhemorrhagic stroke were

13   the two individual endpoints that had significant

14   reductions.

15   On the other hand, the one endpoint that was

16   observed as a hazard was hemorrhagic stroke. This

17   was 1.38 as the hazard ratio. But as shown, this

18   was not a significant difference between the two

19   groups.

20   We've plotted here and specified this as

21   another endpoint, exploratory endpoint, of one

22   that's used in many cardiovascular trials, and this

1   is cardiovascular death, MI, or stroke. This

2   showed a similar pattern, although the reduction

3   was a 10 percent reduction on this so-called hard

4   endpoint, as it's sometimes referred to. Event

5   rates went from 22 percent down to 20 percent,

6   roughly, in the two groups.

7   Illustrated here are the 23 prespecified

8   subgroups that we looked at. And as we're often

9   taught to look at the pattern of consistency across

10   subgroups, as you can see, the blue diamonds,

11   almost all of them, fall to the left of the line of

12   unity that favors ezetimibe/simvastatin.

13   Of these, two had an interaction p-value.

14   The age over 75, although age split at 65 did not,

15   and diabetes were the two out of this entire list

16   that had a p-value fall below 0.05 for the

17   p interaction.

18   Now, another analysis that is being

19   increasingly done is to look not just at the first

20   event that occurs in patients, but the total number

21   of events. So this is an analysis that's done, in

22   press at JACC, where the first events are the

1   darker bars at the bottom that we've looked at that

2   show a significant reduction for ezetimibe/

3   simvastatin.

4   But you can see that there were an

5   additional, about 44 percent more events, so that

6   there were just under 10,000 events in this

7   combined analysis of all events. And those

8   additional events were also fewer.

9   So using the Andersen-Gill method, the

10   hazard ratio was 0.928, a p-value of 0.013. And

11   you can see that there are actually more second

12   events prevented and more than doubles the number

13   of events avoided when looking at this patient-

14   oriented focus of what happens during the entire

15   period of the trial.

16   Another sensitivity analysis that Mike

17   Blazing led is to look at the on-treatment

18   population, and so looking at events between the

19   two groups during the period that patients were

20   receiving study medication or the next 30 days

21   afterward, other sensitivity analyses carrying out

22   also beyond a year following treatment.

1   This is the 30-day post-treatment. And as

2   would be expected, each of the hazard ratios is

3   slightly further to the left, and this is true on

4   each of the endpoints. So this is a supportive

5   analysis of the overall finding.

6   So now turning our attention to adverse

7   events, this is the high-level categorization of

8   the number of patients who had any adverse event

9   reported. Drug-related ones, serious adverse

10   events, about 40 percent in both groups, had

11   serious adverse events reported over this median of

12   6 years of follow-up. Discontinuations of study

13   medication due to adverse events of any of the

14   different categories, as shown, is also well-

15   balanced between the two groups.

16   Turning to more specific types of adverse

17   events, beginning with muscle- and liver-related

18   safety events, as shown, there was no significant

19   difference in any of these. So beginning with

20   rhabdomyolysis or significant myopathy,

21   rhabdomyolysis in particular, or simply CK

22   elevations 10 times the upper limit of normal, all

1   of these were balanced between

2   ezetimibe/simvastatin and simvastatin alone.

3   The liver-related endpoints, the standard

4   3 times elevation was again balanced, as was an

5   even 10 times increase in liver enzymes.

6   Gall bladder-related adverse events are the

7   top three that we had prespecified, and these were

8   also balanced, with no difference at all. FDA

9   asked for a few other endpoints, pancreatitis and

10   the others listed, and again, no difference in any

11   of those endpoints.

12   Then as I noted, Mike Blazing again

13   presented these data on the issue of new onset

14   diabetes that had been raised with statins. And

15   with this primary analysis and five other

16   sensitivity analyses, he found no difference in the

17   rate of new onset diabetes with the addition of

18   ezetimibe.

19   Then finally, the issue of cancer had come

20   up, so this is the longest-term experience with,

21   again, the Kaplan-Meiers plotted through 7 years,

22   that we saw no difference in the adjudicated rates

1   of new, relapsing, or progressing malignancy.

2   We've looked at all sorts of different definitions

3   and found no difference in any definition of

4   cancer. And on the right, death due to cancer also

5   was not different with the addition of ezetimibe.

6   So to summarize, we found that the treatment

7   with ezetimibe and simvastatin, compared with

8   simvastatin alone, reduced the risk of the first

9   occurrence of a primary composite endpoint, so our

10   primary endpoint was achieved.

11   The treatment effect was generally

12   consistent across the three composite secondary

13   endpoints, across the various exploratory

14   endpoints, and the greater than 20 subgroups

15   assessed. As noted, the treatment effect began

16   after about a year and continued during that 6-year

17   median follow-up period.

18   With regard to safety, we summarized the

19   data to say that ezetimibe as add-on therapy was

20   very well-tolerated. It was consistent with the

21   known safety profile of add-on ezetimibe, and in

22   particular, no increase in the risk of cancer was

1   seen. So putting these two together, the overall

2   clinical benefit and a favorable safety profile is

3   a good benefit to risk ratio.

4   So stepping back again to the question we

5   asked of would this nonstatin drug lead to a

6   clinical benefit, we concluded that the IMPROVE-IT

7   trial has demonstrated that the addition of

8   ezetimibe to statin therapy does indeed reduce

9   cardiovascular events.

10   Thank you all very much for your attention.

11   I'll call up Dr. Paul DeLucca, who will discuss the

12   data completeness.

13   **Applicant Presentation – Paul DeLucca**

14   DR. DeLUCCA: Good morning. I'm Paul

15   DeLucca, director of biostatistics at Merck, and

16   the lead statistician for the IMPROVE-IT study. As

17   Dr. Cannon mentioned, over 9 years of the study,

18   approximately 91 percent of the potential follow-up

19   was achieved for the primary endpoint. So we don't

20   believe missing data is a major concern regarding

21   the validity of the study results. We did perform

22   several analyses to assess data completeness and

1   the impact of missing data.

2   The goal of the analyses was to see what

3   happens to the primary endpoint when we add events

4   in the unobserved experience based on reasonable

5   conservative assumptions, with more events added to

6   the ezetimibe/simvastatin group in the unobserved

7   experience, even though less events were actually

8   observed in the ezetimibe/simvastatin group during

9   the study.

10   Prior to presenting our data completeness

11   and missing data results, I'd like to review why

12   potential biases that could affect the missing data

13   analyses are unlikely in the IMPROVE-IT study.

14   First off, the study was double-blind. It

15   would be difficult for subjects and investigators

16   to be inadvertently unblinded since there are no

17   characteristic side effects associated with

18   ezetimibe that would lead to unblinding.

19   The overlap between treatment groups in LDL-

20   C lowering was such that it would be difficult to

21   unblind down to a subject level. Finally, the

22   pattern of lost opportunity for follow-up was

1   similar between the two groups for the primary

2   endpoint.

3   So to confirm that last point, we performed

4   an analysis of time to lost opportunity for

5   follow-up for the primary endpoint. As can be seen

6   on the Kaplan-Meier plot, there were more early

7   discontinuations in the ezetimibe/simvastatin

8   group.

9   By the end of the study, there were only

10   20 more subjects with lost opportunity for

11   follow-up in the ezetimibe/simvastatin group

12   compared to the simvastatin-only group. This

13   results in a hazard ratio of approximately 1 and a

14   p-value of 0.7, indicating a similar pattern of

15   lost opportunity between the two groups over the

16   course of the study.

17   Our interest in performing supportive

18   analyses of missing data is to assess its impact on

19   the primary endpoint. And a key question is, what

20   do we mean by missing data for the primary

21   endpoint? The focus is on the opportunity subjects

22   had to be included in the primary endpoint and not

1   how many make it to the end of the study.

2   Subjects with missing data for the primary

3   endpoint were those that did not experience a

4   primary endpoint event, did not die during

5   follow-up, and did not have a final visit on or

6   after May 1, 2014, which was the operational start

7   of study closeout.

8   Now, the potential follow-up time in the

9   study where every subject would have had a primary

10 endpoint, would have died while being actively

11 followed, or would have made it to the end of the

12 study, would have been approximately 88,000

13 subject-years. The amount of actual observed

14 follow-up was a little over 80,000 subject-years.

15   So the percent lost opportunity for

16 follow-up was about 8.8 percent, and it was similar

17 between the two groups.

18   It's important to note that the Merck plan

19 for missing data and comments from FDA were

20 documented prior to database lock and unblinding.

21 In our missing data analyses, we simulated events

22 in the unobserved experience using an exponential

1   distribution, which uses the average event rate

2   over time. We then performed Cox regression using

3   the observed and simulated data.

4   Now, given that the event rates were a

5   little bit higher in the first year and dropped

6   over time, we performed additional analyses in

7   which we simulated events using a Weibull

8   distribution. This approach takes into account the

9   change in event rates over time, applying higher

10   event rates early in the unobserved experience,

11   such as year 1, and lower event rates over time.

12   And it's worth noting that the event rates over

13   time estimated using the Weibull distribution and

14   using our simulations closely matched the rates

15   presented in table 4 of the FDA briefing book.

16   Again, we performed Cox regression using the

17   observed and simulated data, and we found that the

18   approaches using the exponential distribution and

19   the Weibull distribution provided similar results.

20   Of the missing data analyses we performed,

21   I'm going to focus on three representative

22   scenarios using the exponential distribution. Some

1   of the additional scenarios are less conservative

2   and some are more conservative for the

3   ezetimibe/simvastatin group, and the full set of

4   analyses using the exponential distribution can be

5   found in the Merck briefing book.

6   In the first scenario, we assume the event

7   rate in the unobserved experience in the

8   simvastatin-only group is equal to the observed

9   simvastatin-only event rate. In contrast, the

10 greater event rate is assumed in the unobserved

11 experience in the ezetimibe/simvastatin group, the

12 upper bound of the two-sided 95 percent confidence

13 interval of the observed simvastatin-only event

14 rate.

15   The scenario addresses sensitivity to a

16 situation for which the unobserved experience for

17 the ezetimibe/simvastatin group is worse than that

18 for the simvastatin-only group.

19   The second scenario is called a tipping

20 point analysis, which targets the final alpha of

21 the trial and examines what disparity it would take

22 in the unobserved experience to tip the trial from

1   statistically significant to not significant.

2   Again, the event rate in the unobserved

3   experience in the simvastatin-only group is equal

4   to the observed simvastatin-only event rate. We

5   then fixed the p-value at 0.0394 and worked

6   backwards to find the corresponding event rate in

7   the unobserved experience in the

8   ezetimibe/simvastatin group that will tip the p-

9   value.

10   In the third scenario, the assumed event

11 rate in the unobserved experience in both groups is

12 set to the observed, pooled, off-treatment rate

13 across the study. This scenario is potentially

14 representative for what the unobserved experience

15 for both groups could be since the unobserved

16 experience for both groups is in an environment

17 without randomized treatment. And it's worth

18 noting that the off-treatment event rates were

19 similar between the two groups.

20   For reference, the observed results of the

21 primary endpoint, which Dr. Cannon just presented,

22 are provided in italics in the upper right-hand

1   corner of the table. For the three scenarios that

2   I'll present in the body of the table, the bolded

3   numbers are the drivers of the simulations.

4   In the first scenario, the assumed event

5   rate in the unobserved experience in the

6   simvastatin-only group is set to 6.64 events per

7   100 subject-years of follow-up, which is equal to

8   the observed simvastatin-only event rate.

9   The assumed event rate in the unobserved

10   experience in the ezetimibe/simvastatin group is

11   set to 6.99 events per 100 subject-years of

12   follow-up, which again is the upper bound of the

13   two-sided 95 percent confidence interval of the

14   observed simvastatin-only event rate.

15   This leads to 233 extra events in the

16   ezetimibe/simvastatin group on top of the 2,572

17   observed events, and 211 extra events in the

18   simvastatin-only group on top of the 2,742 observed

19   events. The resulting hazard ratio is 0.944, and

20   the p-value is 0.033, which indicates that

21   statistical significance is maintained in this

22   scenario.

1   In the tipping point analysis, the p-value

2   is first set to the final alpha level of the trial,

3   0.0394. The assumed event rate in the unobserved

4   experience in the simvastatin-only group is again

5   set to 6.64 events per 100 subject-years of

6   follow-up.

7   This results in an event rate in the

8   unobserved experience in the ezetimibe/simvastatin

9   group of 7.17 events per 100 subject-years of

10   follow-up, which turns out to be the upper bound of

11   a one-sided 99.8 percent confidence interval of the

12   observed simvastatin-only event rate.

13   To tip the p-value from significant to not

14   significant requires 237 extra events in the

15   ezetimibe/simvastatin group compared to 211 extra

16   events in the simvastatin-only group.

17   We believe it would be unlikely to observed

18   this outcome, given that it requires an extreme

19   result in the ezetimibe/simvastatin group, the

20   upper bound of a one-sided 99.8 percent confidence

21   interval of the observed simvastatin-only rate, and

22   given that there's no obvious reason why the event

1   rates in the unobserved experience should be

2   different between the two groups.

3   In the third scenario, the assumed event

4   rate in the unobserved experience in both groups is

5   set to 9.59 events per 100 subject-years of

6   follow-up, which is the pooled off-treatment event

7   rate across the study.

8   This leads to 300 extra events in the

9   ezetimibe/simvastatin group compared to 285 extra

10   events in the simvastatin-only group. The

11   resulting hazard ratio is 0.942, and the p-value is

12   0.029, which indicates that statistical

13   significance is maintained in this scenario.

14   In conclusion, the results support treatment

15   effect in the presence of missing data under

16   reasonable conservative specifications that are not

17   favorable to the ezetimibe/simvastatin group. And

18   these analyses reaffirm the conclusion of the

19   primary endpoint of the benefit of ezetimibe.

20   Thank you for your attention, and now

21   Dr. Braunwald will discuss the clinical

22   implications of the IMPROVE-IT study.

Applicant Presentation – Eugene Braunwald

1

2   DR. BRAUNWALD: Good morning. My goal today

3 is to try to place the results of the IMPROVE-IT

4 trial into a clinical perspective. I think I

5 should note that Dr. Robert Califf was the co-

6 chairman of the trial and worked very hard for 9

7 and a half years until he joined this agency.

8   So background. I believe that there is

9 widespread agreement on these points.

10 Atherosclerotic cardiovascular disease remains the

11 most common cause of death in industrialized

12 nations. Now, numerous adult experiments and

13 genetic studies, including some based on Mendelian

14 randomization, have shown that LDL cholesterol is a

15 risk factor for atherogenesis.

16   Of course, LDL cholesterol-lowering drugs,

17 which have associated adverse effects, which are

18 unrelated to the LDL cholesterol, may not be

19 beneficial even though they may lower the LDL

20 cholesterol.

21   Many people who receive statins at the

22 present time do not achieve optimal levels of LDL-

C, as recommended by worldwide practice guidelines.

Even those who receive statins, residual risk

following an acute event remains a major unmet

need.

Now, insofar as this last point is

concerned, that is, residual risk despite taking

statins, this slide shows a KM curve of residual

risk in 8,900 patients who were enrolled into the

placebo arm of one of our recent trials, TRA-2P.

These were patients who entered the trial a median

of 70 days following an MI.

Like the patients in IMPROVE-IT, these

patients were well-treated according to

contemporary guidelines. A large percentage, who

were on aspirin and statins, had undergone coronary

revascularizations, and received a beta blocker and

dual antiplatelet therapy.

But as you can see, despite this, the

serious endpoint of cardiovascular death, recurrent

nonfatal MI, and nonfatal stroke occurred in

10 percent of these patients after three years.

Obviously, there was substantial residual risk in

1   this well-treated contemporary population.

2   Now, how well do patients do? This is a

3   registry of patients with high-risk coronary artery

4   disease, the NHANES registry. And as you can see,

5   the guidelines at that time for patients with high-

6   risk CAD was an LDL under 70 milligram per

7   deciliter. And you can see that 78 percent didn't

8   achieve that, and 35 percent didn't even achieve

9   the 100 milligrams per deciliter, which was the

10   guideline recommendation for patients with

11   uncomplicated coronary artery disease.

12   The current guidelines, the most recent

13   guidelines, indicate that there should be at least

14   a 50 percent reduction in the LDL cholesterol.

15   These are the 2013 guidelines.

16   This comes from a registry, a Voyager

17   registry, in Australia that consists of 32,000

18   coronary heart disease patients, and they were

19   given the two most potent lipid-lowering agents,

20   atorvastatin at high dose and the highest dose, and

21   also rosuvastatin.

22   You can see that these are the numbers of

1   patients who did not achieve 50 percent reduction

2   of the LDL cholesterol, getting these high doses of

3   very effective statin drugs. So between 27 percent

4   and 59 percent failed to reach the target.

5   So IMPROVE-IT, as you've heard, addressed

6   three principal questions. The first, is the LDL

7   cholesterol lowering that occurs when ezetimibe is

8   added to a statin associated with a clinical

9   benefit in patients with coronary heart disease?

10   The second is LDL cholesterol lowering with

11   ezetimibe and a statin to levels below

12   70 milligrams per deciliter beneficial in patients

13   with coronary heart disease? And finally, is

14   ezetimibe when co-administered with a statin well-

15   tolerated without substantial risks beyond those

16   identified with statin therapy alone?

17   Well, you've seen this slide already, and it

18   really addresses the first question, is it of

19   clinical benefit? And you can see that the

20   prespecified primary endpoint and three

21   prespecified secondary composite endpoints also

22   showed that there was a significant clinical

1   benefit.

2   The second question concerned, does LDL

3   cholesterol lowering below 70, is that beneficial

4   in patients with coronary heart disease? And here

5   you can see what the LDL cholesterols actually

6   were. So you can see that there was a comparison;

7   really, the median time-weighted averages was 69.5

8   and 53.7.

9   Now, as we did this trial, there was a lot

10   of discussion about this. And a number of people

11   said, oh, you will do the wrong trial. You should

12   have started with much higher levels of LDL, then

13   you would see a pretty big bang out of adding

14   ezetimibe. There was even a publication in a major

15   cardiovascular journal that took us to task for

16   doing that.

17   Well, as Dr. Cannon pointed out, we

18   purposely set it at this level because we thought

19   that it would be unethical to have a control group,

20   a control group of patients who had LDLs that were

21   not consistent with the guidelines that existed at

22   that time. And yes, I think we probably would have

1   seen a bigger difference, but it would not have

2   been appropriate to do that.

3   The third question, is it well-tolerated?

4   Well, IMPROVE-IT added more than 97,000 additional

5   patient-years of total clinical follow-up, and that

6   supplements the previous very large safety database

7   that you heard about. And the results really

8   strongly support the conclusion that the risks to

9   ezetimibe add-on therapy to statin are quite

10   limited.

11   So I think we have answered the three

12   questions in the affirmative. Yes, LDL-C lowering

13   that occurs when ezetimibe is added to a statin is

14   associated with a clinical benefit. Secondly, yes,

15   LDL-C lowering with ezetimibe and a statin to

16   levels below 70 milligrams per deciliter is

17   beneficial in patients with coronary heart disease.

18   And yes, ezetimibe co-administered with a statin is

19   well-tolerated without substantial risks beyond

20   those identified with statin therapy alone.

21   Now, the question of the use of a statin,

22   what would have happened had we used other statins,

1   natural question to ask. Well, here are some

2   important data from a number of studies, and it

3   showed that atorvastatin, simvastatin, pravastatin,

4   as well as other statin, including rosuvastatin, in

5   widespread doses. So all statins studied at all

6   doses studied, and even the absence of a statin,

7   all result in about a 22 to 24 percent reduction in

8   LDL cholesterol. So there's nothing unique about

9   simvastatin in this regard.

10   You saw the primary endpoint results

11   earlier, and I would point out, really, three

12   features of these KM curves. First is that the

13   hazards are much higher in the first year than they

14   are later on, and we have seen that in our trials

15   and many trials of post-ACS, that many events occur

16   early. Then the curves separate, and that

17   separation is maintained.

18   So we believe that after a year or a year

19   and a half, these patients have, if you will,

20   graduated from being post-ACS to being patients

21   with chronic coronary heart disease. And the

22   majority of patients with chronic coronary heart

1   disease actually have had one or more, at some

2   point, episodes of ACS.

3   The question has come up, how do the

4   findings in this trial relate to the findings in

5   the CTT meta-analysis? And the green box

6   represents the IMPROVE-IT trial. The size of the

7   boxes is related to the number of events, and you

8   can see that the green box is larger than the other

9   boxes, and that's because of the 5,290 events that

10   we observed. It's important that there was a

11   modest reduction, about 3 tenths of a millimole of

12   LDL, and there was a corresponding reduction in

13   vascular events.

14   To us, the most important point from this

15   slide is that the IMPROVE-IT data sits right on the

16   line of all the other trials. And I might say that

17   the majority of the other trials that make up the

18   CTT were patients with chronic coronary heart

19   disease.

20   Insofar as the endpoint is concerned, I

21   think that this trial was designed about 10 and a

22   half years ago, and the cardiovascular endpoints

1   that most people have used since then, and we have

2   used in the TIMI group, has been the triple

3   endpoints of the hardest endpoints of CV death,

4   nonfatal MI, or nonfatal stroke. And as you can

5   see, there was a 10 percent benefit in HR of 0.90,

6   made up almost entirely of nonfatal MI and nonfatal

7   stroke.

8   So what are the implications of IMPROVE-IT

9   for the medical community? Well, we believe that

10   the results of IMPROVE-IT can be extended to adding

11   ezetimibe not only to simvastatin but to all

12   statins. We believe that the results of IMPROVE-IT

13   can be extended to the coronary heart disease

14   population overall. And we think that

15   cardiovascular risk reduction with ezetimibe

16   observed in IMPROVE-IT is consistent with its LDL

17   cholesterol-lowering, and we think that is

18   clinically important.

19   In conclusion, patients with coronary heart

20   disease have a significant residual risk for

21   subsequent events even when they are treated to an

22   LDL-C level of 70 milligrams per deciliter.

1   IMPROVE-IT provides evidence that further LDL-C

2   lowering with ezetimibe can produce clinical

3   benefits. And the fact that ezetimibe can

4   accomplish this with minimal additional adverse

5   events makes it a valuable option to address an

6   important unmet medical need for both patients and

7   caregivers.

8   Thank you for your attention.

9   **Clarifying Questions**

10   DR. R. SMITH: Thank you. I would like to

11   thank all the speakers on behalf of Merck. We have

12   some time now for clarifying questions by advisory

13   panel members. And what I would ask you would do

14   is if you would signal to Dr. Begansky, and we will

15   take you in order. And if we miss opportunities

16   this morning, we'll have time later today.

17   Again, these are for clarifying questions.

18   This is not getting to the discussion questions

19   directly yet. And I ask if you'll please state

20   your name for the record before you speak. And if

21   you can direct your question to a specific

22   presenter, that might be helpful.

1   So Dr. Kaul?

2   DR. KAUL: Thank you. Sanjay Kaul. Thank

3 you for a very clear and crisp presentation. I

4 have two questions.

5   You showed us the data for the subgroups for

6 the efficacy endpoints. Did you do the similar

7 analysis for the safety endpoints?

8   DR. TERSHAKOVEC: So doing all adverse

9 events across all subgroups?

10   DR. KAUL: I'm particularly interested in

11 the diabetic and the age over 75.

12   DR. TERSHAKOVEC: We did not do specifically

13 subgroup analysis, breaking down the adverse events

14 relating to subgroups. The issue you get into,

15 especially with the important adverse events, such

16 as muscle and liver, tends to be relatively low

17 events, and subdividing things you end up getting

18 very small numbers and analyses are difficult to

19 interpret.

20   DR. KAUL: I understand. The reason why I'm

21 asking is that there is a large -- if you were to

22 believe that the interaction was not due to a play

1 of chance, there's a large subgroup in which

2 treatment benefit was not observed. As a

3 clinician, in order for me to make a benefit/risk

4 assessment, I like to understand if there was any

5 heterogeneity in the safety endpoints that would

6 help me make that decision.

7   The second clarifying question I have is,

8 you had an opportunity here, with a median follow-

9 up of 6 years, to perhaps capture some of the

10 downstream events following myocardial infarction

11 and stroke. The nonfatal MI and nonfatal stroke

12 were the drivers of a statistically significant

13 treatment difference.

14   As a clinician, I would like to understand,

15 what was the clinical relevance of these endpoints?

16 Did they translate into more LV systolic

17 dysfunction, heart failure, arrhythmia, disability

18 in terms of stroke? Was that information captured?

19   DR. TERSHAKOVEC: Well, the total events

20 analysis, which was presented in this, wasn't

21 looking at total events. But as far as the

22 follow-up relating to the disabilities that you

1   mentioned were not in information that was

2   collected in the trial.

3   Dr. Blazing wants to add some information.

4   DR. BLAZING: In subsequent analysis that

5   had been done with regards to at least two

6   subgroups, the diabetes and age, no difference

7   between the two compounds and adverse events has

8   been seen. We have not done it for all of the two

9   subgroups, but those two specific subgroups have

10   been looked at, and there have not been any

11   differences.

12   DR. R. SMITH: Dr. Packer?

13   DR. PACKER: I had a couple questions for

14   Chris Cannon.

15   Chris, looking at this trial from the point

16   of view of a clinical investigator, I guess it

17   would be fair to say I sort of feel your pain.

18   This trial was an ambitious undertaking, large,

19   targeting a relatively small effect size, which

20   went on for a long time as the investigators

21   struggled to keep people in the trial. It almost

22   seemed as if the longer you went on, the harder

1   things got, and you were very, very happy when the

2   trial finally ended.

3   Let me ask a question. Can you

4   explain -- you targeted a 10 percent reduction in

5   risk with a 2900 original sample size that was

6   resized to about 5250 because of the recognition

7   that the events in the first year would be -- or

8   the effect size in the first year would be about

9   25 percent less than anticipated.

10   Is that approximately right?

11   DR. CANNON: Well, thank you for the

12   comments. On the sample sizing, we started this

13   again, I guess, 10 and a half years ago, we

14   planned, so the CTT hadn't even been published.

15   That came out soon after we had set up the

16   assumptions, so we learned a lot from that.

17   We had also done a meta-analysis of the four

18   high-dose versus regular-dose statin groups, and so

19   looking at those two meta-analyses to say what

20   clinical benefit could we expect from a 1 milligram

21   per deciliter difference. So it was 1.6 or 1.8 in

22   the two different analyses that was done.

1   So making it more quantitative was able to

2   be done, so using that new information was one

3   major thing. The discounting of the benefit early

4   on was a second one as well. So all together, I

5   think we had a more quantitative look overall to

6   resize the trial to the --

7   DR. PACKER: Maybe I can try to reframe it.

8   The resizing from 2900 to 5250 is a sizeable

9   resizing. Was it driven primarily by the

10   anticipation of a 25 percent reduction in the

11   effect size in the first year? Because that seems

12   like a big increase in sample size for that reason

13   alone.

14   DR. CANNON: That's certainly a component.

15   The bigger part was being more quantitative in the

16   benefit. So before the CTT existed, we had to

17   judge what could we expect in terms of a clinical

18   benefit from the expected difference in LDL. So we

19   could turn that into a quantitative relationship

20   post our meta-analysis and the CTT. So that's

21   probably the bigger one.

22   I think the other thing, that gets back to

1   your first point, is that the long duration of the

2   trial was in part because the late event rates were

3   low. And of course that's good news for the

4   patients in the trial because they were having low

5   event rates. So that became a big -- so what was

6   the late event rate is a big driver of the number

7   of events.

8   DR. PACKER: I hear your answer. I'm still

9   struggling with how the thinking process changed

10   during the trial. I know that CTT wasn't done, so

11   I understand that. What did you learn that caused

12   you to go from 2900 to 5200? I think you mentioned

13   two things. One was a reduction in the effect size

14   in the first year, and the second was something

15   that you learned from CTT. Can you just clarify

16   what that is?

17   DR. CANNON: Well, the issue is really -- so

18   detecting small things -- and I'll call up others

19   with more statistical background than myself. But

20   the differences in the number of events to detect

21   small differences in clinical endpoints becomes

22   very large, so it looks like a big change.

1   The difference was we had more precision

2   about the relationship; well, what does 1 milligram

3   per deciliter translate into over time?

4   DR. TERSHAKOVEC: Professor Baigent wants to

5   comment.

6   DR. PACKER: Between the two of you, I'm

7   sure you can answer this question. When you

8   calculate the slope of LDL lowering to reduction in

9   events, did that slope change as a result of the

10 CTT analysis, which caused you to increase your

11 sample size? I'm trying to figure out --

12   DR. CANNON: Yes. Yes. We didn't even have

13 a slope before when we designed it. We tried the

14 best we could from the literature and said, oh, we

15 expect about this, and so it shifted to have a

16 slope and a calculation between the CTT and our

17 other meta-analysis.

18   DR. PACKER: Would it be fair to say,

19 without getting into any specifics, that initially

20 you had hoped that a delta LDL cholesterol would

21 translate into a greater reduction in

22 cardiovascular events with the CTT then reported,

1   and that caused you to resize the trial; and that

2   was the major reason, not so much the reduction in

3   the risk in the first year? I just want to make

4   sure that I understand.

5   DR. CANNON: Definitely the precision around

6   that relationship is what was the big change, and

7   then part of it was the discounting.

8   DR. BAIGENT: Just to summarize, Milton, the

9   things that I believe impacted on most of the

10   decision, which incidentally followed the meeting

11   at which I presented the CTT and tried to

12   understand it together with the real team -- the

13   things that impacted, in the first year there was a

14   higher event rate in the IMPROVE-IT study than

15   there is later on.

16   So anything that happens in the first year,

17   we learned from the CTT that the effect size in the

18   first year -- this is the statin trials, of course.

19   But in the first year, if you lower LDL

20   cholesterol, you get about half the effect size

21   that you get later on. And that has a major impact

22   on sample size calculations simply because the

1   event rate is much higher in the first year.

2   DR. PACKER: That's in stable coronary

3   disease or in --

4   DR. BAIGENT: I'm talking about in

5   IMPROVE-IT.

6   DR. PACKER: In IMPROVE-IT? Okay.

7   DR. BAIGENT: You could have 13 and a half

8   percent event rate in the first year, from memory,

9   and then later on it becomes flatter, as you see

10   from the Kaplan-Meier plots.

11   DR. PACKER: It does.

12   DR. BAIGENT: Okay. So in the first year,

13   if you end up learning from the CTT that actually

14   you don't get -- you only get about half the effect

15   size in the first year, but you've got a high event

16   rate in the first year, then that has a big impact

17   on sample size calculation.

18   The second thing, as you surmised, is that

19   the CTT suggested a somewhat smaller effect per

20   millimole than had been assumed in the original

21   sample size calculations. So I think those two

22   things together led to the resizing that we saw.

1   Did the CTT conclude that the treatment

2   effect in the first year was to be reduced by

3   25 percent because of the nature of the mechanism

4   of action or the patient population studied?

5   DR. BAIGENT: It was purely the mechanism of

6   action, that this drug was lowering LDL

7   cholesterol. Essentially, the high process that

8   lay behind it was that if you lower LDL

9   cholesterol, you reduce risk in line with what

10   we've seen in the statin trials. That was the

11   underlying thinking.

12   DR. PACKER: Now, can I ask Chris a

13   question, just to make sure? One of the great

14   challenges to clinical trialists is trying to make

15   these trials doable because the perfect trial

16   requires an astronomical number of patients.

17   So in trying to make this trial doable, we

18   had some choices to make. First choice is, were

19   you going to go to a higher risk population, for

20   example, patients after ACS? And you did do that,

21   realizing that the higher risk that they had, which

22   was during the first year, was a risk that might

1   not be modifiable. Is that fair?

2   DR. CANNON: That certainly -- we evolved,

3   realizing that more as CTT came out.

4   DR. PACKER: Right. And similarly, when you

5   constructed a primary endpoint, you constructed a

6   primary endpoint to get as many events as possible,

7   realizing that of course some of those components

8   of a primary endpoint are not as, quote, "hard" as

9   other components of the primary endpoint.

10   In other words, in order to list the number

11   of events, the 5200, you went into a patient

12   population whose risk was greater but whose risk

13   during the first year might not be modifiable. And

14   you went to a primary endpoint where the components

15   were more numerous but not necessarily modifiable,

16   as you saw.

17   DR. CANNON: Well, certainly we observed

18   that only MI and stroke were the ones significantly

19   reduced. The endpoint is almost identical to what

20   we had used in the PROVE-IT trial, so including

21   revasc. Also, revascularization has been part of

22   the major vascular events that has been part of all

1   of the various statin trials in the CTT.

2   The one added thing we had in our endpoint

3   was the unstable angina leading to

4   rehospitalization. That ended up not being very

5   common. So it was pretty similar to the major

6   vascular events that have been reported in most

7   trials.

8   DR. TERSHAKOVEC: I would note also that

9   even if you say that there were events that are

10   softer, and if there was a time that the drug

11   wasn't having efficacy in the early part, even with

12   all those things, we had a positive trial.

13   DR. PACKER: No, no, no. I'm not doubting

14   that. I am bemoaning, or lamenting might be a

15   better term, the fact that clinical trialists often

16   try to make their trials efficient by either

17   increasing the risk population or increasing the

18   definition of components of an endpoint, often to

19   find at the end of the study, they almost wish they

20   hadn't; that if they had, quote, "stuck to" a

21   patient population that wasn't front-loaded in

22   terms of risk or didn't have all of these

1   additional components, that at least in this study

2   appear to be dilutional, one would have been able

3   to finish this trial in less than a lifetime.

4   DR. CANNON: Of the endpoints, I think all

5   have, again, been reported and seen in the various

6   studies. I think the key here was that we were

7   studying low LDL patients, and so we needed to have

8   the adequate power. So that was what had been

9   missing from all the prior studies; we don't have

10   enough events.

11   So the key was to get a definitive answer

12   with the adequate 90 percent-plus power to say. So

13   having used the endpoint in our immediate prior

14   study, it seemed very reasonable to do, but

15   thankfully, can give a good answer.

16   Out of the long duration of the trial,

17   another nice thing for us as clinicians is to have

18   this long-term safety. And that's always a

19   question; interestingly, it still comes up as a

20   question with statins. So to have this median of

21   six years of follow-up with the large number is

22   very helpful in the end on the safety of the

1   profile as well.

2   DR. R. SMITH: I would like to move on to

3   others, and we can maybe swing around back again

4   later.

5   Dr. Proschan, you had a question?

6   DR. PROSCHAN: Yes. I'm trying to

7   understand. Slide 27 assumed a difference in LDL,

8   the original assumptions of 15, and it says that

9   they expected 9.375 percent reduction in events.

10 But if you look at slide 10 or Dr. Braunwald's

11 slide 76, it looked like they had expected a

12 22 percent reduction for a 39 milligram difference.

13 And that doesn't seem to be consistent. I mean, I

14 get that if there's a difference of 15, you should

15 expect an 8.6 percent reduction instead of a

16 9.375 percent reduction.

17   I also was wondering, what was the actual

18 reduction in LDL? Because on this slide, it's

19 showing that the IMPROVE-IT results are right on

20 the line. So I'm assuming the actual reduction

21 must have been only like about 12 or so. Is that

22 right?

1   DR. TERSHAKOVEC: Yes. Dr. Cannon can

2   address this. There were differences in the

3   IMPROVE-IT endpoints and the methodology that's

4   used in CTT that's important to consider in

5   comparing IMPROVE-IT result directly to CTT. And

6   Dr. Cannon can discuss that more directly.

7   DR. CANNON: You've picked up on two very

8   important points, I think, is that we had our

9   primary endpoint at a specified difference; and

10   then this was actually something that Professor

11   Baigent came up to me after I presented the initial

12   results at the AHA meeting.

13   The calculation of the reduction in LDL that

14   was done uniformly in the CTT analysis accounted

15   for patients who didn't have a blood sample drawn.

16   So while we observed at 15, or at the one-year time

17   point that is plotted in all the trials, it was

18   16.7 milligrams per deciliter difference. But then

19   of the people who'd either died or didn't come back

20   to the clinic, the CTT method is to impute the

21   baseline LDL, so essentially no difference.

22   So that brings the observed difference in

1 the group, according to their method, of

2 12.8 milligrams per deciliter, so that's where this

3 green box is plotted along the X-axis.

4   Then the Y-axis is the major vascular

5 events; so without unstable angina in the endpoint

6 to make it match all the other trials. So that's a

7 7.2 percent benefit on the endpoint in the CTT, so

8 that's the difference of how it plots.

9   DR. PROSCHAN: I thought it would be helpful

10 to know what the baseline LDL was in some of those

11 other trials because I'm just wondering if the

12 points that are below the line are in people whose

13 baseline LDLs are lower, then you would expect less

14 of a benefit in this trial.

15   DR. TERSHAKOVEC: In general, the dots that

16 are at the upper right will have higher LDL levels,

17 a bigger change. But Professor Baigent could

18 specifically talk to your question.

19   DR. BAIGENT: Yes. The 14 trials on here

20 showing LDL differences ranging from about 0.3,

21 which is where you've got IMPROVE-IT sitting, right

22 up to 1.7, which was the 4-S study, the first trial

1   that reported, with most of them clustering around

2   1 millimole. It was typically the average absolute

3   risk reduction at one year that was observed in

4   these trials.

5   There's just a scatter around that line,

6   which I don't really think you can interrogate or

7   understand particularly. It's just a matter of

8   variation that you've seen in these types of

9   studies. I don't think there's anything we can say

10   about it.

11   DR. R. SMITH: Dr. Kaul, did you have a

12   clarifying point or --

13   DR. KAUL: Yes, just a follow-up to that.

14   Does the sponsor have a similar plot for percent

15   LDL reduction rather than the absolute LDL

16   reduction? That will help address Mike's question

17   regarding what the baseline LDL was.

18   DR. TERSHAKOVEC: We have tried to mimic the

19   CTT analyses and to be able to compare apples to

20   apples. That's what we've done, is with the

21   millimoles per liter.

22   DR. R. SMITH: Dr. Wilson?

1   DR. WILSON: Thank you. Figure 7 in the

2   Merck data, it would be really interesting to see

3   that for diabetic patients. This is a large trial

4   for diabetic patients, and it's a subgroup of

5   particular interest. Do you have such information;

6   just the total group? And also, the NNT for

7   diabetics versus nondiabetics.

8   DR. TERSHAKOVEC: I'm not familiar offhand.

9   I haven't memorized all the figure numbers.

10   DR. WILSON: What I'm talking -- this is

11   figure 7 as a Kaplan-Meier plot for the total

12   group, what Dr. Braunwald described as the extended

13   endpoint, but for either the trial specified

14   endpoint or the extended endpoint; Kaplan-Meier

15   survivals for diabetics. Do you have that?

16   DR. TERSHAKOVEC: The primary endpoint

17   result for -- Kaplan-Meier curves?

18   DR. WILSON: Yes, primary or the extended,

19   either one.

20   DR. TERSHAKOVEC: We've not plotted

21   Kaplan-Meier curves as part of our analysis, again,

22   because of different issues on subgroup analyses

1   and the sample size related to that. So we've not

2   done the Kaplan-Meier.

3   DR. WILSON: And number needed to treat

4   overall in the trial is 1 in 50, approximately.

5   What is the NNT for diabetics?

6   DR. TERSHAKOVEC: That's not something that

7   we've calculated for diabetics.

8   DR. WILSON: Could you provide the numbers

9   so we could do it? It's not very hard.

10   DR. R. SMITH: Yes. If you could pull those

11   data, and if you can do a calculation, fine. And

12   maybe this afternoon we could revisit that point.

13   DR. TERSHAKOVEC: We'll do that.

14   DR. WILSON: Great.

15   DR. R. SMITH: Thank you.

16   DR. R. SMITH: Dr. Shamburek?

17   DR. SHAMBUREK: Just as a clinician, I just

18   wanted some clarification on the designer and the

19   population. As Dr. Braunwald very elegantly

20   stated, this was not a trial, which many other

21   trials do, where you go for high LDL. So your

22   typical population, on here about heterozygous FH,

would have been excluded based on their high LDL.

I also noted, looking at the average triglyceride, it's 137 and HDL is 42, so it's not a real extreme group. But what I do see is we hear a whole lot about the patients who are near goal, if you want to consider an LDL of 100 as goal, who still, with acute coronary, have an unmet need. And it's a very important population, as we've heard.

So it does reaffirm where we're probably going to be looking at a population where they've had longer exposure to high cholesterol. Some people call that cholesterol score years. So we would be looking at probably bigger effects in an older population. And perhaps, as we heard, with diabetics, since they have a higher risk, we're not focusing on the high LDL.

So that comes to the two questions I'd like to clarify. Well, first with the STEMI patients, it was about 28 percent of the population. So one question is, when you would go down to the emergency room or the CCU, of the STEMI patients

1   who met criteria, what percentage of those

2   enrolled, or was it reluctance of needing PCI or

3   something in that first week? It stated in the

4   entry, they could do it. So of the STEMI, how many

5   of those actually would have enrolled, be the

6   denominator, really?

7   We also heard that 18,144 patients were

8   randomized with acute coronary syndrome. Another

9   important number I would like is when your

10   investigator went down to the ER or the CCU, how

11   many patients with acute coronary syndrome were

12   excluded due to the entry?

13   Do you have any idea of how many patients

14   does this really represent in a CCU or percentage,

15   roughly?

16   DR. TERSHAKOVEC: Dr. Cannon can address

17   your question.

18   DR. CANNON: We did not collect screening

19   logs to have the full denominator of all acute

20   coronary syndromes. But to clarify how these

21   patients were approached, post-stabilization was

22   the entry criteria. So patients had to be

1   stabilized. So they would be approached after

2   their PCI. As we saw, 70 percent overall had PCI.

3   So it's really at the time of discharge,

4   largely, is when patients were being considered.

5   So they'd get all their usual stuff, and then

6   three-quarters were on statin at the time of

7   randomization, given during the hospitalization.

8   So it was really, then, at the time of

9   discharge going forward that they said, oh, are

10   they eligible for the study? But again, we don't

11   have the full universe from whom they came.

12   DR. TERSHAKOVEC: Dr. Blazing wanted to add.

13   DR. BLAZING: We did not collect data on

14   everybody that was evaluated. We did, however,

15   when we were trying to do enrollment, have some

16   information with regards to the biggest reason for

17   not qualifying, and that was very simple. It was

18   the LDL criteria.

19   It was finding people who actually met the

20   LDL criteria, getting the LDL on time, and having

21   an LDL, which actually qualified, which was our

22   biggest detriment to enrolling individuals into

1   this trial. It wasn't actually wanted to be in the

2   trial; the investigators were quite interested in

3   getting people in and often wanted to exceed that,

4   and we had to say no frequently.

5   DR. R. SMITH: Dr. Everett?

6   DR. EVERETT: Thank you. I just wanted to

7   ask perhaps Dr. Cannon or somebody from the sponsor

8   who might know. I'm interested in the lack of

9   difference in events during the first year with an

10   average event rate of about 13 percent, the second

11   year it's about 5 percent, and after that, it's

12   about 3 percent.

13   Did the nature of the events that were

14   adjudicated and detected by the CEC and as part of

15   the trial change, given that we're seeing such

16   a -- it seems like the preponderance of the

17   beneficial effect of ezetimibe is on nonfatal MI

18   and nonfatal stroke. I'm just wondering if the

19   events that occurred during the first year are

20   different. And this might form our consideration

21   of what kind of population the drug might be best

22   suited for use in.

1   DR. CANNON: We haven't formally compared

2   the percentage of types of events in the first year

3   versus later events. But all the Kaplan-Meier

4   curves generally follow that same curve. You'll

5   see a stroke is more linear, but all the other

6   coronary events are curvilinear, with higher event

7   rates early, so that the general pattern is

8   similar.

9   I think we found -- we, on the basis of the

10   CTT, do expect, and I think it fits the concept of

11   lipid lowering, that it takes time to get the

12   lipids out of the blood and then out of the plaque

13   to stabilize things. So having seen the time lag

14   in most every trial, that it wasn't surprising to

15   see it here as well.

16   DR. EVERETT: Does that observation hold for

17   intensive statin therapy after an acute coronary

18   syndrome?

19   DR. CANNON: There are five trials of

20   high-dose statin versus regular-dose statin

21   therapy. In the PROVE-IT trial that we were

22   involved with, the curves did seem to separate

1   early. Interestingly, it's a small trial by

2   comparison. It had just a thousand endpoints and

3   just 2 years median follow-up.

4   The A-to-Z trial didn't see as big an early

5   separation, so it had absolutely nothing in the

6   first 4 months. Then the other three high-dose

7   versus regular-dose statin trials, so SEARCH and

8   TNT and whatnot, they all had about a year's time.

9   This is just looking at the KM curves. So

10   it's an imprecise thing of how soon there's

11   benefit. But there was generally also some time

12   lag seen in most of the trials, less so in the

13   PROVE-IT trial.

14   DR. EVERETT: Maybe one more quick question

15   for Dr. Baigent. I seem to remember seeing in one

16   of the CTT supplements a regression between percent

17   reduction in LDL cholesterol and benefit. You're

18   shaking your head, so I'm incorrect. Dr. Kaul

19   seems to think I'm correct.

20   DR. BAIGENT: No, you haven't seen that, and

21   you haven't seen that because there's a reason why

22   you wouldn't want to look at that. And that is the

1   epidemiology of the relationship between LDL

2   cholesterol and coronary risk is log linear,

3   positive log linear.

4   So what matters is the absolute change in

5   LDL cholesterol when you're considering how to

6   adjust analyses, which is the whole purpose of

7   having it within the CTT. So you haven't seen it

8   in there, and I would argue that actually it makes

9   more sense to adjust using what you'd expect to see

10   on the basis of the known epidemiology than it does

11   to use proportional changes.

12   DR. EVERETT: Thanks.

13   DR. TERSHAKOVEC: Actually, slide up. One

14   thing I'll also note is Dr. Baigent did perform

15   this analysis for us also, which compares the two

16   ACS trials to the CHD trials, looking on outcomes

17   of major vascular events. And you can see on the

18   bottom, the test for difference is a p of 0.32, so

19   a consistent result with CHD and the ACS trials.

20   DR. R. SMITH: Ms. Hallare, did you have a

21   question?

22   MS. HALLARE: I have a few questions, and I

1   would like to ask first if -- I believe you

2   mentioned earlier that there are no subgroups

3   within the diabetics group. Right? Like, for

4   instance, those who have comorbidities such as

5   kidney disease or hypertension, for instance.

6   Also, I would like to ask if within the

7   diabetics versus the nondiabetics, has there been

8   any further look into the adverse events rate?

9   DR. TERSHAKOVEC: Was your first question

10   whether there are differences of other concomitant

11   or other disease states with the diabetics and

12   nondiabetics, like hypertension?

13   MS. HALLARE: Yes.

14   DR. TERSHAKOVEC: Yes. If you look at those

15   patterns, they're generally consistent with what

16   you'd expect, with diabetics having other diseases

17   related to their diabetes compared to the

18   nondiabetics. And then Dr. Blazing noted the

19   adverse events looking in the diabetics, and showed

20   that they were consistent in diabetics and

21   nondiabetics.

22   MS. HALLARE: Thank you.

1   DR. R. SMITH: Dr. Heckbert?

2   DR. HECKBERT: Yes. I have a question

3   regarding the presentation by Dr. DeLucca on data

4   completeness. In slide 49, it was shown that there

5   was a suggestion of slightly more lost opportunity

6   for follow-up in the ezetimibe/simvastatin group

7   than in the simvastatin group in the early period,

8   the first year or so. Then, of course, we've also

9   established in our discussion here that the event

10   rates are higher in the first year than they are

11   later on.

12   Going then to slide 60, I just want to make

13   sure I understand the slide right. There are two

14   scenarios presented here, the first scenario, and

15   then in the second scenario that you're calling the

16   tipping point analysis.

17   Is it correct that in the tipping point

18   analysis, there only would have been the need for

19   four more events in the ezetimibe/simvastatin group

20   versus the analysis shown just above it, scenario

21   number 1? So you go from 233 more events in

22   scenario number 1 to 237 more events in scenario

1   number 2? Only four more events are needed to make

2   that change?

3   DR. DeLUCCA: That's correct. The

4   difference between scenario 1 and scenario 2,

5   scenario 1 added 233 extra events in

6   ezetimibe/simvastatin. Scenario 2 added 237 extra

7   events in ezetimibe/ simvastatin.

8   DR. HECKBERT: Right. And the number of

9   imputed events in the simvastatin group alone

10   doesn't change, obviously.

11   DR. DeLUCCA: Correct. That was held

12   constant between the two scenarios.

13   DR. HECKBERT: Thank you. I wanted to make

14   sure I understood that right.

15   DR. TERSHAKOVEC: But just to note that the

16   first scenario is already at the 95 percent upper

17   bound, so that's already an unlikely scenario.

18   DR. R. SMITH: I know there are more people

19   who have questions, and again, we will have

20   opportunity later. I'm aware that I went a little

21   beyond the agenda in time, but I wanted to fit as

22   many of these questions in as I could immediately

1   after the Merck presentations. But we will have an

2   opportunity to revisit those.

3   It's now time for us to take a break, a

4   15-minute break. And again, panel members, please

5   remember that there should be no discussion of the

6   meeting topic during the break among yourselves or

7   with any member of the audience. We will resume at

8   10:15 sharp. Thank you.

9   (Whereupon, at 10:01 a.m., a brief recess

10   was taken.)

11   DR. R. SMITH: I'd like to ask people to

12   please take your seats and we'll start the next

13   part of this meeting. We'll resume the

14   discussions. In the next part of the schedule,

15   we'll have the FDA presentations.

16   **FDA Presentation – Iffat Chowdhury**

17   DR. CHOWDHURY: Good morning, members of the

18   panel. My name is Iffat Nasrin Chowdhury, and I'm

19   a medical officer with the Division of Metabolism

20   and Endocrinology Products in the Office of New

21   Drugs.

22   I will present first an introduction to the

1   IMPROVE-IT trial. Dr. Jennifer Clark will follow

2   me with a presentation of the statistical

3   assessment of efficacy. I will then return to

4   present other efficacy analyses and the safety

5   review.

6   I will begin with a brief summary of the

7   product information and current and proposed

8   indications. I will then move on to the trial

9   design and procedures, then give the clinical

10   endpoint committee's definitions or criteria for

11   endpoint adjudication, and finish this part of the

12   presentation with the baseline characteristics and

13   disposition of the study population.

14   Zetia, or ezetimibe, is a lipid-lowering

15   drug that inhibits the intestinal absorption of

16   cholesterol and related phytosterols via inhibition

17   of the NPC1L1 transporter. It was approved in 2002

18   and is indicated to modify lipid parameters in the

19   various lipid disorders listed here.

20   There is a limitation of use on the current

21   Zetia label that states, "The effect of Zetia on

22   cardiovascular morbidity and mortality has not been

1   determined."

2   Zocor, or simvastatin, is an HMG-CoA

3   reductase inhibitor. It was approved in 1991 and

4   is indicated to reduce the risk of coronary heart

5   disease mortality in cardiovascular events. It is

6   also indicated to modify lipid parameters in

7   patients with primary hypercholesterolemia and

8   other lipid disorders.

9   Vytorin is a fixed combination drug product

10   of ezetimibe and simvastatin. It is indicated to

11   modify lipid parameters in patients with primary

12   hyperlipidemia, mixed dyslipidemia, and homozygous

13   familial hypercholesterolemia. It does carry a

14   limitation of use: "No incremental benefit of

15   Vytorin on cardiovascular morbidity and mortality

16   over and above that demonstrated for simvastatin

17   has been established."

18   With this supplemental NDA submission of the

19   IMPROVE-IT trial, the applicant proposes the

20   following indication for the ezetimibe label:

21   "Zetia, administered in combination with an HMG-CoA

22   reductase inhibitor, is indicated to reduce the

risk of cardiovascular events, cardiovascular

death, nonfatal MI, nonfatal stroke,

hospitalization for unstable angina, or need for a

revascularization in patients with coronary heart

disease." A very similar indication has been

proposed for Vytorin.

Moving on to trial designs and procedures,

IMPROVE-IT was a randomized, double-blind,

controlled cardiovascular outcomes trial of 18,144

patients with acute coronary syndrome. The

objective was to evaluate the clinical benefit of

treatment with ezetimibe/simvastatin versus

simvastatin monotherapy.

Clinical benefit was defined as a reduction

in the risk of the composite endpoint of

cardiovascular death, major coronary events, and

nonfatal stroke. As you've heard already this

morning, major coronary events is comprised of

nonfatal MI, hospitalization for unstable angina,

and coronary revascularization beyond day 30.

IMPROVE-IT was initiated on October 26,

2005, and the last patient and last visit occurred

1   on September 18, 2014. Patients were considered to

2   have completed the trial if a final visit occurred

3   on or after May 1, 2014.

4   Patients were enrolled at 1,147 sites in

5   39 countries. They were randomized one to one to

6   either ezetimibe/simvastatin or simvastatin alone.

7   Patients were stratified by whether or not they had

8   participated in the EARLY-ACS trial, their

9   experience with previous lipid-lowering therapy,

10   and whether they qualified with a non-ST elevation

11   MI, unstable angina, or with ST elevation MI.

12   After randomization, visits occurred at the

13   end of month 1, month 4, and every 4 months

14   thereafter. The study continued until each patient

15   was followed for a minimum of 2.5 years and a

16   primary endpoint was documented in at least 5,250

17   patients.

18   Major inclusion criteria was whether a

19   patient was within 10 days of a hospitalization for

20   unstable angina, non-ST elevation MI, or an ST

21   elevation MI. Age was greater than 50 years, and

22   LDL was between 50 to 125 milligrams per deciliter

or between 50 and 100 milligrams per deciliter if
on a prior lipid-lowering therapy.

Major exclusion criteria were CABG for the
treatment of the index ACS event, chronic statin
therapy more potent than simvastatin 40 milligrams,
estimated creatinine clearance of less than
30 milliliters per minute, and active liver
disease.

Prior to June 2011, if a patient's repeat
LDL-C was greater than 79 milligrams per deciliter,
up-titration to simvastatin 80 milligrams was
allowed in a blinded manner in either treatment
arm. To maintain study blind, the protocol called
for dummy up-titration in random patients in a
prespecified ratio to those who actually required
up-titration of simvastatin.

To align with a change to the simvastatin
label after June 2011, simvastatin 80 milligrams
was restricted within the trial. Only patients who
had tolerated 80 milligrams for greater than
12 months could continue on that dose. Other
patients had to be titrated down to a maximum of

1   simvastatin 40 milligrams. To keep up the blind,

2   even the dummy up-titration patients were included

3   in procedures to decrease back down to simvastatin

4   40 milligrams.

5   Moving on to adjudication procedures, to

6   identify clinical events that required

7   adjudication, investigators filled out case report

8   forms at each visit, which asked questions such as,

9   "Since the last visit, did the patient experience

10   hospitalization for any reason: death, MI,

11   unstable angina, chest pain, or stroke?" If an

12   answer was yes, then additional questions led to

13   the collection of information on dedicated case

14   report forms and triggered the need for

15   adjudication.

16   Other procedures such as review of adverse

17   events, as well as review of reasons for

18   hospitalizations, were also used to identify

19   potential events for adjudication. Note that

20   revascularization procedures were not adjudicated.

21   The next few slides summarize the clinical

22   endpoint committee's criteria for adjudication for

1   the components of the primary composite endpoint.

2   Death was classified into three categories,

3   cardiovascular death, noncardiovascular death, or

4   unknown. Only cardiovascular deaths were included

5   in the primary composite endpoint.

6   Cardiovascular death was further

7   subclassified as death due to atherosclerotic

8   coronary heart disease, atherosclerotic vascular

9   disease, or other vascular disease. This

10   classification was not important for the primary

11   endpoint, but it did influence secondary or other

12   endpoints that only included coronary heart disease

13   deaths, for example.

14   The CEC defined a myocardial infarction when

15   the clinical scenario was consistent with an MI

16   and, on an ECG, a new Q wave in two or more

17   contiguous leads was present, or there was an

18   elevation of a cardiac marker, such as troponin or

19   CK-MB, greater than an upper limit of normal, or a

20   total CK greater than or equal to two times upper

21   limit of normal. As shown on this slide, there

22   were other criteria if an MI occurred following a

PCI or CABG.

The CEC positively adjudicated unstable angina if the episode of ischemic discomfort consistent with unstable angina occurred before hospital presentation. The ischemic discomfort had to be either at rest, or new onset, or in an accelerating pattern lasting greater than or equal to 10 minutes.

At the hospital or ER, the patient had to experience another episode of ischemic discomfort at rest lasting at least 10 minutes, or there were new ST segment or T wave changes consistent with ischemia in two or more leads.

Coronary revascularization did not require CEC review or adjudication. All PCI and CABG performed greater than or equal to 30 days after randomization counted as an endpoint event. These procedures were further classified as urgent or non-urgent.

An urgent procedure was classified as one that occurred during a hospitalization prompted by an MI or a recurrent unstable angina. Note that

1   this subclassification is not important for the

2   primary composite endpoint, as both non-urgent and

3   urgent revascularization procedures were included.

4   However, urgent revascularizations were part of a

5   secondary endpoint.

6   Stroke was defined as an acute neurological

7   deficit ending in death or lasting greater than

8   24 hours, and classified by a physician as stroke.

9   Stroke was further classified as primary

10   hemorrhagic, nonhemorrhagic, nonhemorrhagic with

11   hemorrhagic conversion, and uncertain. All types

12   of stroke were included in the primary endpoint.

13   Moving on to baseline characteristics and

14   disposition, the treatment arms were fairly similar

15   in terms of baseline characteristics of the study

16   population. The mean age was 64 years.

17   Approximately 25 percent were female, 27 percent

18   were diabetic, and 21 percent had had a previous MI

19   prior to their index ACS event, and 35 percent had

20   been on prior lipid-lowering therapy.

21   Mean LDL-C was 94 milligrams per deciliter,

22   HDL-C was 42, median triglycerides was

1   120 milligrams per deciliter, and median CRP was

2   9.6 milligrams per liter.

3   Moving on to patient disposition, a patient

4   was considered to have completed the study if a

5   visit occurred through at least 5/1/2014,

6   regardless of whether the patient was on therapy or

7   off therapy; or if the patient died during the

8   trial, these patients were considered completers.

9   In the IMPROVE-IT trial, patient disposition

10   was similar between the two treatment arms.

11   Approximately 11 percent of patients died during

12   the trial; 14 percent did not complete the study;

13   76 percent of patients completed the trial, with

14   47 percent having completed the study on study

15   drug, and 28 percent completing the study off of

16   study drug.

17   That completes my presentation of the

18   introduction to the IMPROVE-IT trial. Dr. Clark

19   will now present.

20   **FDA Presentation – Jennifer Clark**

21   DR. CLARK: Good morning. My name is

22   Jennifer Clark. I will be providing an overview of

1   the FDA statistical assessment of efficacy for the

2   IMPROVE-IT trial.

3   The topics I will cover include primary

4   endpoint results, along with an assessment to see

5   if death from any cause could have affected these

6   results. We will also break down the components

7   for the primary endpoint to see what may be driving

8   the efficacy.

9   We will characterize the missing data for

10   the primary endpoint and perform a tipping point

11   analysis where for given event rates, we impute

12   possibilities for the missing data on each

13   treatment arm and determine how different the event

14   rates need to be before statistical significance is

15   lost.

16   Lastly, we will look at some subgroup

17   analysis findings, specifically, subgroups based on

18   diabetes status and whether subjects are 75 years

19   old and older.

20   A Cox proportional hazard model, which

21   adjusted for stratification factors, was

22   prespecified for the statistical analysis. The

1   primary endpoint results based on the Cox model

2   showed a hazard ratio of 0.94, with corresponding

3   95 percent confidence interval of 0.89 to 0.99.

4   The primary endpoint was a composite of five

5   different cardiovascular endpoints. This includes

6   CV death as one of the components. Those who

7   experienced a non-CV death without having a prior

8   CV-related event had their time censored at death,

9   or in other words, they were considered event-free

10   at death.

11   One of the secondary endpoints replaces the

12   CV death component with all-cause mortality in the

13   primary composite. The resulting hazard ratio of

14   0.95 with 95 percent confidence interval of 0.9 to

15   0.996 is still less than 1.

16   You can see here the IMPROVE-IT study had a

17   five-year randomization period, from October 2005

18   to July 2010. Continued follow-up was specified to

19   occur every 4 months until study end. Data was

20   considered complete if subjects had continued

21   follow-up until May 1, 2014. This table shows the

22   number of events and censorings that occurred for

1   each year of follow-up during the trial.

2   Since the last subject was randomized in

3   2010, most subjects censored within the first four

4   years would not have been because of study cutoff.

5   We can see that the highest event rate for both

6   groups occurs in the first year after

7   randomization. This is also when we have the most

8   censorings occur that were not due to study cutoff.

9   You can see there are more time censored in the

10   first year for ezetimibe when compared to control,

11   with 517 versus 430 censorings.

12   Here we have the Kaplan-Meier curves for the

13   primary endpoints. The corresponding hazard rates

14   for each year of the study can also be seen in the

15   table to the right. These rates are given per

16   100 patient-years.

17   In the previous slide, we saw many events

18   occurring in year 1. This corresponds to the much

19   higher hazard or event rate that we see in both

20   groups during year 1. After year 1, we do see

21   separation of the Kaplan-Meier curves, which is

22   when the event rates are lower.

1   Here we have the number of subjects that

2   experienced a primary endpoint event for both

3   treatment groups. This was 2,572 in the ezetimibe

4   group and 2,742 in the simvastatin group. The

5   primary endpoint is actually a composite of five

6   different cardiovascular events.

7   These five components are cardiovascular

8   death, nonfatal MI, hospitalized UA, PCI or CABG at

9   least 30 days after treatment, and nonfatal stroke.

10   While subjects could have more than one of these

11   events, the primary endpoint will only capture the

12   time until the first event occurs.

13   So these columns show how many first events

14   each component makes up of the composite endpoint.

15   If you sum the individual components in the

16   ezetimibe column, you'll get 2,572, and in the

17   simvastatin column you'll get 2,742. While

18   revascularization makes up a majority of the events

19   in the primary endpoint, we don't see much

20   difference between the two groups. The biggest

21   differences we see are actually in MI and stroke.

22   These last columns show the total number of

1   subjects that experienced each of these events.

2   Before, we were only looking at the first events

3   that a subject experienced with the primary

4   endpoint. The differences between MI and stroke

5   that we saw within the first events for the primary

6   endpoint can also be seen here.

7   We used these last columns with time until

8   each event to run Cox regression models for the

9   hazard ratios and 95 percent confidence intervals.

10 This was done for the primary endpoint and each of

11 the components seen here.

12   This figure shows the hazard ratio results

13 from those analyses. We've drawn a reference line

14 where the hazard ratios would be 1, denoting equal

15 hazard rates between the two treatment groups.

16 From this figure we can also see how MI and

17 nonfatal stroke are driving most of the differences

18 seen for the primary endpoint.

19   We examine study follow-up to better

20 understand how much missing data we may have for

21 the primary endpoints. In this table we've split

22 all randomized subjects for this study into four

1   different categories.

2   The first group is everyone who experienced

3   a primary endpoint event. The next group is those

4   who were censored at or after May 1, 2014. The

5   third group is those who continued to be monitored

6   in the study until they were censored at death

7   before May 1, 2014. The last group consists of all

8   those who were censored due to early

9   discontinuation from the study.

10   It is this last group of subjects that would

11 have missing time-to-event follow-up for the

12 primary endpoint. When looking at total study

13 follow-up, this was approximately 13 to 14 percent.

14 However, when looking at this group relative to the

15 primary endpoint, we see they represent just over

16 11 percent of subjects in the study, with slightly

17 more in the ezetimibe treatment arm.

18   Subjects in that last group will have

19 different amounts of missing follow-up. These

20 figures show the timing of when these subjects

21 discontinued from the study.

22   On the right is a histogram. Each bar

1   represents the number of subjects discontinuing

2   during every 4-month period after randomization.

3   We see that a majority of the dropouts occur in the

4   first year, and is slightly higher in the ezetimibe

5   group.

6   For each treatment arm, the plot on the left

7   shows the cumulative number of subjects that have

8   discontinued from the study at any given time point

9   after randomization. We can see a large number of

10   dropouts occurring during year 1. After year 1,

11   the cumulative amount of dropout is more similar

12   between the arms as time increases.

13   However, early discontinuation is more

14   problematic than later discontinuation since it

15   means there will be more missing follow-up time in

16   a time-to-event analysis.

17   This table shows the number of observed and

18   unobserved patient-years relative to the primary

19   endpoint for each treatment arm. As we would

20   expect from the figures and tables in previous

21   slides, there is slightly more unobserved time for

22   the ezetimibe group.

1   So taking into account all the missing data

2   components we've seen for this study, we can try

3   and characterize the missing data to better assess

4   how it could influence the study results. In order

5   to do this, we ran what is known as a tipping point

6   analysis. For given event rates, we imputed

7   possibilities for the missing data on each

8   treatment arm and determined how different the

9   event rates need to be before statistical

10   significance is lost.

11   A tipping point analysis simulates the

12   missing data under different scenarios until it

13   eventually tips from being statistically

14   significant to nonsignificant. Because of interim

15   analyses performed during the study, the final

16   alpha value was adjusted from the usual 0.05 to

17   0.0394 in order to protect the type 1 error. We

18   will consider any scenario where results have a p-

19   value greater than 0.0394 to be tipped.

20   In order to simulate data, we must first

21   make assumptions about the missing data. For this

22   analysis we will make two assumptions. First we'll

1   make an assumption about what the event rate is

2   within the missing data of the simvastatin arm.

3   The second assumption is about the hazard ratio for

4   the missing data in both treatment groups. This

5   would be the ratio of the event rates in only the

6   missing data, comparing the ezetimibe group to the

7   simvastatin group.

8   The usefulness of running this type of

9   sensitivity analysis lies in having plausible

10 scenarios for missing data or missing follow-up.

11 This means making reasonable assumptions that would

12 more accurately reflect what the missing data may

13 actually look like.

14   The tipping point analysis has multiple

15 scenarios. These scenarios slowly increase the

16 differences between the missing follow-up in the

17 treatment groups until the results tip. These

18 scenarios can sometimes more accurately reflect

19 what may happen in a real world setting.

20   So if we can make reasonable assumptions

21 that would accurately reflect what could happen in

22 practice, we can see whether the missing data will

1   tip results from statistically significant to

2   nonsignificant.

3   In order to make reasonable assumptions, we

4   looked at various event rates within the observed

5   data. Using these rates, we can create different

6   scenarios for the simvastatin missing follow-up.

7   The first set of scenarios is based on the

8   estimated event rate in the simvastatin arm. This

9   was approximately 6.64 events per 100 patient-

10   years. So if the results for those who

11   discontinued follow-up prematurely in the

12   simvastatin group would be accurately represented

13   by those remaining in the study, then this would be

14   a reasonable assumption.

15   Our second set of scenarios uses 9.6 events

16   per 100 patient-years. This rate only includes

17   subjects who stopped taking the study treatment but

18   continued follow-up in the study. This is similar

19   to those with missing follow-up since these

20   subjects will also typically stop study treatment.

21   If the results from subjects who stop follow-up

22   would be more accurately reflected by those who

1   stopped study treatment but continued with follow-

2   up, then this would be a more reasonable

3   assumption.

4   Our third set of scenarios is to use 13.5

5   events per 100 patient-years. You may recall this

6   was the observed event rate that we saw in the

7   Kaplan-Meier curves for the first year after

8   randomization. If the event rate for the missing

9   data in the simvastatin group is accurately

10   reflected by the first year, then this would be a

11   reasonable assumption.

12   Our last set of scenarios is to use the rate

13   of 19.7 events per 100 patient-years. This was the

14   estimated rate in the pooled off-treatment subjects

15   during the first year based on over 4200 subjects

16   who discontinued treatment during the first year

17   but would continue to be followed for CV events.

18   This table shows results from the tipping

19   point analysis. We imputed missing follow-up,

20   assuming the different event rates we described

21   earlier for the simvastatin group. These event

22   rates are shown in the first column.

1   For each of these rates, we slowly increased

2   the hazard ratio to see at what point the results

3   would tip from statistically significant to

4   nonsignificant. The hazard ratio assumptions that

5   we used are shown in the top row.

6   We started with a hazard ratio of 1.01 and

7   increased up to 1.08 in this table. If we had a

8   hazard ratio of 1, then we would be assuming equal

9   event rates for the missing follow-up in both arms.

10   With larger hazard ratios, we are assuming more

11   disparate event rates for the missing follow-up

12   between the two arms.

13   By slowly increasing the number of events

14   that we were imputing in the ezetimibe arm by

15   increasing the hazard ratio, we can see at what

16   point we lose statistical significance. All the

17   scenarios in which the results are statistically

18   nonsignificant are highlighted in grey.

19   Within the table we have the resulting

20   hazard ratios, 95 percent confidence intervals, and

21   p-values for each scenario. These results are

22   based on combining the observed data, which remains

1   the same for all scenarios, and the imputed data

2   for the missing follow-up, which changed depending

3   on the assumptions we're under.

4   So for example, if you look at the second

5   row scenario, which assumes an event rate of 9.6,

6   the results finally tip with a hazard ratio of

7   1.04. This means we are assuming a 4 percent

8   higher event rate for the missing follow-up in the

9   ezetimibe group. When we combine this imputed data

10   with the observed data, we see the results tipping

11   with a hazard ratio of .95 and a p-value of 0.042.

12   The tipping point occurs much sooner as we

13   increase the event rate in the missing follow-up

14   for simvastatin. These three scenarios, where we

15   first see the results tip, will be further detailed

16   to better assess how plausible they are.

17   For the first tipping point, we assume the

18   missing data has 6.64 events per 100 patient-years

19   in the simvastatin group. This was the estimated

20   rate in those who continued follow-up for this

21   group.

22   Here we see results tipping with a hazard

1   ratio of 1.08 in the missing follow-up. Based on

2   these two assumptions, the corresponding rate for

3   the missing data in the ezetimibe group would be

4   7.17 events per 100 patient-years.

5   In this scenario, the assumed rows of

6   difference of events just within the missing data

7   was 8 percent higher for the ezetimibe group. In

8   our imputation analyses, we averaged around

9   212 imputed events in the simvastatin group and

10   240 imputed events in the ezetimibe group.

11   Our second tipping point uses the off-

12   treatment rate of 9.6 events per 100 patient-years

13   for missing data in the simvastatin group. We see

14   the results now tip at a hazard ratio of 1.04. So

15   for this scenario, we have a rate of 9.98 events

16   per 100 patient-years in the ezetimibe group.

17   The relative difference of events for the

18   missing data is 4 percent higher in the ezetimibe

19   group. In our multiple imputation analysis, we

20   averaged around 286 events in the simvastatin group

21   and 312 in the ezetimibe group.

22   The third tipping point assumes the first

year Kaplan-Meier rate of 13.5 events per 100

patient-years for the simvastatin group. This

tipped relatively early, with a hazard ratio of

1.01. The corresponding rate in missing data for

the ezetimibe group was 13.64 events per 100

patient-years.

With this scenario, the assumed relative

difference for the missing data event rate was

1 percent higher in the ezetimibe arm. Our

multiple imputation analyses averaged around 368

imputed events in the simvastatin arm and 391

events in the ezetimibe arm.

There are consequences to having more

missing data in the treatment arm, some of which we

saw more easily in the last row of scenario, which

assumes the highest event rate of 19.7 for the

simvastatin missing data.

Higher hazard ratios will lead to early

tipping for the study. In some cases, there may be

almost no relative difference in event rates

between the two treatment groups. This is because

we are imputing more follow-up for the ezetimibe

1   arm.

2   The highest event rate scenario tips with a

3   hazard ratio just below 1. We see results tip to

4   nonsignificant with 472 events simulated in the

5   simvastatin arm and 493 for the ezetimibe arm.

6   Many subgroups were also evaluated for this

7   study. Most of the findings indicated similar

8   hazard ratios between subgroups. There were,

9   however, some disparate findings from looking at

10   subgroups concerning diabetes and age, which are

11   shown here.

12   The table here has some corrections from

13   table 11 on page 18 of the FDA statistical summary.

14   So we need to be careful when interpreting subgroup

15   findings, as many subgroups were investigated for

16   this study.

17   In these subgroups, we do see a stronger

18   treatment effect for the diabetic subgroup as well

19   as those who are 75 or older. These subgroups,

20   respectively, make up 27 percent and 15 percent of

21   the study population. The findings in their much

22   larger complimentary subgroups show little to no

effect.

We performed a supplementary analysis in order to further parse out these subgroups. Here we see a strong treatment effect in the older population, regardless of diabetes status.

This effect carries over to a lesser degree in the younger diabetic group, but we see no real treatment in the younger nondiabetic subgroup, which makes up the largest portion in this study, with 62 percent of subjects. The breakdown of the number of subjects and the number of events in these subgroups are provided in table 10 on page 17 of the FDA statistical summary.

You may recall when we broke down the composite primary endpoint into its five cardiovascular components for the overall study population. Efficacy was primarily driven by MI and nonfatal stroke.

We also looked into how missing could affect these results. The current analysis makes the assumption that subjects with missing data have the same behavior and outcomes as those in the same

1   treatment arm who continued with follow-up in the

2   study.

3   We looked at different qualities of the

4   missing data and further characterized it through

5   the tipping point analysis in order to gain a

6   better idea on how robust the study results are.

7   Looking at these results, we can better determine

8   whether or not the results tip under reasonable

9   assumptions, especially scenarios that could be

10   similar to what is seen in practice. There were

11   also very different effects in the diabetic

12   subgroup in those 75 and older.

13   This completes my statistical summary of

14   efficacy for the IMPROVE-IT study. Dr. Chowdhury

15   will come back to talk more about the efficacy and

16   safety in this study. Thank you.

17   **FDA Presentation – Iffat Chowdhury**

18   DR. CHOWDHURY: Thank you, Dr. Clark.

19   Now, I will continue with the efficacy

20   review, and then conclude with highlights from

21   safety.

22   This slide shows the mean percent change in

1   lipids and CRP from baseline to 12 months, as well

2   as the differences between treatment arms. Note

3   that the differences between treatment arms for the

4   parameters shown in this figure were all

5   statistically significant, with p-values less than

6   0.001.

7   As you can see regarding LDL-C, there was a

8   difference between the group means of 19 percentage

9   points. This corresponds to an absolute difference

10   of approximately 17 milligrams per deciliter.

11   As you've already seen this morning, this

12   slide shows the result of the primary composite

13   endpoint. Compared to simvastatin, the combination

14   of ezetimibe/simvastatin significantly reduced the

15   risk of the primary composite endpoint by

16   6.4 percent. The absolute risk reduction in this

17   ACS population was 1.8 percent.

18   As Dr. Clark has already mentioned, the

19   effect on the primary composite endpoint appears to

20   be driven by the effect on the risks of nonfatal MI

21   and nonfatal strokes. In the next few slides, I

22   will present descriptive data regarding some of the

1   characteristics of the nonfatal MI and nonfatal

2   stroke events that contributed to the primary

3   endpoint.

4   This slide summarizes the types of nonfatal

5   MIs that contributed towards the primary endpoint.

6   As you can see, in both arms, 98 percent of the

7   component nonfatal MIs were nonprocedural MIs, and

8   only 2 percent were post-procedural.

9   This slide summarizes the adjudication

10   criteria that were met for the nonprocedural MIs

11   that contributed towards the primary endpoint. The

12   majority of the nonprocedural MIs were positively

13   adjudicated based not on ECG criteria but on

14   troponin and/or CK-MB criteria; 716 MIs in the

15   ezetimibe arm and 834 in the simvastatin arm were

16   adjudicated based on biomarker changes. Fifty-

17   three MIs in the ezetimibe arm and 51 in the

18   simvastatin arm were adjudicated based on ECG

19   criteria.

20   Moving on to nonfatal strokes, at the time

21   of completing the case report form related to the

22   occurrence of a potential cerebrovascular event,

the investigator was asked whether there was a

resolution of the neurological signs and symptoms.

The investigator could select yes, complete

resolution, yes, partial resolution, or no

resolution.

Responses were not adjudicated by the CEC.

According to this report, approximately 60 percent

of events that contributed to the primary composite

endpoint as nonfatal strokes had not completely

resolved at the time the investigator reported the

event.

Information regarding persistence of

symptoms or stroke-related disability was not

collected at subsequent visits for these patients,

so the extent to which some of these symptoms

eventually resolved is unknown.

There was a slightly higher incidence of

hemorrhagic stroke with ezetimibe compared to

simvastatin monotherapy. The difference between

treatment arms was not statistically significant.

The hazard ratio was 1.377, with the upper bound of

the 95 percent confidence interval at 2.

1   In an analysis with the on-treatment

2   population, which censored events occurring beyond

3   30 days after study drug discontinuation, there

4   were 32 hemorrhagic strokes with ezetimibe and 34

5   with simvastatin.

6   Dr. Clark reviewed with you the results of

7   the subgroup analysis that showed that the observed

8   treatment effect was larger in diabetics than in

9   nondiabetics. This slide summarizes the baseline

10   characteristics in these patient groups.

11   The mean age was 65 years in diabetic

12   compared to 63 years in nondiabetics. There were

13   slightly more females in the diabetic group than in

14   the nondiabetic group. Forty-six percent of the

15   diabetics were on prior lipid-lowering therapy, as

16   compared to 29 percent in the nondiabetics. And

17   the mean LDL-C was 89 milligrams per deciliter in

18   diabetics compared to 96 milligrams per deciliter

19   in nondiabetics.

20   In comparing the baseline characteristics of

21   those younger or older than 75 years, in the older

22   age group, 34 percent were female compared to

1   23 percent in the younger group. The older age

2   group had an average calculated creatinine

3   clearance of 58 milliliters per minute compared to

4   95 milliliters per minute in the younger age group.

5   Forty percent in the older group were on prior

6   lipid-lowering treatment compared to 32 percent in

7   the younger age group. And the mean LDL-C was 90

8   in the older group and 95 milligrams per deciliter

9   in the younger group.

10   This slide shows the difference between

11   treatments in changes from baseline to time-

12   weighted average for the lipids and CRP by diabetes

13   status. In diabetics, the difference in LDL-C was

14   negative 15.8 milligrams per deciliter as compared

15   to nondiabetics, which was a minus 13.6 milligrams

16   per deciliter; and the differences for the other

17   parameters are as shown.

18   This slide shows the difference between

19   treatments in changes from baseline to time-

20   weighted averages for lipids and CRP by age greater

21   than or equal to 75 years, or less than 75 years.

22   In the older age group, the difference in LDL-C was

1   a minus 13.6 milligrams per deciliter as compared

2   to the younger age group, which was a minus

3   14.3 milligrams per deciliter. Again, the changes

4   for the other parameters are as shown.

5   In concluding efficacy, some of the main

6   points are as follows. Treatment with ezetimibe

7   resulted in a 6.4 percent relative risk reduction

8   and a 1.8 percent absolute risk reduction of major

9   cardiovascular events in patients with acute

10   coronary syndrome. Primary endpoint results were

11   driven by nonfatal MI and nonfatal stroke.

12   In subgroup analyses, the unadjusted

13   interaction p-values, for age less than 75 years

14   versus greater than or equal to 75 years, and

15   diabetes, yes versus no, were a p of 0.005 and a p

16   of 0.023, respectively. Differences between these

17   groups in lipids and CRP changes were small and

18   unlikely to contribute towards the differences in

19   the observed effects.

20   Eleven percent of patients were censored

21   for the primary endpoint prior to 5/1/2014. Most

22   censoring occurred during the first year of the

trial, with more patients censored with ezetimibe

than with simvastatin.

I will begin the safety review of the

IMPROVE-IT trial with a summary of drug exposure,

AEs leading to drug discontinuation, serious

adverse events, and then adverse events of special

interest such as cancer, new onset diabetes,

rhabdomyolysis and myopathy, hepatic events, and

gall bladder-related events.

Duration of study drug exposure was defined

for each patient as the interval from the day of

randomization to the last day for which trial

medication was supplied. Mean exposure to

ezetimibe was 3.8 years as compared to mean

exposure to simvastatin at 3.9 years.

This slide shows the number and percent of

patients who received simvastatin 40 milligrams,

80 milligrams, or both during the trial. In the

ezetimibe/simvastatin arm, 91 percent of patients

only ever received simvastatin 40 milligrams

compared to simvastatin monotherapy arm, in which

71 percent received only simvastatin 40 milligrams.

1   In the simvastatin arm, a total of 27 percent

2   received simvastatin 80 milligrams at some point in

3   the trial, as compared to 7 percent with ezetimibe.

4   Overall, 1,180 patients discontinued study

5   drug due to an adverse drug experience. The

6   incidence of approximately 10 percent was similar

7   in both treatment arms. There were more

8   discontinuations due to musculoskeletal events in

9   the ezetimibe arm at 4.3 percent than with

10   simvastatin at 3.8 percent.

11   Approximately 40 percent of patients

12   reported at least one serious adverse event, but

13   the incidence was similar in both treatment arms.

14   The most commonly reported SAE by system organ

15   class was neoplasms, infections, and

16   gastrointestinal disorders. Again, the incidence

17   was similar in the treatment arms.

18   Both any cancers due to malignancy and death

19   due to a new malignancy were similar in the two

20   treatment arms. For any death, the hazard ratio

21   was 1.03, with the upper bound of the confidence

22   interval at 1.22. For death due to a new

malignancy, the hazard ratio was 1.02, with the

upper bound of the 95 percent confidence interval

at 1.22.

This is the Kaplan-Meier curve for any death

due to malignancy. The incidence of new,

relapsing, or progressing malignancy was

approximately 8 percent in both arms, with a hazard

ratio of 1.03 and the upper bound of the 95 percent

confidence interval at 1.14.

The incidence of any new malignancy was

7.6 in the ezetimibe arm and 7.5 in the simvastatin

arm. The hazard ratio for any new malignancy was

also 1.03, with an upper bound of the 95 percent

confidence interval at 1.14. This slide shows the

Kaplan-Meier curve for any new, relapsing, or

progressing malignancy, excluding nonmelanomic skin

cancer.

To explore the incidence of new onset

diabetes mellitus, the occurrence was defined as

the initiation of an antidiabetic medication during

the trial or if two consecutive fasting glucose

measurements were greater than or equal to

1 126 milligrams per deciliter. Patients were

2 excluded if they were previously on an antidiabetic

3 medication or had elevated glucose at

4 randomization.

5 With this definition, the incidence of new

6 onset diabetes mellitus was 13.6 percent in the

7 ezetimibe arm versus 13 percent in the simvastatin

8 group. The hazard ratio was 1.04 with a 95 percent

9 confidence interval between 0.94 and 1.15.

10 The incidence of CEC-determined

11 rhabdomyolysis was 0.1 in ezetimibe versus 0.2 in

12 simvastatin, and the incidence of myopathy was 0.2

13 with ezetimibe versus 0.1 with simvastatin.

14 Lastly, the incidence of investigator-reported

15 unexplained myalgia was 17.7 percent with ezetimibe

16 versus 17.2 percent with simvastatin.

17 The definition of Hy's law is as shown on

18 this slide. A similar percent of patients met the

19 biochemical criteria of Hy's law in the two

20 treatment arms. There were three patients, two on

21 ezetimibe and one on simvastatin, without a

22 convincing alternative cost for Hy's law, but there

1 was limited clinical information available.

2   The incidence of ALT or AST at various

3 thresholds above upper limit of normal was similar

4 between the two treatment arms. With respect to

5 liver-related safety, there was no clinically

6 relevant differences between the two treatment

7 groups.

8   This is a summary table of the incidence of

9 the adverse events of interest. In addition to

10 the other safety events I previously discussed,

11 cholecystectomies and gall bladder-related events

12 are listed here. The incidence of those events are

13 not different in the two treatment arms.

14   In concluding safety, there was no overall

15 difference of cancer deaths or incidence of

16 malignancy between the treatment groups. There was

17 no clinically meaningful difference between

18 treatment groups in the incidence of new onset

19 diabetes.

20   Overall, musculoskeletal, hepatic, and gall

21 bladder-related AEs occurred with similar

22 frequencies between treatment groups, and the

1   results of the safety review was consistent with

2   the known safety profile of ezetimibe/simvastatin

3   and ezetimibe.

4   Dr. Clark and I would like to acknowledge

5   the mentorship of our colleagues mentioned on this

6   slide as well as many others across the agency.

7   **Clarifying Questions**

8   DR. R. SMITH: Thank you to the FDA.

9   What we would like to do now is take some

10   time for clarifying questions. And I know there

11   are some carry-forward questions for the sponsor

12   from this morning, but I would like in particular

13   to emphasize at the beginning of this clarifying

14   questions for the FDA. Again, if you would give

15   your name and direct your question to an individual

16   if you're able to do that.

17   We'll start with Dr. Hiatt, who is present,

18   as a reminder, with us by a phone connection.

19   Dr. Hiatt, are you there?

20   DR. HIATT: Yes. Thank you, and I

21   apologize. My travel schedule did not allow me to

22   attend this. But I have a question for Dr. Clark,

1   the statistical reviewer.

2   Does the FDA think that the missing data in

3   any way invalidates the trial or makes the trial

4   uninformative?

5   DR. CLARK: The missing data, the tipping

6   point analysis is just mainly to characterize the

7   missing data and give a broader viewpoint so that

8   if there are other -- because the current analysis

9   assumes that those who are missing follow the same

10   response as those who are observed.

11   So the tipping point analysis is meant

12   mainly to allow you to see if you believe that

13   those who are missing for whatever reasons might be

14   different, then you can see how that would affect

15   the results. But it shouldn't invalidate the

16   results, depending on how you see everything

17   tipping.

18   DR. HIATT: The reason I ask is that in

19   previous reviews of cardiovascular outcome trials,

20   a significant amount of missing data has been a

21   cause of great concern. In this situation, the

22   tipping analyses and the other sensitivity analyses

1   are really appreciated, but there's really no

2   conclusion from the FDA review as to whether you

3   believe that this is posing a problem in terms of

4   the overall validity of the results or not.

5   DR. ROTHMANN: Dr. Mark Rothmann, FDA, lead

6   mathematical statistician. I think what we have

7   here, both in a primary analysis and after

8   sensitivity or a tipping point analysis, is

9   something that is not overwhelming. It's fairly

10   borderline.

11   So that's what makes it a little difficult

12   to come to a firm conclusion. And I think we are

13   very much interested in the views of the committee

14   members and the statisticians on the committee and

15   how they think the missing data affects the

16   interpretability of the results.

17   DR. HIATT: Well, thank you.

18   DR. R. SMITH: Okay. Dr. Kaul?

19   DR. KAUL: I wanted to follow up on what

20   Dr. Hiatt's was. I find it ironical that your

21   conclusion on missing data was missing on your

22   final slide. It's considered to be a sensitivity

1   analysis, so the question I have for you is, when

2   you look at the primary endpoint analysis, you run

3   through various scenarios, and it only takes in

4   excess of 21 to 28 events to tip the data into

5   non-significance.

6   But I want to ask you a question about

7   another sensitivity analysis, where you include all

8   revascularizations, not just revascularizations

9   beyond 30 days. And the p-value for that result is

10   0.036, which makes it more vulnerable to

11   missingness. In other words, it may become

12   intolerable missingness, perhaps only at 2 or 4

13   excess events.

14   Did you do that kind of analysis?

15   DR. CLARK: No. We concentrated mostly upon

16   the primary endpoints since that's what we base a

17   lot of decisions on.

18   DR. KAUL: Two quick questions, if I may.

19   Again, I want to try to get an answer to my earlier

20   question about the clinical relevance of the

21   myocardial infarction and stroke events.

22   Now, you clearly outline that 98 percent of

1   the nonfatal MIs were nonprocedural, so that's very

2   reassuring. But you also said that only 53 versus

3   51 were Q wave myocardial infarctions, the MIs that

4   most of us here, the clinicians, consider

5   clinically relevant.

6   You also said that MIs driven by biomarkers

7   were the majority of these. Did you quantify what

8   was the magnitude of the infarct size by these

9   troponin or CK-MB elevations? I'm trying to figure

10   out whether these are clinically relevant MIs.

11   In your briefing document, you do mention a

12   tertiary endpoint analysis for congestive heart

13   failure, which was not adjudicated. And there was

14   no difference; if anything, there was a numerical

15   imbalance not favoring the active treatment. So as

16   a clinician, I want some answer to the question,

17   are these clinically relevant MIs or not?

18   With regards to stroke, you mentioned that

19   60 percent of them did not have complete or partial

20   resolution even though there was a treatment effect

21   in favor of the active therapy. And since

22   disability or disutility was not captured, again, I

1   have difficulty understanding what the clinical

2   relevance of this is.

3   The third question I wanted to ask you is,

4   even though I know the LDL hypothesis is not on

5   trial here, but how do you interpret the results of

6   the subgroup analysis you have and equivalent

7   reduction in LDL in the diabetic and the

8   nondiabetic cohort in the treatment effects

9   exclusively seen in one group? Same with the age

10   75. Does that weaken or confirm the LDL

11   hypothesis?

12   DR. CHOWDHURY: I'll take a couple of those

13   questions. We did try to give you the peak

14   troponin values surrounding the selected

15   nonprocedural MIs in the briefing document on page

16   63, table 21, which shows the median values for

17   those biomarkers to give you an idea of the

18   magnitude of the myocardial infarction.

19   DR. KAUL: But is that correct that the

20   median value of troponin was 1.8, ranging from 0.4

21   to 9.45? Is that correct?

22   DR. J. SMITH: That's not a range. That's

1   an interquartile range.

2   DR. KAUL: Interquartile.

3   DR. J. SMITH: But that is correct, for all

4   the nonprocedural MIs without Q waves that met one

5   of the troponin criteria.

6   The applicant may wish to address that

7   somewhat. They've confirmed the numbers based on

8   what was in the database that we used. They had a

9   couple caveats when we shared that data with them;

10   for example, that not all troponin levels were

11   recorded in the safety database, but they were part

12   of the adjudication package.

13   So this should be regarded as exploratory,

14   but that's the data that we had to work with in the

15   database.

16   DR. CHOWDHURY: As far as your other

17   question about what do I make of the subgroup

18   analyses and the LDL hypothesis, I think it's

19   interesting that although diabetics made up only

20   27 percent of the population, they had 36 percent

21   of the primary events compared to 27 percent of the

22   nondiabetics. And also, those patients who were

1   older than 75 years made up only 15 percent of the

2   population, but they had 36 percent of the primary

3   events compared to 28 percent in the younger group.

4   I'm not sure why we see this difference, but

5   the difference between the groups in the lipids and

6   CRP to me seem unlikely to account for the

7   differences in the observed effect.

8   DR. KAUL: I asked a very simple question.

9   Do these data confirm or weaken the LDL hypothesis?

10   DR. J. SMITH: Dr. Kaul, I think we could

11 toss that back to you to discuss in the afternoon.

12 I think you have to take a starting point of what

13 do you think of the subgroup results. Right?

14 Because if you think the subgroup result is a

15 chance finding, then perhaps difference in LDL is

16 perfectly consistent with that.

17   If you think the subgroup difference is

18 real, then that might weaken your confidence in the

19 LDL hypothesis. So I think this is not a

20 straightforward question, and we look forward to

21 what your conclusions are.

22   I think with regard to you -- you also asked

1   a question about stroke. Let me emphasize that the

2   data that we showed about stroke, as Dr. Chowdhury

3   said, with regard to symptom resolution, no

4   resolution, partial, or complete resolution, that's

5   something the investigator checked off at the time

6   that they reported the event on a case report form,

7   which although we didn't look at the dates of the

8   case report form and the dates of symptoms, I

9   presume that would probably usually be within

10   4 months at the next site visit.

11   So that data was not collected, as she said,

12   longitudinally. So that really can only give us a

13   snapshot of whether or not symptoms had resolved at

14   that time early on. Without additional disability

15   data, it's difficult to say really what the impact

16   was.

17   With regard to the MI, I was going to point

18   you to the same thing about CHF. We didn't look at

19   arrhythmia, but you saw the CHF result already.

20   DR. KAUL: But is it fair to say that if you

21   don't collect information about disability, perhaps

22   use fatal stroke as a proxy for large disabling

strokes? And the data there are not favorable for

the active therapy, 52 versus 43 for all strokes.

For nonhemorrhagic stroke, they are

favorable, 24 versus 32. For hemorrhagic stroke,

they're not favorable. They are 28 versus 11, with

a hazard ratio of 2.55, with a confidence interval

that excludes a hazard ratio of 1.

DR. R. SMITH: And again, we will have ample

time to come back to thoughts from the committee on

some of these questions as well.

Dr. Fleming, you have a question?

DR. FLEMING: Yes. I think Sanjay's getting

into some of my questions, which relate to your

final slides, 7, 6, and 5.

But when you're pulling up slide 7, just

quickly, to follow up on somebody that Bill Hiatt

had mentioned, to me the issue here isn't whether

the missingness, which as he was talking about

invalidates, does it meaningfully influence the

interpretation?

When people are off study, they're not

getting the same benefit, they are at higher risk

1   of events, and there's more missingness early. So

2   it absolutely influences the interpretation when

3   the results are already so fragile without

4   missingness. But we'll talk about that this

5   afternoon.

6   So on slide 7 of your last set is where you

7   talk about hemorrhagic stroke, Dr. Chowdhury. And

8   it's following up with what Sanjay was just talking

9   about. You give a hazard ratio there of 1.377,

10   .11. But these are just the nonfatal strokes.

11   Correct?

12   DR. CHOWDHURY: Yes. That's correct.

13   DR. FLEMING: So when you add the fatal

14   strokes, which Sanjay pointed out are 28/11, I get

15   87/54. So the real answer is all strokes. It's

16   87/54 for all hemorrhagic strokes, and by my

17   calculation, p-value is 0.005, a nominal p-value.

18   But there's a clear excess.

19   Are those numbers right; i.e., when you put

20   the nonfatal strokes here with the fatal strokes,

21   there's a clear increase in hemorrhagic stroke.

22   Correct?

1   DR. CANNON: Those numbers in hemorrhagic

2   stroke include fatal and nonfatal.

3   DR. R. SMITH: If you would use the

4   microphone for the --

5   DR. CHOWDHURY: The hemorrhagic

6   strokes -- hold on.

7   DR. CANNON: Those numbers reported include

8   fatal and nonfatal hemorrhagic strokes.

9   DR. FLEMING: Could we look then also at

10   table 25 in the FDA briefing document, table 25?

11   It's important to understand this. Table 25,

12   page 66 -- page 66 in the FDA briefing

13   document -- separates out stroke into fatal

14   hemorrhagic/nonhemorrhagic, nonfatal

15   hemorrhagic/nonhemorrhagic. And the 59/33 seems to

16   be the hemorrhagic nonfatal strokes, and 28/11

17   seems to be the hemorrhagic fatal strokes.

18   DR. KAUL: I think there is an error.

19   DR. CHOWDHURY: Yes. I noticed, too. I

20   think there's an error. There's got to be a bunch

21   of errors.

22   DR. KAUL: It's 59 versus 43 for the

1   nonfatal hemorrhagic stroke, and 28 versus 11 for

2   the fatal hemorrhagic stroke. There is a typo.

3   There's an error in that table 25.

4   DR. FLEMING: So just one more time. In

5   table 25, the hemorrhagic fatal strokes are 28/11,

6   as you were saying, Sanjay.

7   DR. KAUL: Correct.

8   DR. FLEMING: Yes. Then how many

9   hemorrhagic nonfatal strokes? The table says

10 59/43. The table is now giving nonfatal stroke at

11 the bottom, and it talks

12 nonhemorrhagic/hemorrhagic.

13   DR. KAUL: Yes.

14   DR. FLEMING: So nonfatal actually is 31

15 versus 32. Total hemorrhagic stroke is 59 versus

16 43. So that table is incorrect at the bottom. Is

17 that right? You see where I'm -- so the table

18 clearly says --

19   DR. CHOWDHURY: Can I ask the sponsor to

20 confirm? This is the sponsor's data.

21   DR. TERSHAKOVEC: Slide up. So the question

22 we have on hemorrhagic strokes total you see is 59

1   and 43, and fatal stroke is 52 versus 43, and then

2   breakdown of nonhemorrhagic or known or

3   hemorrhagic.

4   DR. FLEMING: So this is inconsistent with

5   the table that we just saw. But what we're hearing

6   is -- the truth is -- there are 28 versus 11 fatal

7   hemorrhagic strokes. That's not being contested.

8   Overall, hemorrhagic stroke is 59/43. Is that what

9   we're hearing?

10   DR. TERSHAKOVEC: Yes.

11   DR. FLEMING: Okay. So let's then go to

12   slide 6 from the FDA presentation at the end.

13   Slide 6. So what FDA had indicated, and it's my

14   sense as well, is that the composite is driven by

15   the stroke and the MI, and so understanding those

16   consequences of those is important. Slide 6

17   divides out these overall strokes, which are 296

18   against 345. This is just showing the nonfatal

19   components. But because of the excess in

20   hemorrhagic, overall fatal strokes are 9 in excess

21   on the combination arm.

22   The nonfatal, what we're seeing here is in

1 complete resolution, more than half of all of the

2 nonfatal strokes that are in excess on simvastatin

3 alone are in the complete resolution category. So

4 in essence here we have in stroke about 34 excess

5 strokes that are nonfatal, no resolution/ partial

6 resolution when you're pooling both hemorrhagic and

7 nonhemorrhagic; but you also have 9 excess net

8 fatal strokes, hemorrhagic/nonhemorrhagic.

9   Then the previous slide, slide 5, is getting

10 at understanding the MI, which is the other

11 component that's favorable. And what we're seeing

12 here is when you're looking at Q waves, which are

13 more definitive, there's no difference.

14   So the differences that are favoring the

15 combination are in the enzyme leak category. And

16 what you didn't show here, but I think you're

17 showing in the briefing document, is when you also

18 divide them up -- and this is your table 19 -- into

19 traditional non-STEMI/STEMI/unstable angina

20 categories, where many of us would worry the most

21 about ST elevation MIs in terms of major damage to

22 the myocardium and the downstream consequences for

1   heart failure and substantial arrhythmias and

2   death, those are only 16 in excess.

3   So most of the difference in MIs are in the

4   troponin leak categories and are not in the ST

5   elevation MI category, but are in the more

6   uncertain clinical consequence category. Am I

7   interpreting that correctly?

8   DR. CHOWDHURY: Yes, that's true.

9   DR. R. SMITH: Okay. Dr. Blaha, you have a

10 question?

11   DR. BLAHA: I had a follow-up question on

12 the diabetic subgroup. I was interested, and

13 Dr. Kaul brought this up earlier, in the comment

14 that the differences between the groups, that is,

15 the diabetic and nondiabetic, in lipid and CRP

16 changes was small and unlikely to contribute to the

17 differences in the observed effects.

18   I guess maybe I should interpret that as all

19 the differences unlikely to be explained. But I

20 did notice that there is a difference in the LDL

21 reduction and the triglyceride reduction, and one

22 interpretation of the LDL hypothesis is an

1   atherogenic lipoprotein hypothesis.

2   So my two questions are, number one, would

3   it be fair to say that you meant all the

4   difference, and it was really a calculation done to

5   figure out what part of the difference might be

6   explained by changes in LDL cholesterol or

7   triglycerides, for example?

8   Number two, do you have data, or we will ask

9   the sponsor later, on non-HDL or ApoB differences,

10   lowering differences, between diabetic and

11   nondiabetic groups?

12   DR. CHOWDHURY: I'm trying to answer your

13   second question first. We don't have that data,

14   but we can get it for you later about the non-HDL

15   and ApoB differences in the diabetes subgroups.

16   As far as your question about maybe there

17   are other components that could explain this

18   difference in observed treatment effects, it's

19   possible --

20   DR. BLAHA: I guess what I'm asking is

21   how -- that comment was notable, but I didn't know

22   to what degree that was explored in terms of

1   supporting that comment, that the differences were

2   unlikely to be due to the differences in lipid

3   change.

4   DR. CHOWDHURY: That was just a comment --

5   DR. BLAHA: Whether it was explored

6   statistically.

7   DR. CHOWDHURY: Right. No. That was just a

8   comment on one part based on if you're looking at

9   the CTT analysis curve, then that kind of observed

10   treatment difference wouldn't be expected if you

11   look at the slope of that curve for the LDL.

12   DR. BLAHA: Within the range of confidence.

13   I just couldn't tell how confident we were in that

14   statement. So it doesn't sound like it was tested,

15   but just estimated.

16   DR. CHOWDHURY: Right.

17   DR. R. SMITH: Okay. Dr. Budnitz?

18   CAPT BUDNITZ: Yes. Just a clarifying

19   question on adverse events. I understand the main

20   safety analysis was for the ITT population, but in

21   the materials, it says the applicant also conducted

22   safety analyses with an on-treatment safety

1   population. But we didn't see very much of that.

2   We saw a little bit for rhabdo.

3   Is it FDA's assessment that there were no

4   clinically significant differences in adverse

5   events when you did an on-treatment assessment that

6   I appreciate being submitted by the sponsor?

7   DR. CHOWDHURY: Frankly, when we're looking

8   at safety data, we considered the ITT population.

9   And the on-treatment population, the applicant can

10   confirm your question.

11   CAPT BUDNITZ: I'll just follow up. I do

12   appreciate the on-treatment safety assessment

13   because it's hard to have an adverse event when

14   you're not on the treatment.

15   DR. TERSHAKOVEC: I can confirm that the

16   on-treatment analysis specifically related to

17   muscle did not show any increase compared to the

18   ITT.

19   CAPT BUDNITZ: And the other adverse events?

20   That's what I was specifically asking about.

21   DR. TERSHAKOVEC: Yes. They're generally

22   confirmatory, the ITT, and no increases in the

1   on-treatment.

2   DR. R. SMITH: Okay. We have three more

3   minutes before a break. Dr. Packer, you're next.

4   If we can try to keep it within that because I want

5   to break at 11:30.

6   DR. PACKER: I only have one question. I

7   don't think one can assume that the rates in the

8   missingness, in patients with missing, are the same

9   as the people on treatment being followed. I

10   understand you used various scenarios.

11   Here's the scenario I would be most

12   interested in, and that is that you assign 19.7 to

13   the patients who were missing in the first year

14   because that is the effect, that is the rate, in

15   the patients who were followed off-treatment in the

16   first year, and that for each subsequent year, you

17   use bins, for example, of how the people lost

18   follow-up, but relying primarily on the

19   off-treatment but followed event rates.

20   If you did that, my guess is that you would

21   essentially have a tipping point if there was no

22   difference between ezetimibe and the control group.

1   In other words, I'd assume that 19.7 first year

2   event rate in the missingness, with the imbalance

3   in the missingness, that would bring you pretty

4   much close to neutrality for the patients with

5   missingness to have a p-value that was no longer

6   statistically significant. Is that fair?

7   DR. CLARK: We ran some preliminary

8   analysis, nothing that can be presented here today.

9   But the results, when we look at different rates

10   for the first year, are fairly similar to what we

11   found for just some more moderate tipping point

12   analysis scenarios.

13   DR. PACKER: I just want to make sure.

14   Since there's an imbalance in the first year, since

15   the first year event rates are higher than any

16   other, since the event rates are particularly high

17   in people off treatment who were being followed,

18   19.7 percent, given the imbalance in the first

19   year, if you assigned people lost to follow-up in

20   the first year, the appropriate imputation for the

21   patients off-treatment in the first year -- same

22   thing for the second year, same thing for the third

1 year, same thing for the fourth year -- my sense

2 is, based on the analysis you presented, if

3 ezetimibe and a control group had a risk ratio of 1

4 but you assumed the event rates appropriate to

5 their bins, you would have a nonsignificant result?

6   DR. CLARK: That's not something that we

7 have been able to look at.

8   DR. R. SMITH: Yes. A connected comment or

9 question?

10   DR. TEERLINK: Just a quick follow-up. I

11 thought, with slide 13, what Dr. Packer just

12 suggested is what you represented in slide 13, or

13 what's on the bottom row.

14   DR. PACKER: John, I think this assumes 19.7

15 for all missingness as opposed to missingness only

16 in the first year.

17   DR. TEERLINK: Oh, okay. Got it.

18   DR. R. SMITH: Yes. Dr. Fleming?

19   DR. FLEMING: I totally agree, Milt, and

20 that's setting the stage for this afternoon. But

21 what is very clear here, and it's not shocking, is

22 that people who are off study are different.

1   The argument that was given by the

2   sponsor -- although I want to credit both the

3   sponsor and the FDA for incredibly thoughtful

4   missingness analyses that exceed the thoughtfulness

5   that we usually see -- but the argument that the

6   rates are the same or where we have randomization

7   does not protect you against the adverse effect of

8   missingness because when you're not being followed,

9   you're not being treated, predominately, and those

10   people aren't getting benefit.

11   They are also fundamentally different, as

12   Milt pointed out. They have a higher rate. And

13   there's an imbalance, as both the sponsor and the

14   FDA showed, in terms of where missingness occurs.

15   There's more of it in the first year, where that

16   rate is in fact higher.

17   So Milton's exactly right. That alone could

18   readily explain a tipping point 1.03. So in fact,

19   there's no conservatism here whatsoever in these

20   analyses that are imputing the average of the

21   observed follow-up when you're not being treated

22   for those that were followed versus those who

1   aren't.

2   If you put just that logical assumption that

3   Milton just went through, you're going to be

4   already at a point of unclear whether it's even

5   statistically significant. It doesn't make the

6   study relevant. The hazard ratio goes from 0.937

7   to about 0.947. So instead of a 6 percent

8   reduction, it's a 5 percent reduction. But that p-

9   value now is lurking right around 0.05.

10   DR. R. SMITH: Clearly, this is not fully

11   resolved, and we're going to discuss this some

12   more. Are there any data presentations that might

13   be feasible to prepare by this afternoon that

14   anyone would like to request? It looks like not.

15   Dr. Proschan, if it's absolutely critical

16   and takes about 15 seconds, because I really am

17   over time and need to --

18   DR. PROSCHAN: Right.

19   DR. R. SMITH: We know you're there.

20   DR. PROSCHAN: Yes. No, I just was

21   responding to your question, is there any data

22   presentation that would be helpful.

1   I would like to see an analysis where you do

2   things slightly differently, which is you say,

3   okay, given the missing data, let me make some

4   assumptions, as they have, both sides have, on the

5   missing data, and now treat it and say what's the

6   conditional probability that if we had these

7   missing data that were observed, that it would be

8   statistically significant?

9   So it's like a conditional power kind of

10   approach, where you treat the entire trial as

11   everyone, if you could have their data and the

12   missing people. So you could calculate, what's the

13   probability that if you had these data, the result

14   would be statistically significant?

15   Then you could look at that. And if it's

16   95 percent, that's great. If it's 60 percent,

17   that's not so great. So that's another way to look

18   at missing data. I don't know how feasible it

19   would be to do that before the --

20   DR. R. SMITH: So would the FDA or the

21   sponsor like to comment on feasibility of that?

22   We're talking about looking at some actual numbers

1   by later this afternoon. Just really knowing

2   whether it's possible. I don't want to go further

3   with this issue. We'll come back to this.

4   DR. DeLUCCA: Okay. Just a couple quick

5   comments. Number one is, while we matched many of

6   the numbers with FDA, we did not match the

7   19 percent off treatment. We're fairly close, but

8   we didn't match it.

9   But we do have analyses that look at some of

10   the analyses that were suggested, such as applying

11   a higher rate in year 1 and then lower rates as you

12   move on in time. So we do have those results that

13   we could share.

14   DR. PACKER: I would very much like to see

15   those.

16   DR. R. SMITH: For sure, yes. So let's plan

17   this afternoon, if you can have that so we can see

18   it. That would be great. Thank you.

19   Okay. So we are now going to break for

20   lunch. We are going to reconvene in this room at

21   12:30, slightly less than an hour. I know that's

22   15 minutes off the agenda, so particularly for the

1   open public hearing speakers, please note that.

2   We're looking forward to your input, but it's going

3   to start at 12:30.

4   Please take any personal belongings you may

5   want with you at this time. Committee members,

6   please remember that there should be no discussion

7   of the meeting during lunch among yourselves, with

8   the press, or with any member of the audience.

9   Thank you. We'll see you back here at

10   12:30.

11   (Whereupon, at 11:36 a.m., a luncheon recess

12   was taken.)

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

2   (12:30 p.m.)

3   **Open Public Hearing**

4   DR. R. SMITH: I'm going to call the

5   afternoon part of this review to order, and we

6   start with the open public hearing session.

7   Both the Food and Drug Administration and

8   the public believe in a transparent process for

9   information-gathering and decision-making. To

10   ensure such transparency at the open public hearing

11   session of the advisory committee meeting, FDA

12   believes that it is important to understand the

13   context of an individual's presentation.

14   For this reason, FDA encourages you, the

15   open public hearing speaker, at the beginning of

16   your written or oral statement, to advise the

17   committee of any financial relationship that you

18   may have with the sponsor, its product, and if

19   known, its direct competitors. For example, this

20   financial information may include the sponsor's

21   payment of your travel, lodging, or other expenses

22   in connection with your attendance at the meeting.

1   Likewise, FDA encourages you at the

2 beginning of your statement to advise the committee

3 if you do not have any such financial

4 relationships. If you choose not to address this

5 issue of financial relationships at the beginning

6 of your statement, it will not preclude you from

7 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

11 and this committee in their consideration of the

12 issues before them.

13   That said, in many instances and for many

14 topics, there will be a variety of opinions. One

15 of our goals today is for the open public hearing

16 to be conducted in a fair and open way, where every

17 participant is listened to carefully and treated

18 with dignity, courtesy, and respect. Therefore,

19 please speak only when recognized by the

20 chairperson. Thank you for your cooperation.

21   Will speaker number 1 step up to the podium

22 and introduce yourself? Please state your name and

1   any organization you are representing for the

2   record.

3   DR. RUPP: Thank you for the opportunity to

4   speak today. My name is Dr. Tracy Rupp. I was

5   previously a clinical pharmacist at Duke University

6   Medical Center, and am now director of public

7   health policy initiatives at the National Center

8   for Health Research.

9   Our research center analyzes scientific and

10   medical data and provides objective health

11   information to patients, providers, and

12   policymakers. We do not accept funding from the

13   drug or medical device industry and have no

14   conflicts of interest.

15   IMPROVE-IT is a good illustration of the

16   difference between statistical significance and

17   clinical significance. In this trial, the addition

18   of ezetimibe to simvastatin in patients with a

19   recent acute coronary event was associated with a

20   statistically significant reduction in the

21   composite primary endpoint of death from

22   cardiovascular disease, a major coronary event, or

1   nonfatal stroke after 7 years.

2   However, the result was not robust, with an

3   absolute risk reduction of only 2 percent for the

4   composite primary outcome. The statistically

5   significant outcome was primarily driven by

6   reductions in heart attack and stroke, and was not

7   related to a reduced risk of death.

8   Is a 2 percent reduction in risk for heart

9   attack and stroke clinically meaningful? Since the

10   number needed to treat to prevent one CV event is

11   50 patients who are at high risk for 7 years, there

12   is about a 1 in 350 chance that an individual, very

13   high-risk patient will be prevented from having a

14   heart attack or stroke in any given year as a

15   result of taking Vytorin.

16   In other words, a patient's chances of

17   handing in the hospital are reduced for 1 out of

18   350 patients taking Vytorin for a full year, and

19   the chance of dying is not reduced at all for any

20   of those 350 patients. And as we have heard today,

21   the chances of benefitting from Vytorin are even

22   less for patients without diabetes and those age

less than 75.

A significant concern is the fact that the proposed indication, which states that adding ezetimibe to statin therapy will reduce the risk of CV events, will probably cause many providers to think that the risk of death is reduced when this is not the case.

Of course, it is better to not have a heart attack or stroke than to have one. But the small absolute risk reduction found in IMPROVE-IT was one of the smallest effects ever observed in statin trials. In fact, this study achieved statistical significance simply because of the enormous sample size.

In order to show such a small difference, the investigators had to study more than 18,000 patients with a very high baseline risk. In fact, the protocol had to be amended to increase the sample size and extend the length of the trial.

If they hadn't made that post hoc change, the tiny absolute benefit of Vytorin would not have been statistically significant, and it is possible

1   that the results would not have been statistically

2   significant if we had had the data from those

3   participants with missing follow-up time.

4   As we heard today, more patients in the

5   Vytorin group were missing follow-up time in the

6   first year after randomization, which is when a CV

7   event would most likely have occurred. So we do

8   not know if the results would still be

9   statistically significant if we'd had this data.

10   It is important to remember that before the

11   trial began, the investigators decided that an

12   absolute risk reduction of 3 percent was needed to

13   show that Vytorin was beneficial compared to

14   simvastatin alone. But after it became obvious

15   that Vytorin wasn't effective, the investigators

16   changed the criteria to a 2 percent improvement for

17   patients taking the drug for 7 years.

18   The investigators had not initially believed

19   that such a small difference was clinically

20   meaningful. One has to assume that they changed

21   the study design to gain FDA approval by showing a

22   statistical difference, not by making a difference

1   in patients' lives.

2   The benefit is minimal for Vytorin,

3   especially compared to high-potency statins such as

4   atorvastatin and rosuvastatin. And since Vytorin

5   is already on the market, we know that the cost of

6   preventing one event is expensive, just under

7    $900,000. The cost of preventing one event is much

8   higher when Vytorin is taken by patients at low or

9   moderate risk instead of those at high risk.

10   We know that Vytorin will be prescribed to

11   low-risk outpatient populations for primary

12   prevention, as has occurred with other statins and

13   with Vytorin itself. If Vytorin is used in lower-

14   risk patients, the number needed to treat to

15   prevent one heart attack or stroke, as well as the

16   cost, will increase exponentially, money that would

17   be better spent on more effective treatments.

18   FDA is not supposed to take cost into

19   account, but they should take treatment options

20   into account. And this panel should consider

21   whether Vytorin represents the kind of innovation

22   we want for our healthcare system or the kind of

1   costly mediocrity that we need to avoid.

2   The results of IMPROVE-IT have led some to

3   proclaim that the use LDL cholesterol as a

4   surrogate endpoint for cardiovascular events has

5   been proven. Although the patients in the

6   simvastatin plus ezetimibe group did experience

7   lower LDL cholesterol levels and a slightly lower

8   rate of the primary endpoint, the trial does not

9   prove that the effect was mediated by lowering of

10   LDL levels.

11   Some studies have suggested that ezetimibe

12   may have beneficial effects unrelated to LDL

13   lowering that are responsible for its modest

14   decrease in coronary events. Some of these non-LDL

15   effects may have been responsible for the small

16   beneficial effect of ezetimibe seen in IMPROVE-IT

17   since levels of high-sensitivity C-reactive protein

18   were significantly lower in the simvastatin plus

19   ezetimibe group than in the simvastatin-only group.

20   Similarly, since patients with diabetes are

21   particularly likely to benefit from reductions in

22   triglycerides, the greater decrease in triglyceride

1   levels in the simvastatin plus ezetimibe group may

2   explain why patients with diabetes experienced more

3   improvement than patients without diabetes with the

4   combination drug.

5   We also cannot extrapolate any benefit from

6   simvastatin plus ezetimibe to high-potency statins.

7   Some physicians might assume that adding Zetia to a

8   high-potency statin would be a good idea. But in

9   the absence of any evidence, we don't know what the

10   risks and benefits of such a combination would be.

11   Lastly, we all know that statins have

12   painful side effects that some are not able to

13   tolerate. Since Vytorin contains a statin, it does

14   not eliminate the risk of developing those painful

15   side effects.

16   In summary, the very small chance of any

17   potential benefit and the high cost of preventing

18   one CV event lead us to conclude that ezetimibe is

19   not the cure most patients desire.

20   We recommend revising the drug label to

21   limit the indication for Vytorin and Zetia to

22   patients with diabetes and patients older than age

1   75. The benefits in this group should be confirmed

2   with a study specifically designed for this

3   purpose. The label should also make it clear that

4   an effect on mortality has not been found.

5   IMPROVE-IT also cannot tell us anything

6   about the validity of LDL cholesterol levels as a

7   surrogate endpoint for CV events, or whether

8   patients who are already on high-potency statins

9   will benefit from the addition of ezetimibe.

10   Thank you for the opportunity to comment

11   today and for consideration of our views.

12   DR. R. SMITH: Thank you.

13   Will speaker number 2 please step up to the

14   podium and introduce yourself? Please state your

15   name and any organization you are representing for

16   the record.

17   DR. WOLFE: Good afternoon. I'm Sid Wolfe,

18   Public Citizen's Health Research Group, and do not

19   have any conflict of interest.

20   Before getting into some of the slides, I

21   thought it would be worthwhile reviewing the

22   context in which this comes. As has been pointed

out by a number of people, at this point, there's

no drug other than a statin that's approved for the

clinical benefit.

Obviously, if you inhibit cholesterol

synthesis or absorption, you lower LDL, and the

drugs that are on the market do all of these

things. But only the statins thus far have a

clinical benefit. So I'd like to review four of

the key studies that the FDA, in a memo about

5 years ago, admitted were the basis for the first

clinical approval.

First is a study, which again many of you

know, called WOSCOPS. It was a study done in

Scotland. The study was published in 1995, and it

was for primary prevention of pravastatin versus

placebo. There were about 6 and a half thousand

patients. In contrast to the relative risk

reduction in IMPROVE-IT of 6 percent, the relative

risk reduction was 31 percent, absolute risk

reduction 2.4 percent, and the upper 95 percent

confidence level was 0.43, again as opposed to

0.99.

1   The next one was also a pravastatin study

2   published in '96 and was for secondary prevention,

3   a study called CARE, which some of you may have

4   been involved in; 4,000 patients. Relative risk

5   reduction 24 percent, absolute 3 percent, and the

6   upper confidence level 0.36, again much lower than

7   the 0.99, the fragile 0.99 that's being discussed

8   today.

9   The third one was a fluvastatin study

10   published in 2002, a study called LIPS, and it had

11   just 1677 patients in it, a 20 percent relative

12   risk reduction. This is of clinical outcomes,

13   cardiovascular risk and heart attack, strokes.

14   Absolute risk reduction was 5.3 percent. And the

15   upper confidence level was 0.95.

16   Finally, the study that is most recent of

17   these, 2006. It was the study on atorvastatin

18   using high versus low dose, 10,000 patients, called

19   TNT. The acronyms of these studies are amusing at

20   best. The relative risk reduction there was

21   22 percent, absolute risk reduction 2.2, and the

22   upper 95 percent confidence level 0.89.

1   So those are the kinds of standards that

2   were used for changing from just cholesterol

3   lowering to a clinical benefit, and I would argue

4   that we need to retain those. The first slide

5   really goes over that for the -- can we turn the

6   lights down? Maybe not. Okay.

7   IMPROVE-IT, as you've heard this morning,

8   exemplifies not only the fragility of the

9   statistical significance, missing data, et cetera,

10   et cetera. If you took out the diabetics and the

11   people over 75, you would have a completely

12   insignificant finding.

13   I would just point out that 85 percent of

14   the patients in this trial, or close to that, were

15   diabetic -- excuse me, were over 75, yes -- under

16   75. So most of the patients in this trial, the

17   majority of patients, are either

18   diabetic -- nondiabetic, rather, or under 75. And

19   for that group, there isn't any statistical

20   significance.

21   So in addition to the fragility of the

22   statistical findings, the important difference

1   between statistical significance and clinical

2   relevance is also missing. This is figure 2 from

3   the Cannon paper that was published in June of this

4   year, and the lower left-hand including, as was

5   pointed out, the results from IMPROVE-IT, the big

6   circle there, the other three studies were not

7   statistically significant.

8   The studies that I've just gone over all up

9   here, where they are statistically significant,

10   with much more comfortable, less fragile, upper

11   95 percent confidence intervals, a larger relative

12   risk reduction, and a larger absolute risk

13   reduction.

14   These again are the data on the diabetics

15   age 75. So 15,000 of the patients in this

16   18,000 trial were under 75. Some of them were

17   diabetic also. So you still wind up with somewhere

18   between 65 and 70 percent of the people are either

19   under 75 or not diabetic. And the statistics there

20   show a p-value of 0.49 and 0.34 for the people that

21   are respectively nondiabetic and age under 75. So

22   no effect there.

1   So the question, the voting question that

2   you are faced is, do the efficacy and safety data

3   from IMPROVE-IT provide substantial evidence to

4   support approval of a claim that adding ezetimibe

5   to statin therapy reduces the risk of

6   cardiovascular events? I would vote no, for a

7   number of reasons.

8   One, which has been the subject of a lot of

9   the discussion this morning, is that the

10   statistical significance with a few events going

11   one way or another on the primary endpoint would go

12   1 or over 1 and would not be statistically

13   significant. Also, the clinical relevance is

14   small. As was pointed out, it's 2 percent absolute

15   risk reduction.

16   The tipping kind of concept has not only

17   been used for a primary analysis, but if you just

18   think again about the very vexing issue, which

19   several people mentioned in the discussion this

20   morning of hemorrhagic stroke. The hemorrhagic

21   stroke upper 95 percent confidence bound is 2.04

22   something, and the lower one is 0.95. Not too many

1 extra strokes would have to happen to make that

2 statistically significant.

3   So let's look at risk in the context of

4 nondiabetes and under age 75. The company, without

5 having the actual data, said, and I have no reason

6 to disbelieve them, that the risks in the under-75

7 and the nondiabetic were the same. So look at

8 these groups of people now who have no clinical

9 benefit but have the same risks, whether they are

10 taking simvastatin alone or simvastatin plus

11 ezetimibe.

12   How does it make sense to approve a drug the

13 majority of people who will be taking it, by the

14 desired labeling that the company seeks, will not

15 have any benefit and they will have -- they already

16 have reasonably low LDLs, as the company said and

17 properly designed their study not to be going for

18 people with higher LDLs.

19   So these people will have no benefit, no

20 statistically evident or even close to

21 statistically evident benefit, and some significant

22 risk, which might, with a few cases changed on the

1   hemorrhagic stroke, be increased for that.

2   So I think that, in summary, in comparison

3   with these other studies that I mentioned, which

4   were the pivotal studies according to this 2010 FDA

5   memo, that led to the approval for the various

6   primary or secondary clinical indications, this is

7   not even in the same ballpark at all.

8   They have obviously tried to get it there,

9   and the 18,000 people was a way of doing it. Some

10   of these other statistically insignificant studies

11   down in the relative risk range of this drug didn't

12   make it because they weren't powered enough.

13   But to power it up that high and still get

14   an upper confidence bound of 0.99 that is so

15   fragile, I don't think this justifies approving

16   this drug for anything other than what it is

17   approved for already, lowering cholesterol. No one

18   disputes that. Thank you.

19   **Clarifying Questions (continued)**

20   DR. R. SMITH: Thank you.

21   The open public hearing portion of this

22   meeting has now concluded, and we will no longer

1   take comments from the audience. The committee

2   will soon be addressing the discussion questions.

3   But before we do that, I'd like to continue some of

4   the discussion that we were having earlier, which

5   is not focused, in a sense, on the specific

6   questions, but just some final things to clarify

7   data. And so I'd really like to be focusing on

8   that.

9   I think to start, the sponsor has some data,

10   some slides, that perhaps we could start with and

11   work our way along.

12   DR. TERSHAKOVEC: Yes. Thank you. There

13   are a number of questions that came up in the

14   earlier discussion that we wanted to provide some

15   clarifying information. Dr. Paul DeLucca will

16   start out discussing some of the additional

17   supportive analyses that were mentioned that we do

18   have.

19   DR. DeLUCCA: There was some discussion

20   before the break about the amount of lost follow-up

21   in year 1. So I'd like to offer a few clarifying

22   comments first, and then we can move into some of

1   the additional analyses that were requested. Slide

2   up.

3   Of the approximately 8,000 potential lost

4   subject-years of follow-up that I had mentioned in

5   my presentation and FDA had presented in their

6   briefing book, this is a breakdown of where those

7   lost years of follow-up occurred.

8   Of the 8,000 potential lost years of

9   follow-up, about 8 percent of that occurred in

10 year 1. So about 92 percent of the potential lost

11 follow-up occurred after year 1. So I just wanted

12 to make that point clear first. So about 8 percent

13 year 1, and then about 92 after year 1.

14   So with that as a background, we did do some

15 stepwise analyses that looked at event rates per

16 year, as was discussed, and applied those event

17 rates in the year that the lost opportunity for

18 follow-up occurred. Could I see slide S-11,

19 please? Slide up.

20   What I'm displaying here are the observed,

21 pooled, off-treatment event rates by year. And as

22 has been discussed, the rates were higher in

1   year 1, so 15.6 percent in year 1, and then

2   declined to about 4.7 in year 2, and then a little

3   bit more after that.

4   So the approach we did with the stepwise

5   regression applied those rates directly in each

6   year of the study for lost opportunity for follow-

7   up. And the rates were similar between the two

8   treatment groups, and we could see no reason to

9   penalize one treatment group more than the other,

10   given that both were entering an experience off of

11   randomized treatment. So those are the rates we

12   used in the stepwise. Can we move to slide S-32?

13   Slide up.

14   So similar format to the results that I

15   presented earlier. This uses the stepwise

16   approach, applying those event rates per year. And

17   what you can see is on top of the 2,572 observed

18   ezetimibe/ simvastatin events, another 385 were

19   added, and another 380 were added in the

20   simvastatin-only group.

21   The hazard ratio that was observed using

22   this approach was 0.94, and the p-value was 0.024.

1   And just to compare the hazard ratio and the p-

2   value to what I had shown previously using the

3   exponential, which averaged over the entire off-

4   treatment period, the hazard ratio was 0.942, so

5   compared to 0.940, and the p-value was 0.029,

6   compared to the 0.024 that we observe here.

7   So quite similar results, at least from the

8   hazard ratio and the p-value, using the stepwise

9   approach, applying event rates by year in the

10   off-treatment period, compared to taking the

11   average off-treatment period event rate. Thanks.

12   DR. TERSHAKOVEC: Thank you.

13   DR. R. SMITH: Dr. Packer, a question?

14   DR. PACKER: I just wanted to ask one

15   question. You used 15.6 for the pooled

16   off-treatment for year 1, and the FDA had 19.7.

17   Can someone explain why those numbers are

18   different?

19   DR. DeLUCCA: For year 1, we were not able

20   to match the [inaudible - off mic].

21   DR. R. SMITH: Does the FDA have a comment

22   on that that might be helpful?

1   DR. CLARK: Yes. It looked like the Kaplan-

2 Meier rates. What we did was we used the data set.

3 What had previously been done, that we looked at

4 the sponsor code, was using a weighted scheme by

5 previous lipid-lowering status to estimate. We

6 estimated using that. And we also discounted

7 on-treatment time. So that decreased the number of

8 patient-years. So that can make it look a little

9 worse for only counting off-treatment time, during

10 the first year only.

11   DR. PACKER: Just so I understand, you did

12 it a little differently?

13   DR. DeLUCCA: We did also use the weighting

14 of the prior lipid-lowering therapy. Our analyses

15 were stratified by prior lipid-lowering therapy

16 versus not. And apparently we used a slightly

17 different method. I think an important point to

18 note is that only about 8 percent of that lost

19 follow-up occurred in the first year.

20   DR. PACKER: No, no, I understand. I just

21 wanted to make sure that what Jennifer just said

22 was that she looked at the events during the period

1 lost to follow-up. Did you --

2   DR. DeLUCCA: Yes. We did --

3   DR. PACKER: Did you do to the same thing?

4   DR. DeLUCCA: We did the same thing.

5   DR. PACKER: The difference between 19.7 and

6 15.6 may or may not sound big or small, and I

7 understand it's only referring to 9 percent of the

8 population. But that 19.7 could easily tip that

9 p-value to nonsignificant. And I'm just trying to

10 figure out what the difference is between the two

11 approaches.

12   DR. DeLUCCA: Yes. We did use the first

13 year off-treatment experience. We did attempt to

14 match the number. We did match many of the numbers

15 that were common in the briefing book, but we were

16 not able to match that number.

17   DR. R. SMITH: Yes. Dr. Fleming?

18   DR. FLEMING: So my understanding is -- in

19 fact, while I'm giving this number, could you pull

20 up the slide number 62 that the sponsor had shown

21 in your presentation?

22   My understanding is there is 9.1 percent of

1   the total person-years are missing from the

2   combination arm, and 8.6 percent are missing from

3   the simvastatin-alone arm. So there's about a

4   6 percent larger relative amount of missing data.

5   The sponsor's slide number 62, as soon as

6   they pull it up, was based on -- let's use the

7   off-treatment rate without the sophistication that

8   Dr. Packer had brought to the issue.

9   Let's just use the 9.59, the higher rate,

10   and use that higher off-treatment rate, assuming

11   it's exactly the same pattern of missingness in the

12   two arms, and there is an addition of 300 events

13   and 285 events, which makes sense because that's

14   consistent with 5.9 percent relative more missing

15   data on 300 events. It's going to be 15 extra

16   events.

17   Now, when you take into account the fact

18   that you also had a different pattern of

19   missingness where you were missing more early, the

20   sensitivity analysis that you were just showing us

21   is 385 against 380. That goes in the reverse

22   direction of what would logically be the case when

1   you take into account, as Dr. Packer said, not only

2   the higher event rate when you're off and the

3   6 percent higher amount of missingness, but factor

4   in the timing of the missingness.

5   So this analysis you showed makes sense.

6   The analysis you just showed now is illogical.

7   DR. DeLUCCA: The piecewise exponentially,

8   you mean, is illogical?

9   DR. FLEMING: So what is completely logical

10   is when you have 6 percent more missing data and

11   you assume a constant event rate, there will be

12   6 percent more imputed values. That's what you

13   showed, 300 against 285.

14   That doesn't take into account, though, the

15   differential timing of those missing values, which

16   are more frequently incurring early in the

17   combination arm when the event rate is higher.

18   When you factor that in, you would amplify this 15

19   difference. You decreased it.

20   So that last calculation you showed is

21   paradoxical. I'm trusting that this calculation

22   you're showing is correct. It's logical.

1   DR. PACKER: Can you explain what Tom just

2   said? Because I -- no, no, no, no, what I'm saying

3   is, what Tom's saying is that by imputing

4   appropriately, you should have, in the ezetimibe

5   group, 6 percent more events in the ezetimibe group

6   than in the placebo group. But your analysis

7   showed that you don't. How is that possible?

8   DR. DeLUCCA: The updated analysis we did

9   also had more events in the ezetimibe/simvastatin

10   group. But the difference is, the amount of

11   follow-up in the first year where the higher event

12   rate is occurring makes up a small amount of the

13   event rate. It takes into account how the event

14   rate changes over time. So it's going to be

15   completely dependent on how the event rate changes

16   over time and how it has to match up with where the

17   missing data experience is.

18   The analysis here smooths it all out and

19   takes an average over time and applies that

20   regardless of where the missing data is. But you'd

21   have to go back to the other slide and try to match

22   up where the rates are, how different the rates

1   might -- well, we applied a pool rate, but where

2   the rates are, and then the amount of missing over

3   time for that rate.

4   So if there's more missing data in a certain

5   time period, that rate is going to only influence

6   that time period.

7   DR. FLEMING: So my sense is we should go on

8   because there are more issues here that will be

9   very influential. Even if we take this bottom line

10   here as a reasonable approach, which reflects the

11   fact that the event rates are higher when you're

12   off study, you have 6 percent more missing on the

13   combination arm.

14   You would then impute 6 percent more events

15   as we get -- the hazard ratios now move from 0.936

16   to 0.942. The p-value is now coming very close to

17   the 0.039. Some of us would believe that this,

18   however, is not taking into account Dr. Milt

19   Packer's insight about timing, and the analysis

20   we've just heard is odd because it reverses the

21   direction of the correction.

22   I would just leave it that whether this is

1   the truth or, in fact, there's some greater

2   attenuation, one is lurking in the area of a 5 to

3   5.8 percent relative reduction, with p-values that

4   are in the neighborhood of 0.03 if not 0.04.

5   DR. R. SMITH: Do you have another comment

6   from the sponsor?

7   DR. KOCH: Just very briefly. Gary Koch.

8   My only relationship with the sponsor is through a

9   cooperative agreement with my university.

10   As was shown in an earlier slide in

11   Dr. DeLucca's core, the Kaplan-Meier curves for

12   time to study discontinuation come together. So

13   even though in year 1, there are a few more

14   patients discontinuing on the combination, in

15   year 2 it's starting to reverse, and in year 3

16   also.

17   So when you take these yearly rates into

18   account, you could get a somewhat different picture

19   because these curves are coming together. Whether

20   that's the full explanation, I don't know, but that

21   does need to be taken into account because by the

22   time you get -- slide up, please -- so by the time

1   you get out to years 5, 6, and 7, the curves are on

2   top of each other.

3   So I think the sponsor did try to do a

4   calculation taking yearly rates into accounts,

5   numbers of people discontinuing in each successive

6   year with each of their successive years of

7   follow-up. And that was the numbers that were

8   reported by Dr. DeLucca.

9   DR. R. SMITH: Dr. Fleming, did you have a

10   follow-up?

11   DR. FLEMING: Just for 10 seconds. All of

12   those comments have already been addressed in what

13   everybody has stated. The FDA and the sponsor were

14   very careful to look at total person-years missing.

15   The area between the curves reflect that difference

16   even though the curves come back together at the

17   end.

18   So there is 6 percent more total person-

19   years missing. That's been stated by everyone.

20   That, when you assume a constant rate, will lead to

21   15 excess events before you get to Dr. Packer's

22   correction. Those are facts. I don't think we're

1   quibbling about any of that.

2   At the end of the day, though, there will be

3   other issues that will also be very influential.

4   And I don't know that it's worth digging deeper

5   into this except to say that missingness does

6   matter here because it's occurring in more than 11

7   percent of people, and it's leading to 9 percent of

8   person-years missing when people are off study.

9   When they're off study, they're different.

10   They have higher event rate. And that event rate

11   is differential across time, and it's greater

12   missingness in the combination arm. And when you

13   make those corrections, you are attenuating the

14   estimate in about exactly the amount that you would

15   think.

16   That wouldn't matter if the estimate was

17   0.84 because we'd be making it 0.85. When it's

18   0.94 and we're making it 0.95, and the p-value is

19   now lurking around 0.05, maybe it does matter.

20   DR. R. SMITH: So that anticipates the

21   discussion, as I know you knew. And we will come

22   back and make sure we adequately, with the whole

1   panel, really, work our way through that point.

2   Now, I think there was more data that the

3   sponsor was going to present?

4   DR. TERSHAKOVEC: Yes. There were a few

5   other questions. There was a question on MI

6   severity. Dr. Cannon will address that.

7   DR. CANNON: Slides up. Two of the first

8   two slides are actually tables from the briefing

9   book, so that the first is table 19, to say how the

10   MIs were categorized. Slide up when you have them.

11   So this is again from the briefing book,

12   table 19. This displays the type of MI at the time

13   of presentation. So ST elevation MI, you can see,

14   is a quarter of all of these recurrent MIs. So a

15   large one, the vast majority, were categorized

16   initially as non-STEMIs.

17   When the CEC looked at all the troponins,

18   those that were unstable angina in this table were

19   actually positive. So the starting point, a

20   quarter of these are STEMIs who were sent off for

21   primary angioplasty, et cetera.

22   The next one is table 19 from the -- sorry

1   for the delays here; we had it all lined up,

2   but -- just to walk through what troponin values

3   mean clinically. So looking, this

4   characterizes -- and please, slide up -- so here

5   again, we have it broken out across the top. But

6   looking at the categories of troponin, T and I, one

7   needs to know the upper limit of normal.

8   So the CEC used this for each case, that

9   they had on each individual case, and said, is this

10 meeting the criteria greater than upper limit of

11 normal, et cetera? So this analysis is very

12 helpful, I think, but the difficulty is that the

13 upper limit of normal differs at every hospital.

14   So for troponin T, at the Brigham it's 0.04.

15 At Duke it's 0.1. So taking either of these of the

16 non-STEMIs and the STEMIs, those are either 3 to 6

17 times the upper limit of normal, or for the STEMIs,

18 sometimes like 20 to 30 times the upper limit of

19 normal. Then the same is for troponin I.

20 Similarly, at the Brigham it's 0.04. So that 1.6

21 is then 40 -- these are large MIs if one factors in

22 what is the upper limit of normal.

1   So setting aside troponin because we all go

2   crazy with troponins, but the next is death. And

3   so we just did a 2 by 2 table, my level of

4   statistics, of people who had -- slide up -- an MI

5   of yes versus no. And then over the rest of the

6   trial, and so these aren't Kaplan-Meier rates, just

7   a 2 by 2 table.

8   So people who had one of these MIs

9   categorized by the CEC died 3 times more frequently

10   than those who did not have the MIs; so another way

11   to say that these were bad events. Thank you.

12   DR. R. SMITH: Yes. Dr. Kaul, follow-up on

13   that?

14   DR. KAUL: Yes. I just want to respond to

15   that. I think what Dr. Cannon is talking about

16   refers to analytical sensitivity, but the following

17   slide refers to what the clinical relevance of

18   those MIs are. What I was interested in, just by

19   looking at the levels of troponin, is are you able

20   to quantify the extent of myocardial damage, which

21   then will lead to downstream events?

22   So these are three separate issues. I did

1   my own analysis, and when you look at the total

2   number of MIs and how many of them were fatal, so-

3   called case fatality rate, for MI, it's roughly

4   about 3 percent. And for stroke, the case fatality

5   rate is 17 versus 12 percent.

6   Then you further break it down to

7   hemorrhagic stroke. The case fatality rate is 47

8   versus 26 percent. So even though there were fewer

9   hemorrhagic strokes, a much higher proportion,

10 roughly about seven- to eightfold compared to

11 myocardial infarction, resulted in death,

12 cardiovascular death.

13   So that's how we can arrive at the clinical

14 relevance of these endpoints. The composite

15 endpoint is essentially driven by nonfatal MI and

16 nonfatal stroke. And we are still grappling with

17 the clinical relevance of those nonfatal events, so

18 that sort of information is quite helpful in

19 arriving at that.

20   DR. TERSHAKOVEC: We wanted to move on.

21 There were questions --

22   DR. R. SMITH: Do you have a comment

1   immediately relevant to that point?

2   DR. CANNON: It's not immediately relevant.

3   DR. R. SMITH: Okay. We'll make sure we get

4   back to that.

5   Yes, sponsor?

6   DR. TERSHAKOVEC: There are questions about

7   subgroups and assessment of subgroups. So Chris,

8   Dr. Cannon, was going to start, and with

9   Dr. Braunwald and --

10   DR. CANNON: I guess the starting point for

11   the subgroups as I presented them is that we've

12   been taught by colleagues in trials that we often

13   get very excited about looking at this or that

14   subgroup. But many have said the key in looking at

15   a subgroup is their consistency across subgroups in

16   general.

17   As I showed, all of the point estimates fell

18   to the left of the line of unity, so there really

19   was good consistency across subgroups. Of the two

20   subgroups out of 23, it's very close to the one

21   that you'd expect simply by dividing the 0.01, 0.05

22   level. So we feel that this is really what would

be expected, is to see one or two subgroups that

might have their interaction p-value.

Now, much has been made of the hazard ratio

in the subgroup. But an interaction p-value -- and

who am I to speak about this. But it says that the

hazard ratio may be different. It doesn't speak to

the effect in each subgroup. For that, one has to

look at the confidence interval in that subgroup.

So in, for example, the diabetes subgroup of

great interest, the nondiabetic subgroup has 3,000

events -- that sounds amazing -- and 15,000

patients. But as we've been discussing in the main

trial, it took every one of our 5,250 events in

order to demonstrate with adequate power the

expected difference in clinical events based on how

much LDL lowering we would have.

So if we then pull out a group with only

3,000 events -- actually, I haven't got the exact

power of that, but it's very low, to expect that we

could determine what is the effect in this

seemingly very large subgroup.

Then the third point on subgroups is to ask

1   had we prespecified this? And many people, in

2   talking about subgroups, they encouraged, you

3   should prespecify if there's a hypothesis. Well,

4   there's no hypothesis that LDL lowering would or

5   wouldn't work in diabetics only or in nondiabetics.

6   In fact, the hypothesis is exactly the opposite.

7   And Colin Baigent will be able to share the data

8   from the CTT, that LDL lowering leads to clinical

9   benefit in just about every subgroup ever looked

10   at.

11   So that's the proviso, I think, in

12   approaching. I guess a final point -- we've

13   alluded briefly to the genetic data supporting

14   genetic variance in HMG-CoA reductase and in

15   NPC1L1. When that's looked at in diabetics and

16   nondiabetics, it's exactly the same lower risk

17   observed in the things with variance.

18   So biologically, we didn't have a hypothesis

19   to support that, and all the data go against

20   picking out that subgroup. So overall, we come

21   back to the overall result. Nonetheless, the

22   Kaplan-Meier curve was asked for. Dr. Braunwald

1   will share that.

2   DR. BRAUNWALD: Could I have the slide up,

3   please? This is two pairs of Kaplan-Meier curves.

4   The upper pair -- dim the lights, please -- shows

5   the solid line, the combination, and the one that

6   is barely made can be seen above it, which is the

7   dotted line. Can the lights go down? No?

8   DR. R. SMITH: We can see it pretty well.

9   DR. BRAUNWALD: It is the simvastatin alone.

10 And there clearly is a marked difference. The

11 hazard ratio is 0.86, as you can see. The bottom

12 two curves are the patients without diabetes, and

13 they are virtually superimposed. The dotted one is

14 a hair above the solid line. And the

15 difference -- oh, thank you -- is a hazard ratio of

16 0.98.

17   So it would be very easy to look at this and

18 to say that patients who are not diabetic are

19 unlikely to benefit from the combination of the two

20 drugs. But I think the fallacy of looking at only

21 one characteristic, a univalent endpoint -- can you

22 go on to the next slide, please -- patients who are

1   nondiabetic -- yes, slide up, please.

2   So this breaks the group down into four

3   groups, under 75 nondiabetic, under 75 and

4   diabetic, over 75 and not diabetic, and over 75 and

5   diabetic. And I call your attention to the third

6   row. These are patients who are not diabetic.

7   They're over 75. They have a hazard ratio of 0.79.

8   This is a group of nondiabetics who appear

9   to benefit from the combination. And if we looked

10   at all of the characteristics of both the diabetics

11   and the nondiabetic patients, we would see a great

12   deal of overlap.

13   One of the things that does become apparent

14   is that as the overall risk goes up, the hazard

15   ratio is reduced. The top line of the under 75 and

16   not diabetic have a Kaplan-Meier percentage

17   of -- 28.8 is the lowest one there, and that's the

18   group that doesn't show any hazard ratio reduction.

19   So the main point is, just because they're

20   not diabetic doesn't mean that they can't enjoy the

21   benefits of these two drugs.

22   DR. R. SMITH: And Dr. Baigent wanted to

1   conclude with some comments on subgroups, and then

2   also a few comments on hemorrhagic stroke.

3   DR. BAIGENT: I'm going to show the slide in

4   a moment. I would like to just begin by reminding

5   people how dangerous subgroups are. Over the

6   years, as cardiologists, and not only in cardiology

7   but many other specialties, we believe subgroups,

8   and we've ended up mistreating patients because

9   we've got it wrong.

10   The truth is that most studies that we do

11   are not big enough on their own to allow a subgroup

12   analysis. Now, the IMPROVE-IT study, even though

13   it had over 5,000 events, had a p-value of 0.016,

14   there simply aren't enough data there to subdivide

15   into subgroups reliably.

16   In order to do that, you really need much

17   larger amounts of data and much, much clearer

18   signals, much bigger effects. So if I go to the

19   slide that I'm going to show, if I may, please,

20   these are data from the Cholesterol Treatment

21   Trialists collaboration.

22   You'll see, if you can see, at the bottom,

1   there are 24,000 major vascular events. And these

2   are big effects that we've seen in the 27 trials

3   that are included in this meta-analysis.

4   So we have a huge amount of data with which

5   to conduct subgroup analysis. And when we do do

6   that with statins, what we see is very clear

7   evidence that for every minimal reduction in LDL

8   cholesterol -- when it's adjusted for the magnitude

9   of the treatment effect, in other words -- the

10   22 percent reduction in risk in major vascular

11   events is consistent in all the subgroups that have

12   been studied.

13   So if you just home in on diabetes, in the

14   second one down, the second subgroup down, you can

15   see it's absolutely consistent in diabetics and

16   nondiabetics. Similarly, there's no interaction by

17   age.

18   So I think we need to be grounded when we

19   start thinking about delving into subgroups in what

20   was a study that was only just large enough to

21   demonstrate the main effect. So we shouldn't be

22   misled into trying to understand more than it is

1   possible to understand from a single study.

2   So that's the first comment I'd like to

3   make. If I could have the next slide, I'd like to

4   comment about hemorrhagic stroke, which has come up

5   in the discussion this morning. Yes, please, thank

6   you.

7   Not everybody is familiar with the evidence

8   on hemorrhagic stroke. Of course, epidemiological

9   studies have suggested that people with lower LDL

10   cholesterol may be at higher risk of hemorrhagic

11   stroke. And it's taken a lot of data from

12   randomized trials of statin therapy to have enough

13   information about hemorrhagic stroke to be able to

14   demonstrate that there is in fact a small excess

15   risk of hemorrhagic stroke in conjunction with

16   statin therapy.

17   So if you look at the bottom there,

18   22 trials in total were able to provide data to the

19   CTT, and there was a 21 percent increased risk of

20   hemorrhagic stroke.

21   So the very fact that we have seen an excess

22   risk of hemorrhagic stroke in the IMPROVE-IT study

1   suggests to me that we are looking at something

2   that is real. If LDL lowering increases the risk

3   of hemorrhagic stroke, we should expect to see a

4   signal in the IMPROVE-IT study. That's the first

5   comment.

6   The second comment is that hemorrhagic

7   stroke is more likely to be fatal than

8   nonhemorrhagic stroke. And so we expect to see an

9   increased risk of fatal stroke as a result of the

10   phenomenon that is associated with statin therapy.

11   In fact, if you look in the CTT, the impact

12   of statin therapy on stroke mortality, there isn't

13   a significant reduction in stroke mortality because

14   a reduction in ischemic stroke mortality is

15   balanced by an excess of hemorrhagic stroke

16   mortality.

17   So we shouldn't expect to see benefits where

18   the statin evidence doesn't suggest that there

19   should be a benefit. On mortality, we only see

20   reductions in coronary mortality in association

21   with statin therapy. We do not see it for stroke

22   mortality.

1   So the question has to be, are the IMPROVE-

2   IT data consistent with what we expect to see based

3   on a small reduction in LDL cholesterol,

4   understanding the evidence on LDL lowering from the

5   CTT? That's the end of my comment. Thank you.

6   DR. R. SMITH: Yes?

7   CAPT BUDNITZ: Dan Budnitz. Just a

8   clarifying question. The first slide that you

9   showed, with subgroups of patients with diabetes

10   and age, just to clarify, those were all for statin

11   trials. Right? Those were not other --

12   DR. BAIGENT: That's correct, yes.

13   CAPT BUDNITZ: Only statin trials?

14   DR. BAIGENT: Yes.

15   CAPT BUDNITZ: Okay. Thank you.

16   DR. R. SMITH: Dr. Shamburek, a question?

17   DR. SHAMBUREK: Is there any data from the

18   SEAS or SHARP data as far as hemorrhagic stroke

19   that could actually be used here?

20   DR. BAIGENT: Yes. The SHARP data are not

21   included in this particular meta-analysis because

22   it appeared too late to be included. But from

1   memory, there were something like 45 versus 37

2   hemorrhagic strokes in SHARP. So it went in the

3   expected direction, but it wasn't on its own

4   statistically significant. I can't recall the

5   result for SEAS.

6   DR. TERSHAKOVEC: Yes. For SEAS, the

7   numbers are very small. They're not imbalanced.

8   And for our overall development program, which

9   mostly in longer-term lipid trials, there is no

10   imbalance. It was very small numbers.

11   DR. R. SMITH: Thank you. Yes, Dr. Packer?

12   DR. PACKER: I was going to ask a question

13   that I didn't have time to ask. Is that okay?

14   From earlier today?

15   DR. R. SMITH: Yes. That would be great.

16   Before that, Dr. Blaha, I think you had

17   asked for some data, then we'll come right back

18   to --

19   DR. BLAHA: Regarding the diabetes question,

20   of course the CTT expresses cholesterol lowering

21   per millimole per liter. So if you had a greater

22   reduction in cholesterol, one could see a greater

1   effect in, for example, a diabetic subgroup.

2   So I was curious to see if we could see the

3   data for non-HDL or ApoB lowering, other

4   atherogenic lipoprotein particle lowering, in

5   patients with diabetes versus no diabetes.

6   DR. R. SMITH: Right. Are those data

7   possibly handy? I know that did come up earlier.

8   Perhaps it wasn't made clearly enough that we were

9   hoping to see that.

10   DR. TERSHAKOVEC: We don't have that. We're

11   working on that.

12   DR. R. SMITH: Okay. If you do -- you're

13   working it right now? So if you do come up with

14   that, just flag us and let us know, and we'll

15   continue. And then we'll get that when you've got

16   it. That's great.

17   Before I go over here, Dr. Kaul? Okay.

18   Yes. We'll go ahead. And then I want to get over

19   to Dr. Packer.

20   DR. KAUL: Yes. Professor Baigent says that

21   the stroke data line up, especially the hemorrhagic

22   stroke data line up, so it must be the LDL. But

1 the diabetes data don't line up. And as was

2 mentioned by Dr. Budnitz, the CTT is based on a

3 statin versus a statin or a statin versus a

4 placebo. The IMPROVE-IT is statin plus something

5 else versus a statin.

6   Maybe there's something unique. So how can

7 we discount that possibility? It's not been

8 systemically explored. Just because the

9 hemorrhagic data line up doesn't necessarily mean

10 this is all LDL-driven.

11   DR. R. SMITH: Again, I want to come back to

12 that when we're actually dealing with discussion

13 questions. Where we are right now is questions

14 that precede what we know is coming in terms of

15 specific discussion.

16   Dr. Packer?

17   DR. PACKER: Yes. I wanted to ask Chris

18 just a question, and maybe you can -- Chris?

19   DR. CANNON: Yes. I'm coming up.

20   DR. PACKER: Oh, okay. I just want to make

21 sure. After an MI, do you measure people's LDL

22 clinically?

1   DR. CANNON: Yes.

2   DR. PACKER: And what number motivates you

3   to do something?

4   DR. CANNON: In my clinical practice, of

5   what would we aim for?

6   DR. PACKER: Well, I don't want to make it

7   complicated. I just want to know what you would

8   normally do.

9   DR. CANNON: Usually start high-dose statin,

10   check LDL, and aim for -- previously less than 70.

11   Currently, I try and aim for more around 50 or

12   thereabouts, 50 plus or minus.

13   DR. PACKER: Okay. So if someone had -- you

14   put them on the high-dose statin and they were 50,

15   you would think that that was okay?

16   DR. CANNON: Yes.

17   DR. PACKER: After an acute coronary

18   syndrome?

19   DR. CANNON: Yes.

20   DR. PACKER: So can you tell me, is

21   ezetimibe indicated in patients post-ACS to reduce

22   coronary vascular events regardless of cholesterol,

1   or only in people with cholesterols that you would

2   treat?

3   DR. TERSHAKOVEC: I can answer. The

4   indication is for lipid-lowering. It's not related

5   specifically to an event.

6   DR. PACKER: No, no, no, no.

7   DR. CANNON: You're asking for --

8   DR. PACKER: No. No. No, no, no. That's

9   not true. No.

10   DR. TERSHAKOVEC: I'm saying the -- I

11 thought you meant the indication now.

12   DR. PACKER: No. I want to know the

13 indication you're seeking. The indication you're

14 seeking is that you don't have to know the

15 cholesterol. After you have an -- the indication

16 you're seeking is -- I just want to make sure.

17   I want to make sure I get it right, that

18 it's to reduce the risk of cardiovascular events in

19 patients with coronary heart disease. And there's

20 no mention that there is a cholesterol trigger to

21 that. Is that correct?

22   DR. TERSHAKOVEC: That's right. That's what

1   the indication is, that it would be up to the

2   physician's judgment of whether they think it would

3   be appropriate.

4   DR. PACKER: Sure. So I'm just asking

5   Chris, if the LDL cholesterol was 50, you would not

6   give it. Right. So the claim that the sponsor is

7   asking for has no cholesterol link to it?

8   DR. CANNON: The regulatory language is

9   probably outside of my realm. But the goal of the

10   trial was to try and provide evidence that if you

11   use the drug to lower LDL, that it would reduce

12   events.

13   DR. PACKER: But that's not what the sponsor

14   is proposing.

15   DR. R. SMITH: Dr. Packer, we will be able

16   to come back to the issues of -- further questions.

17   DR. PACKER: No, no. But I just -- I want

18   to make -- yes. I just want to make sure.

19   Chris, just to make sure, if you had the

20   patient and you put them on the ezetimibe, and the

21   LDL didn't go down after a requisite period of

22   time, would you maintain them on the drug?

1   DR. CANNON: I'd talk to them about

2   compliance because --

3   DR. PACKER: No, no, no.

4   DR. CANNON: I realize. I think you're

5   asking a very good question of -- so what's

6   interesting is we did see -- the FDA presented the

7   current indication label for simvastatin. So it

8   simply says simvastatin is indicated to reduce, in

9   that case, cardiovascular mortality or morbidity, I

10   think. And so that's the way that indications are

11   written. If you've shown that there can be a

12   reduction in an event, that's written that way.

13   I think, very importantly, how would we use

14   this and what patient should get it? So I've

15   actually asked myself the question before we do the

16   trial, would we mean that you have to give each and

17   every single pre-coronary syndrome patient statin

18   and ezetimibe? Or would you do what we always do,

19   is you start with a statin, check the LDL, and add

20   ezetimibe?

21   That's for the guideline committees to sort

22   out, of exactly how and when.

1   DR. PACKER: Oh, my God. I hope you're not

2   going to rely on the guideline committee.

3   (Laughter.]

4   DR. CANNON: Well, Scott Grundy is taking

5   over, so I think we're -- but I think that's a

6   different group. And so what we provide here, I

7   think, is evidence that if you do add it, it will

8   in fact translate into a reduction.

9   DR. PACKER: Here's the --

10   DR. R. SMITH: And for this committee, I

11   think the charge that we really receive from the

12   FDA is really to address the questions that they're

13   asking in the context of what has been presented

14   for --

15   DR. PACKER: The sponsor is asking for a

16   claim not linked to a cholesterol level or a

17   cholesterol reduction.

18   DR. R. SMITH: I understand. And getting

19   clarity on that is helpful. But again, we're not

20   in a position of amending that, I don't believe, in

21   terms of what we're being asked to weigh. We may

22   come back to talk about that as we get to that.

1   DR. PACKER: Well, if we -- I'm sorry. But

2   if we're not allowed to understand what the sponsor

3   wants --

4   DR. R. SMITH: Right. No. We are allowed.

5   And is there clarity? So that I think we have

6   clarity, and I thank you for that. That's helpful.

7   DR. PACKER: But does the sponsor want a

8   linkage to cholesterol in the claim? Is that what

9   the sponsor would like? Right now, the wording of

10   the claim is for every patient who comes in with an

11   acute coronary syndrome or with chronic, stable

12   coronary heart disease, that this drug is indicated

13   to reduce cardiovascular events regardless of

14   whether they have a high or low cholesterol,

15   regardless of whether their cholesterol has been

16   demonstrated to be reduced by the drug. Is that at

17   that correct statement?

18   DR. TERSHAKOVEC: Specific language around

19   the label will be a point of discussion with the

20   agency. If there were requests for restrictions

21   around that relating to recommendations about lipid

22   levels, where they'd be used, then that would be

1 something that we would consider, yes.

2   DR. R. SMITH: And that's something,

3 Dr. Packer, that will be certainly totally

4 appropriate for us to weigh in on in my opinion, as

5 well. Absolutely.

6   DR. PACKER: I just wanted to know what they

7 wanted.

8   DR. R. SMITH: Yes. Dr. Kaul?

9   DR. KAUL: Yes. The treatment effects and

10 improvement are quite distinct from those observed

11 with intensive LDL lowering in the PROVE-IT trial,

12 and I think Dr. Everett already mentioned to the

13 temporal discordance.

14   In the PROVE-IT, the treatment benefits

15 emerge early, by day 30, statistically significant

16 around 6 months. In the IMPROVE-IT, the treatment

17 benefits emerge after one year. So that's one

18 point of discordance.

19   The other one is in the endpoints that are

20 driving the primary endpoint. In the PROVE-IT, the

21 primary composite endpoint, which was very close to

22 the IMPROVE-IT endpoint, was driven by reduction in

1   unstable angina and coronary revascularization, not

2   by nonfatal MI or nonfatal stroke or cardiovascular

3   death. And in all fairness, immediate follow-up

4   was 2 years, and the events were low with regards

5   to these hard endpoints.

6   But in the IMPROVE-IT, it was the opposite.

7   The majority of the events were coronary

8   revascularization, and there was not a

9   statistically distinguishable treatment effect, or

10   in unstable angina, where the numbers were low. It

11   was only seen in nonfatal MI and nonfatal stroke.

12   So how do we reconcile these differences?

13   And this perhaps weighs into Dr. Budnitz's

14   question. In a high-intensity versus low-intensity

15   statin, in an acute coronary syndrome trial, you

16   expect plaque stabilization. You expect reduction

17   in unstable angina. You expect reduction in

18   revascularization.

19   But maybe in this setting, it's quite

20   different. That's why we're not seeing a treatment

21   effect in the endpoints that obviously should be

22   shifted with LDL lowering. So perhaps the sponsor

1   or Dr. Cannon would like to weigh in and explain

2   the discordance between the two trials.

3   DR. CANNON: There's probably less

4   discordance than one would think, thankfully. One

5   of the issues we're talking a lot about is power,

6   et cetera, so PROVE-IT, it's interesting how small

7   it is. It had a thousand endpoints, so that's

8   one-fifth. And the amount of follow-up was 4,000

9   patient-years for a median of 2 years, so that's

10   8,000 patient-years of follow-up. We're talking

11   here about 80,000 patient-years of follow-up, so

12   interesting.

13   So when we look at what was different in

14   PROVE-IT, is that the gold standard, it's precious

15   little data. So we did a meta-analysis of the

16   first four of the high-dose versus regular-dose

17   statin, so including A-to-Z, TNT, and IDEAL. And

18   the pattern is actually very similar, so that there

19   was not a difference in death or cardiovascular

20   death, but there was a difference in MI and stroke.

21   And one slight difference is that the difference in

22   revascularization in those older trials was

1   statistically significant, whereas for us, it was

2   5 percent lower but not significant. So I think

3   they're more similar than different.

4   DR. R. SMITH: Dr. Proschan?

5   DR. PROSCHAN: A lot has been made of the

6   missing data, and I absolutely agree that a lot

7   should be made of the missing data. But one issue

8   is, my understanding is you're not considered

9   missing if you've had the primary outcome. And

10   more people had the primary outcome in the

11   simvastatin-only group.

12   So that does need to be taken into

13   consideration, although, still, the difference in

14   first year seems beyond -- even if you adjust for

15   that, it's pretty overwhelming that there's a

16   statistically significant difference. I'm just

17   wondering, if there's a reason for that, if you

18   know the reason for that.

19   Also, is there a mechanism for why there

20   would be more hemorrhagic stroke? I understand the

21   theory about lowering cholesterol more might itself

22   cause hemorrhagic stroke. But is there any other

1   possible reason for that?

2   Then the final question, in the decision to

3   increase the sample size, I understand that that

4   was based on outside data, not the trial data, in

5   terms of treatment difference. But I'm assuming

6   that that's a decision that was also run by the

7   DSMB to get their approval, and of course the DSMB

8   is seeing data by arm. And I'm just wondering if

9   that's the case.

10   DR. R. SMITH: Thank you. Yes. So there

11   are three points there.

12   DR. PROSCHAN: Right.

13   DR. TERSHAKOVEC: Regarding the modeling

14   that was done and the adjustments, including the

15   dropout rates and things like that, Dr. DeLucca can

16   address.

17   DR. DeLUCCA: You're correct, Dr. Proschan.

18   To have an event meant you had complete follow-up

19   for the primary endpoint. There were more primary

20   endpoints in the simvastatin-only group, so that is

21   one factor.

22   As far as those subjects who discontinued in

1   year one, we did look at medical histories and

2   baseline characteristics in AE profile, and they

3   were similar between the treatment groups. We

4   looked at reasons for dropping out, and the

5   predominate reason was withdrawal of consent. And

6   it was similar between the two treatment groups.

7   So we did look to see if there was anything

8   different in the profile. Nothing that was obvious

9   or jumped out to explain it.

10   DR. TERSHAKOVEC: I'll ask Professor Baigent

11   to address the next two questions. One was the

12   mechanism of hemorrhagic stroke, and also the

13   sample size. I will note that Professor Baigent

14   acted as a consultant for us when we were having

15   the sample size readjustment consideration, so he

16   was well informed about those discussions.

17   DR. BAIGENT: The question whether there's

18   anything else that might explain the hemorrhagic

19   stroke, I don't think anyone really knows why lower

20   LDL cholesterol is associated with increased risk

21   of hemorrhagic stroke. And I'm not aware of any

22   other suggestive mechanism whereby ezetimibe, for

1   example, might be associated with an increased risk

2   of hemorrhagic stroke. So I'm afraid I don't know,

3   is the answer.

4   On the issue of the modeling, what happened

5   was the CTT meta-analysis was something that took a

6   long time to generate because we had to get data

7   from quite a lot of trials, individual patient

8   data, and analyze it. And so IMPROVE-IT got going

9   before the CTT, what eventually became the 2005

10   publication in the Lancet, was published.

11   So when we were asked to help with the

12   IMPROVE-IT study, I presented data. I was asked to

13   think about whether there would be adequate power

14   in the IMPROVE-IT study. And I modeled the data

15   based on what we understood from the 2005 meta-

16   analysis.

17   For the reasons that we discussed this

18   morning, there were a couple of things that we felt

19   had been misjudged. One was the lack of any or the

20   diminished effect in the first year when the event

21   rate is highest.

22   The second was the relationship between the

1 LDL reduction that was likely, making allowance for

2 the fact that you've got dropouts, which is

3 something that we talked about earlier, too, and

4 the risk of the primary event.

5   We didn't have much information from the CTT

6 on the unstable angina, but we were conservative in

7 that, and that resulted in the revised assumption.

8 So none of it was based on IMPROVE-IT data,

9 unblinded data, and in fact, the DSMB, to my

10 knowledge, at least, was not involved in

11 the discussion, as is appropriate because they're

12 unblinded.

13   They wouldn't have been involved in the

14 discussion. What happened was Merck went away with

15 the information from that advisory board and

16 decided, based on what had been presented, to

17 revise the sample.

18   DR. R. SMITH: Dr. Teerlink, did you have a

19 question?

20   DR. TEERLINK: They've been addressed.

21   DR. R. SMITH: Okay. And Dr. Everett, did

22 you have one?

1   DR. EVERETT: Just quickly, and this again

2   maybe is for Dr. Cannon, but the first thing I

3   wanted to say was that prior to the break, there

4   were some comments about the severity or lack of

5   severity of Q wave versus non-Q wave MI.

6   I think Dr. Cannon has addressed those a

7   little bit. But I think that it's important to

8   emphasize that troponin is really the gold standard

9   for defining myocardial infarction, and they're

10   serious, generally speaking.

11   That said, Dr. Cannon, you showed some

12   data that showed that, essentially, the rate of

13   cardiovascular death amongst those who had had an

14   MI was three times those who had not. And yet I'm

15   looking at a point estimate, and I, again, don't

16   expect it to be significant because of the sample

17   size you mentioned earlier, sample size issues.

18   But for cardiovascular death, it's 1.00. And I'm a

19   little bit confused about that, I guess.

20   Then the other thing is the point estimate

21   for coronary heart disease death, which in point of

22   fact excludes death from hemorrhagic stroke, is

1   0.96. Now, of course, both of the confidence

2   intervals are reasonably broad.

3   But if indeed these MIs are significant,

4   clinically significant, which I believe that they

5   are just from my own clinical practice, and they

6   have some conversion rate to cardiovascular death,

7   why are we not seeing even the whisker or the

8   whisper of a signal with respect to cardiovascular

9   death?

10   DR. CANNON: An excellent question. This

11   has actually come up in thrombolysis trials and

12   antiplatelet trials, and the time horizon of the

13   active treatment versus subsequent mortality is

14   likely the best explanation.

15   We're also then talking about just the

16   recurrent MI. So there's a thousand or so, instead

17   of 18,000, to look at what's the outcomes of those

18   thousand that happened under observation of a

19   shorter period of time, so were vastly underpowered

20   to see any subsequent differences in mortality. I

21   think that's the short --

22   DR. EVERETT: Yes. I don't disagree. But

1 you have the benefit of having a long trial,

2 actually, and some amount of events that happened

3 early on, and then an extended -- as opposed, for

4 example, to PROVE-IT, which has 2 years, we now

5 have 6, on average, and some patients for longer.

6   So the surprising thing was the precision

7 with which that estimate hit 1.00 as opposed to

8 0.96 or 0.94 or something like that.

9   DR. CANNON: As you note, coronary heart

10 disease death was 0.96, so a 4 percent

11 difference -- our overall effect was 6 percent, so

12 it's not so far off. I think Mike Blazing did a

13 nice calculation, that for us to have enough power

14 to see a statistical difference of 10 percent,

15 which is already pretty big, on coronary heart

16 disease death using the event rates we had, it

17 would take 60,000 patients and 10 years of active

18 treatment and follow-up.

19   So we have this big trial and it's sort of a

20 paradox of how come we can't see this or that. And

21 we come back to actual power ends up being limited

22 despite the very large sample sizes.

1   DR. R. SMITH: Are there any more clarifying

2   points or questions? Yes, Dr. Kaul?

3   DR. KAUL: Yes. And this is for the FDA,

4   and this is part of the voting question.

5   Could you clarify what you mean by

6   "substantial evidence of benefit"? Are we to take

7   our own meaning of "substantial," or the statutory

8   criteria?

9   DR. R. SMITH: I'm wondering if we should

10   come to those point by point as we go. We

11   absolutely should come to that, but it would be

12   better to step through these?

13   (Dr. Guettier nods head affirmatively.)

14   **Questions to the Committee and Discussion**

15   DR. R. SMITH: So we might be better -- I

16   think we're ready now to move to the questions,

17   discussion questions, and the final one, a voting

18   question. Before we do that, Dr. Smith, do you

19   want to make any comments from the FDA perspective?

20   Go ahead. All right.

21   So we'll proceed with the questions to the

22   committee and, Dr. Kaul, clarifying them as we go,

1 and the panel discussions.

2   I'd like to remind the public observers that

3 while this meeting is open for public observation,

4 public attendees may not participate except at the

5 specific request of the panel. I'll say more about

6 the voting question when we get there. But I think

7 for now we should proceed to the first discussion

8 question. I will read this.

9   Discussion. In the IMPROVE-IT trial, 2572,

10 28.4 percent, of 9,067 patients in the ezetimibe/

11 simvastatin arm and 2742, the percent you see in

12 number, in the simvastatin arm had at least one

13 primary composite endpoint event, defined as

14 cardiovascular death, nonfatal myocardial

15 infarction, nonfatal stroke, documented unstable

16 angina requiring hospitalizations, or coronary

17 revascularization at least 30 days after

18 randomization.

19   According to the primary analysis, intent-

20 to-treat, this yielded a 6.4 percent relative risk

21 reduction for ezetimibe/simvastatin compared with

22 simvastatin, HR 0.94, and with the parameters that

1   you see there, p equals 0.016.

2   Provide your interpretation of the efficacy

3   results from the IMPROVE-IT trial. Specifically

4   discuss the magnitude of the observed treatment

5   effect, the robustness of the result of the primary

6   composite endpoint, considering, for example, the

7   extent and pattern of missing follow-up time, and

8   any comments you may have regarding observed

9   effects on components of the primary composite

10   endpoint or secondary endpoints.

11   So I'd like to first ask the panel members

12   if there are points that they would like to clarify

13   about the question before we dig into your thoughts

14   about the question.

15   (No response.)

16   DR. R. SMITH: Okay. So this is open for

17   comment. And if you have expressed opinions

18   previously relevant to this question, it would be

19   helpful to re-express them now because we really

20   want to bring together a consensus or spread of

21   ideas and opinions and positions from this group.

22   Dr. Blaha, did you have your hand up? Okay.

1   Well, you've got the floor. Oh, did I miss?

2   Dr. Heckbert, excuse me, and thanks for keeping me

3   straight.

4   DR. HECKBERT: Yes, hi. Susan Heckbert.

5   Yes. What is my opinion? It is that, really, the

6   treatment effect is really quite small here. And

7   it's even small before you take into account the

8   issues regarding the potential effect of missing

9   observation time.

10   I agree with the opinion that has been

11   expressed previously, that the assumption that

12   those who are missing observation or follow-up time

13   have the same event rates as those who have

14   complete data really is not a safe assumption, that

15   it's not one we should make.

16   So I guess I would say that my impression is

17   that the results are -- it's a fairly weak effect

18   and it's not a particularly robust effect.

19   DR. R. SMITH: Dr. Blaha?

20   DR. BLAHA: Thank you. I agree that the

21   effect is small, and clearly that's an important

22   thing to take into account clinically. And I think

1   all of us who are clinicians take that into

2   account.

3   But I will say that I'm impressed, though.

4   The results of the IMPROVE-IT trial match what we

5   would have expected from the CTT, from what we know

6   about the LDL hypothesis. And I think this trial

7   is a remarkable trial in terms of its length and

8   the database it produces.

9   So in my opinion, notwithstanding some of

10   our discussions about missingness and so forth, the

11   results of the IMPROVE-IT trial, to me in total,

12   confirm much of what I understand about LDL

13   lowering and produced a small, but expectedly

14   small, effect on clinically important endpoints and

15   I think has practice implications.

16   DR. R. SMITH: Dr. Proschan?

17   DR. PROSCHAN: I also agree that that's a

18   pretty small effect. And I think you have to bring

19   in the hemorrhagic stroke here because -- I know

20   that's coming up later, but you have to consider

21   that with the small effect.

22   It was postulated that LDL lowering itself

1   might lead to hemorrhagic stroke. But in patients

2   at really high risk where you're having a big

3   effect on other things, MIs and ischemic strokes,

4   that's a lot different.

5   You might be able to tolerate a little

6   increase in hemorrhagic stroke if you're having a

7   big effect on other things. Here, you're not

8   having a big effect on other things. So I think

9   that makes it a lot more important.

10   Now, the other issue that it talks about is

11   looking at the components of the primary analysis.

12   This is something that people should not do.

13   People should not look at nonfatal MI because in

14   order to do an analysis of nonfatal MI, what do you

15   have to do with fatal MI? You have to treat it as

16   a censoring mechanism.

17   But we always assume that the censoring is

18   not informative about whether you were about to

19   have an event. Here, if you have a fatal MI, that

20   is clearly informative about whether you were more

21   likely to have -- if you had prevented that death,

22   you're going to be more likely to have a nonfatal

1   MI after that.

2   So the assumption that we always make in

3   these kinds of analysis is clearly not satisfied.

4   And that's why, even though people do this all the

5   time, they should not do this. They should not

6   look at, oh, we'll just look at the components of

7   the primary, if the component is a nonfatal event

8   requiring you to censor when there's a fatal event.

9   So it makes perfect sense to look at all

10   strokes. It makes perfect sense to look at fatal

11   strokes, perfect sense to look at all MIs,

12   et cetera; perfect nonsense to look at a nonfatal

13   event and censor fatal events.

14   DR. R. SMITH: Dr. Teerlink?

15   DR. TEERLINK: Thank you. I'm going to talk

16   some nonsense now.

17   (Laughter.)

18   DR. TEERLINK: First of all, in terms of the

19   magnitude of the treatment effect, I'll reiterate

20   what's been said. And I'll remind everybody that

21   the trialists themselves initially started with a

22   higher treatment effect that they were targeting,

1   then picked 9.375 as the treatment effect that they

2   thought was clinically important enough to power

3   the trial for, and yet they ended up with a

4   treatment effect that was one-third less, in the

5   6 percent range.

6   So the magnitude of the treatment effect is

7   small even by the investigators' own definition of

8   what they thought was going to be an important

9   effect to detect.

10   In terms of the robustness, I think we've

11   already mentioned how the marginal treatment

12   effect, the 1.8 percent absolute reduction, a p-

13   value that's marginal when you take into account

14   the adjustments for the multiple comparisons, and

15   then of course the impact of the differential loss

16   of missing data. So that's another thing that

17   undercuts the robustness of the data.

18   In terms of the components, I absolutely

19   agree that when you have competing risks, and

20   different competing risks, you shouldn't be looking

21   at components. But when you do have, across the

22   board, no mortality benefit, then I think

1   it's -- and it's important, actually, for us to

2   acknowledge the success of our therapy so far in

3   reducing mortality.

4   This is a success story. The fact that it's

5   hard to show benefits in terms of mortality is

6   showing that we've been doing something

7   successfully, and that's good. The challenge is,

8   though, then when you don't see any difference

9   there, I think then it is appropriate to look at,

10   well, where are the differences coming, and are

11   those events important or not?

12   I think it is important to meaningfully

13   reduce -- and emphasis on "meaningfully

14   reduce" -- myocardial infarctions and strokes. But

15   the absence on any of the larger outcomes remains

16   concerning to me, and that's in multiple different

17   areas, including the deaths, because I'd expect,

18   over a 6-year follow-up period in a group that was

19   supposedly selected to be relatively high-risk,

20   something happening there.

21   DR. R. SMITH: Dr. Hiatt?

22   DR. HIATT: Thank you. I've been listening

1   intently and struggling with the results before the

2   meeting. The amount of benefit is obviously quite

3   small, and when I played with the number needed to

4   treat on an annual basis, it was extremely

5   unfavorable.

6   What's interesting is that when you think

7   about drug approval from the FDA, it's not so much

8   driven by the magnitude of effect but really by a

9   frequent -- this view of whether the p-value is

10   positive or negative. And I guess it's to CMS and

11   other bodies to think about whether it's "worth it"

12   or not.

13   But I focused my thinking on, are the

14   results real? And what undermines that is the

15   missing data, which always does that. I think both

16   the sponsor and the FDA did a reasonable job trying

17   to deal with it, but I recognize the committee has

18   voiced residual concerns.

19   So it comes down to whether I think the

20   results personally are "real" or not real. And I'm

21   unable to completely explain this, and so my

22   thought in terms of the first question is that,

1   well, rather, it's clinically unimpressive, that I

2   think it's a positive study that withstands the

3   sensitivity analyses sufficiently to keep it just

4   marginally in the statistically significant range.

5   Thank you.

6   DR. R. SMITH: Dr. Fleming?

7   DR. FLEMING: I think the FDA really very

8   properly wrote this question, essentially stating

9   that you wanted us to comment on the statistical

10   persuasiveness of the evidence, the clinical

11   relevance of the evidence, taking into account the

12   effects on the components, taking into account

13   missingness.

14   You're hearing from a statistician the goal

15   of clinical research should not be to achieve

16   statistical significance. I don't want to put my

17   statistical colleagues out of work, but the goal of

18   clinical research should be to obtain statistically

19   reliable evidence of clinically meaningful effects.

20   And the clinical meaningfulness of it, from my

21   perspective, is even more the focus, and it's

22   certainly the focus in this setting.

1   But to try to address those, in essence,

2   four components, clinical relevance, statistical

3   significance, effects on components, and

4   missingness, starting with the missingness, there

5   is substantial missingness here.

6   We've got 8.9 percent withdrawal of consent,

7   more than 11 percent of people missing, the very

8   careful analyses done by the sponsor and the FDA to

9   characterize that. It's around 9 percent of the

10   person-years are missing.

11   They've both done very thoughtful analyses

12   on how to address that. The missingness matters.

13   It's not acceptable to argue randomization covered

14   this or that it's balanced because, in fact, when

15   people are missing, it's predominately when they're

16   off therapy. They're not getting benefit then.

17   They have much higher rates. And as we've seen

18   also, there's an imbalance in the timing of that.

19   So the analyses that have been done, by my

20   sense, don't invalidate the trial, but they

21   certainly do give us a more balanced understanding

22   of the nature and the interpretability of the

1   evidence. The hazard ratio estimates, from my

2   perspective, go from on the order of 0.936 to on

3   the order of 0.946, somewhere between 5 to 5 and a

4   half percent reduction.

5   That turns out to have some statistical

6   influence also because of the p-values that are

7   lurking in the neighborhood of that 0.039. So

8   essentially, we have a somewhat attenuated estimate

9   of treatment effect and a more marginal level of

10   significance.

11   I'm reminded on this issue, though, of

12   something Ray Lipicky used to always say to us when

13   we were serving on the Cardio-Renal Advisory

14   Committee, and that was, what's 0.025 squared? And

15   if you're going to have a single stand-alone trial,

16   then, in essence, the strength of evidence ought to

17   be that of two trials, each of which were 0.05.

18   As a two-sided p-value, that's 0.001. And

19   one might say, "Well, Fleming, that's just not a

20   reasonable target here." Well, the trial, as we've

21   heard repeatedly, was designed to target a

22   10 percent relative reduction, a relative risk of

1   0.9.

2   If you'd observed a relative risk of 0.9 in

3   this enormous trial, the p-value would have not

4   just been 0.025 squared, 0.001; it would have been

5   0.0001. So the trial was exquisitely powered, you

6   might even say over-powered, although I would argue

7   relevantly, though, powered to understanding

8   effects on components, understanding cancer risks

9   and other things as well.

10   But the fact that we're sitting here

11   debating whether or not this is statistically

12   persuasive is a consequence of the fact that the

13   estimate wasn't 0.9; it was more on the order of

14   0.95. And while that upper limit of 0.95 is

15   lurking around 1, that's the strength of evidence

16   of one trial, the lower limit is lurking around

17   0.9, meaning that these data, while they're

18   marginally inconsistent with no effect, they're

19   also marginally inconsistent with an effect as big

20   as what they were designing the trial to detect.

21   So we can't forget the fact that we are not

22   here today with such a marginal estimate because

1   it's inherently impossible to be able to show

2   effects in this setting. If we had just seen what

3   they were powering the trial to detect, we would

4   have had twice the effect, it would have been

5   easier to make the clinical relevance case, and

6   statistical persuasiveness would have been

7   profound, and missingness wouldn't have impacted

8   that.

9   So very quickly, the other aspect of this,

10   though, is the components. We've heard the hazard

11   ratio for all-cause mortality is 0.99, for

12   cardiovascular is 1.0. Where there are some

13   benefits are the hazard ratios for stroke and the

14   hazard ratio for MI.

15   As FDA guided us, and I think they're right,

16   let's look at that. And we've already talked about

17   this, so I can be pretty brief. But overall, we're

18   looking at 49 fewer patients that have stroke, but

19   it matters whether it's hemorrhagic or

20   nonhemorrhagic. We have 17 excess deaths. So the

21   hemorrhagic strokes are far more impactful.

22   We do have, though -- because we have many

1   fewer nonhemorrhagic strokes, we have 8 fewer

2   nonhemorrhagic strokes. So overall, and I agree

3   with Michael, I'm going to put everybody into the

4   pot. I'm looking at all strokes, not just

5   nonfatal, starting with the fatal.

6   Once I get past the fatal, though, then I

7   will look at the nonfatal. And what we've seen is

8   half of that excess that we're preventing are

9   complete recoveries, but there's half that are not.

10   So I'm coming up with right now, in totality of

11   evidence, there are 16 fewer deaths. That's not 30

12   against 14. That's 1,231 against 1,215.

13   So 2,500 deaths and the difference is 16,

14   the numbers of people that had beyond that effect,

15   reductions in strokes that didn't have full

16   recoveries, about another 34 events.

17   Then we go to the MI scene, where we have

18   about 138 fewer MIs. Most of these aren't fatal;

19   they're 41 against 49. So even accounting, as

20   Michael says, for everything, most of the signal

21   event is in the nonfatal.

22   It is an art form, obviously, to understand

1 what is an important MI. There is a preponderance

2 of evidence that certain MIs are in fact more

3 reliably the real thing in terms of their

4 consequences.

5 I care about MIs not because I care about an

6 enzyme leak. I care about MIs because of what it

7 means for the patient in the future. It means that

8 that person is at a higher risk for heart failure,

9 or serious arrhythmias, or death. And when we look

10 at those events that we have more confidence that

11 we can interpret what it means, ST elevation MIs,

12 there are a lot of them. But there's only 16 more.

13 The difference is only 16.

14 Most of these differences are troponin

15 levels. And by the way, when you look at the

16 slides that they showed us by troponin increases

17 for ST elevation, non-ST elevation, the troponins

18 were through the roof on the ST elevation MIs, you

19 bet.

20 So what I'm confident at the end of the day

21 is that we have 88,000 person-years. We have 5,000

22 primary endpoints. Just in death and nonfatal

1   stroke and nonfatal MIs, we have 5,000 events. In

2   that 5,000, we have 16 fewer deaths, we have 16

3   fewer STEMIs, and we have 34 fewer strokes without

4   resolution.

5   Those 60-some events translate to a

6   reduction of 1.5 per thousand person-years. If you

7   throw in all the rest of the strokes and you throw

8   in all the troponin leaks, you get that up to 4.5

9   per thousand person-years.

10   But the 1.5 are the ones I know about. The

11   other three, I don't know what they mean, although

12   the burden of proof should be on the sponsor, not

13   on the advisory committee, to say what those mean.

14   At the end of the day, I do know what mortality

15   means, and the mortality relative risk is 1.

16   An argument was made that, sure, these MIs

17   that we're getting on troponin leaks means

18   something; we just couldn't prove it. We have

19   2,446 deaths, with a confidence interval that is so

20   tight on mortality that the lower limit is 0.915.

21   That means these data are statistically

22   inconsistent with an effect on mortality that could

1   be as large as 7, 8 and a half percent, with an

2   estimate of no difference.

3   To my way of thinking, we know the truth.

4   So this trial is overpowered for its primary

5   endpoint. Thank you, not because I'm going to

6   interpret a p-value of 0.039 on the primary as

7   something meaningful. I'm going to have a lot of

8   data on the things that I care about, like death.

9   There's no difference at all.

10   To the credit of the sponsor and the FDA,

11   when I look at other things that matter, like

12   STEMIs and like strokes that don't resolve, I have

13   a lot of data on that, and there's almost no

14   difference.

15   DR. R. SMITH: Dr. Kewalramani?

16   DR. KEWALRAMANI: Dr. Blaha has covered a

17   few points that I wanted to make. I'd just like to

18   reiterate three things that have moved me as I

19   heard the discussion today.

20   The first is that, as Dr. Braunwald pointed

21   out, this study is a study that was exploring the

22   lower end of the LDL spectrum to ensure that the

1   ethics around the placebo group were preserved.

2   And therefore, there is a certain level of

3   reduction that we are talking about here that I

4   think we've covered well.

5   But as Dr. Blaha said, with the amount of

6   LDL reduction that was obtained, the CV M&M is not

7   very different than one would have expected. And I

8   compliment both the sponsor and the FDA on the

9   sensitivity analyses that have brought some balance

10   into trying to contextualize this effect and to

11   help us understand what that means.

12   DR. R. SMITH: Thank you. And Dr. Kaul?

13   DR. KAUL: Thank you. I think Dr. Fleming

14   has pretty much encapsulated what I was going to

15   say. He did it very eloquently. I'll be very

16   succinct.

17   In terms of effect size, it's quite modest.

18   In terms of robustness, I'll provide a regulatory

19   perspective and then my own perspective. There are

20   three key elements that trained to be looked into

21   when we talk about robustness of outcomes. One is,

22   was it prespecified? It's a qualitative element

1   and it clearly was prespecified. Was it

2   susceptible to false positive error? No. Type 1

3   error was preserved. Is it replicable? And that's

4   where I have a problem. In other words, is it

5   statistically persuasive?

6   The p-value, as Dr. Fleming alluded to,

7   shows us there is some evidence, but not a whole

8   lot of evidence. It's not statistically persuasive

9   and would not meet the FDA's regulatory criteria

10   for 90 percent replication probability, which is

11   what is required for approval of a drug or a

12   biologic, two trials each with a p-value of 0.05;

13   0.025 times square would be 0.001.

14   But more importantly, I'm struggling with

15   the clinical meaningfulness of the treatment

16   effect. And I independently was not able to

17   convince myself, and from what I heard today, I was

18   not persuaded whether the treatment effect is

19   clinically meaningful. And I think that Dr.

20   Fleming has already gone into detail, so I would

21   not go further.

22   With respect to the missingness, I think the

1   totality of evidence suggests that there is

2   potential for missing data to have a material

3   impact on trial interpretation. So when you factor

4   in the effect size, when you factor in the

5   robustness, both qualitative as well as the

6   quantitative, the clinical meaningfulness, and the

7   fact of potential impact of missingness, I'm not

8   convinced that this is a robust treatment effect, a

9   clinically meaningful treatment effect.

10   DR. R. SMITH: Okay. And Dr. Everett, your

11 thoughts?

12   DR. EVERETT: Thank you. I'm going to be

13 short and sweet here. I think the clinical impact

14 of this, the relative risk reduction seems to

15 me -- I agree with Dr. Fleming -- to be in 5 and a

16 half to 6 percent range, accounting for important

17 issues with missing data that seems to be

18 preferential in the combination therapy arm.

19   We go back and forth between focusing on the

20 basket of the composite endpoint and the individual

21 components, being told we shouldn't, and we do, and

22 we go back to not doing it, and we do it. But I

1 think the overall measure of the success of the

2 trial, of course, is the composite.

3 We are trying to weigh things like total

4 MI, fatal and nonfatal, and total stroke, and the

5 likelihood that these events are reduced by

6 combination therapy as compared to monotherapy.

7 I think it's very hard, as a patient or as a

8 clinician, to weigh, would you rather have an MI or

9 a small stroke? It's just, which would you prefer?

10 It's very hard to do that. Clearly, I think, it's

11 easier to weigh the differences between a fatal

12 event and a nonfatal event.

13 But I do want to point out, having

14 admonished myself for going into the weeds here,

15 that this conversation might be very different if

16 the result was being driven by a statistically

17 significant reduction in revascularization, but not

18 in MI and not in stroke. And I think we'd all feel

19 that at least the clinical relevance of that was

20 less substantial than what we've seen.

21 So I think even though we don't want to

22 parse these and make judgments about which are more

1   serious than others, I think that's probably just

2   like death is more serious than an MI. A

3   revascularization procedure is less serious than an

4   MI. I think that's a reasonable statement.

5   So on that basis, I think it's fair to say,

6   at least to me, that these benefits, while not

7   overwhelming, are nonetheless clinically relevant

8   to my practice. They're modest. They may or may

9   not be substantial, and I think we'll get to that a

10   little bit later.

11   I think that perhaps, in response to

12   Dr. Kaul, they're the best estimate that we're

13   going to get because the perfect is the enemy of

14   the good on some level, and this is a remarkable

15   feat, a Herculean feat of a trial that is not going

16   to be repeated.

17   So we're not going to be able to answer this

18   question a second time. So I think we have to

19   grapple with the data that we have and go with our

20   own impression of how robust we think the results

21   are statistically and clinically.

22   DR. R. SMITH: Other comments? Yes,

1   Dr. Shamburek?

2   DR. SHAMBUREK: When I review this, I looked

3   at what the proposed goal is from the very start,

4   and that was an LDL reduction of 15 milligrams per

5   deciliter. And that was postulated to perhaps have

6   as much as a 9.3 percent decrease in their primary

7   endpoint. So a lot of people looked at this

8   originally, and the study went on. This was felt

9   to be clinically meaningful. This was before we

10   have any data.

11   Well, what was the magnitude? Well, the

12   magnitude was an LDL reduction of 16.8 percent.

13   That was what they were trying to attain, and we

14   can argue about was it 6.4 percent or 5 percent.

15   They were pretty close in decreasing their primary

16   endpoint.

17   So I think you have to look at that. This

18   treatment was what they expected, what they looked

19   for from the beginning. As a clinician, I do

20   strive for such things as the CTT meta-analysis and

21   seeing what happens with events, that yes, this is

22   the first nonstatin. But people have looked at

1   partial ileal bypass, bile acids, which are not in

2   favorable because they're not within the last

3   10 years.

4   But we have to look at also other things,

5   what Mother Nature teaches us, and that small

6   effects have big impacts, but they often take time.

7   And we have to look for hints or marks because

8   we're never going to have another study like this.

9   If you look at the genetics of inactivating

10   NPC1L1 polymorphs, they have a 12 milligram per

11   deciliter decrease in the LDL. Yet when you look

12   at cardiovascular mortality over a long period of

13   time, you get a 53 percent reduction in events. If

14   you look at PCSK9 polymorphs, very small changes in

15   LDL, a slight more than this. You can get as much

16   as 85 percent reduction over a long period of time.

17   So as far as the robustness, they did not

18   choose a group that has very high LDL where you're

19   going to see big effects over a short period of

20   time. They took a population that we heard about

21   was on the lower end, and it's going to take time.

22   It's going to take a long study, and I am

1 glad at least they decided not to pick 4 or

2 5 years, and that they decided to pick endpoints.

3 This is looking at what clinicians are looking for.

4 And there are missing time points. But it's pretty

5 amazing, with the events that went through, I

6 wasn't sure the study would ever get done. And

7 that alone would have been very disappointing.

8   I think the secondary composite endpoints

9 40 percent overlap, so I'm not sure. I think they

10 were consistent, but I don't think that's a strong

11 point. And we have too many unknowns, I think,

12 about the hemorrhagic stroke. They are wanting to

13 be concerned, but I think we have to look at all

14 the data we have. And I would agree with our

15 statistician that fatality is a great endpoint, but

16 it doesn't do very well for follow-up of patients.

17   The nonfatal events really need to be taken

18 account of in clinical trials and are very

19 clinically relevant. And nonfatal MI and nonfatal

20 stroke, as opposed to a fatal event, is very

21 important to patients.

22   So I think, if we look at this with all the

1   limitations, the trial effect was as they expected.

2   A little less, but it answered the original

3   question. It was perhaps more modest than what I

4   thought, but I think it has some very good

5   information for our patients.

6   DR. R. SMITH: Dr. Proschan, did you have

7   another comment?

8   DR. PROSCHAN: Yes, just related to the

9   point just made, I think this is a really important

10 point. What was the cholesterol reduction in this

11 trial? Because you quoted 16.8 percent. I think

12 16.7 appears somewhere. The FDA had like 18

13 something.

14   But the sponsor is saying, well, when you

15 take into account the deaths, it really only

16 amounts to 12.7, I think, percent, and that makes a

17 huge difference, because if you believe that it was

18 16.7 or 18 percent, then you should get a much

19 bigger effect than what was seen.

20   So that slide that showed that IMPROVE-IT

21 was right along the line of what you would expect,

22 that depends heavily on whether you think the right

1   number is 12.7 percent or 16.7 or 18 percent. If

2   you believe that it's more like 16.7, then

3   IMPROVE-IT does not fit right on that line.

4   So I think it's important to really figure

5   out, what do you think the right number is for the

6   reduction in LDL?

7   DR. R. SMITH: Dr. Kaul?

8   DR. KAUL: Yes. And I will just add to

9   that. If you do a percent reduction relative to

10   the baseline LDL in the control, it's 24 percent

11   LDL reduction. So I agree with Mike with regards

12   to that.

13   I just wanted to respond or make an

14   observation about the ethical and the logistic

15   justification for not including ACS individuals

16   with LDL greater than 70. About 50 percent in the

17   control arm had LDL greater than 70. The median

18   LDL level was 70. And the NHANES data in 2007/2008

19   suggested that over 80 percent had LDL levels that

20   were over 70.

21   So I'm beginning to wonder, what were the

22   ethical constraints against not including

1   individuals with LDL greater than 70 post-ACS?

2   DR. R. SMITH: Dr. Packer?

3   DR. PACKER: I think an important point has

4   to be made here about the quality of the trial

5   versus the interpretation of the results. This was

6   one of the hardest, most difficult trials to

7   undertake and to keep together. And when I was

8   saying to Chris that I felt his pain, I say that

9   very sincerely.

10   This was an ambitious trial that took an

11   enormous number of patients. It was conducted

12   under the best of circumstances. And it is really

13   hard to keep patients on drug, or even follow

14   patients off drug for events, over a period as long

15   as this trial went on.

16   The limitations of this trial have nothing

17   to do with the investigators and have nothing to do

18   with the rigor of their conduct and the analyses of

19   the data. The limitations here have to do with the

20   nature of the benefit. The benefit here, it's

21   small. It is not robust. You blink and you miss

22   it. And you wonder whether you care about it or

1   don't care about it.

2   But in that instance, our most important

3   question is not to make judgments as to whether

4   it's big or small, whether we care or we don't

5   care. The real question is, if we gave Chris the

6   task of doing this over again, and I know he

7   doesn't want to hear that --

8   (Laughter.)

9   DR. PACKER: But if we gave him the task of

10   doing this over again, and he did it the same way,

11   would he find the same thing? And I just don't

12   know. That is a coin toss. And I just don't know

13   if he would see it again, and that's what gives me

14   pause.

15   DR. KAUL: Can I answer the question what

16   the replication probability of a p-value of 0.01

17   is? About 73 percent; 0.02 would be close to about

18   65 percent.

19   DR. PACKER: But Sanjay, that is true

20   mathematically. I'm taking the totality of the

21   challenge, the missingness, all of the things that

22   we know are inherent difficulties here.

1   DR. KAUL: I'm giving you the best case

2   scenario.

3   DR. PACKER: I understand.

4   DR. R. SMITH: Dr. Fleming, do you have

5   another comment?

6   DR. FLEMING: It would be interesting to

7   hear Dr. Shamburek's thoughts here. I was

8   listening to what you were saying, and maybe there

9   are two or three things that I'd like to probe with

10   you a little bit.

11   My sense of what you were saying is they

12   more or less got what they had designed the trial

13   to see. And given that they had gone forward with

14   that, then isn't this result therefore in some way

15   a validation? And Dr. Proschan has been mentioning

16   this also.

17   I'm still struggling whether they got what

18   they had intended. I think they got what they had

19   intended in the LDL cholesterol effects. They

20   didn't get what they had thought they were going to

21   get in the primary endpoint.

22   It wasn't a 9.3 percent relative reduction;

1   it was a 5.5 percent relative reduction, or a

2   5 percent relative reduction, which is almost half

3   that. And that's very, very important

4   statistically. It's the difference between having

5   a p-value with many zeroes versus one that's really

6   marginal. And it's also, I think, playing out

7   clinically to be problematic.

8   Second point, you made a good point about

9   look over a longer time in a chronic setting to

10   understand. To credit them, they did. They did.

11   If this study had been done before the change in

12   the numbers of events, and you had in fact had

13   evidence that was predominately in the first three

14   years, the hazard ratio would have been about 0.97

15   to 0.98. The reason that it's as nice, if it's

16   nice, as .95 is because they went out to 4, 5, or 6

17   years.

18   So if you are comparing this result to other

19   trials, as we were hearing in the open public

20   hearing, where the relative risks are 20,

21   30 percent, that's probably not a fair comparison

22   because we weren't five or six. We were two or

1   three or four in that time frame.

2   Then something that's still not been said.

3   I always do look at the U.S./non-U.S. It's not a

4   post hoc subgroup analysis. This is a U.S.

5   regulatory body, and we have thousands and

6   thousands here from patients from the U.S. And

7   while the global result is .936, the U.S. result is

8   .97.

9   So there are multiple different forces

10   pushing us in the direction of saying, this is

11   really marginal. And I agree with Dr. Shamburek's

12   points if they got what they said. I don't see

13   that they got what they said, and I agree with him

14   for the long term. But in fact, it's only in the

15   long term that you even get something that's as

16   really modest as this is.

17   DR. R. SMITH: This has been helpful and

18   valuable, and I'm going to briefly summarize. I'm

19   not going to restate all that's been said, but I'm

20   going to give a brief summary, and then open the

21   opportunity to amend that summary or to add

22   critical items. Again, my goal's not to restate

1   all that's been said. But for the sake of the FDA,

2   I will summarize. And I'm sure the FDA will look

3   at all of these comments, and clearly should.

4   By way of summary, I would say that, pretty

5   universally, the members of the panel who have

6   spoken, those who commented on it -- and I would

7   add my own perspective on that -- is that this has

8   been a remarkable trial in terms of its scope, its

9   duration, and its quality, and that's been helpful

10   and respected by everybody who has been involved in

11   reviewing the data here; that pretty universally,

12   the members of this committee have expressed the

13   view that the effect on the primary endpoint is

14   relatively small.

15   There has been perhaps some difference of

16   opinion about how to manage the apparent

17   statistical significance or the significance of the

18   statistical significance through a host of issues.

19   And there are a number of panel members who have

20   expressed some questions about whether it really

21   convincingly demonstrates significance in achieving

22   endpoints, not really disputing the analysis that's

1   been done, but accommodating questions that have

2   come out of subgroups and some questions about

3   whether or not it's met anticipated goals.

4   At least one other member of the committee

5   has, however, noted that, in particular, the impact

6   on myocardial infarction versus some of the other

7   components is one that -- as we have had many

8   struggles with the subgroup analyses, it's an

9   element of subgroup analysis that may strengthen

10   the question of clinical significance.

11   There has been a general view expressed by

12   the committee of the uncertainty about the clinical

13   significance of the magnitude of effect that has

14   been demonstrated in this study, so that has given

15   pause to multiple members of this panel.

16   There have been some specific points raised

17   about how the missing data was -- how the estimates

18   were generated in handling missing data, and some

19   uncertainties about -- based again on how exactly

20   assumptions were made and calculations were made as

21   to whether the effect truly is of a magnitude,

22   based on the LDL lowering, that one would project

1   based on statin data. And that raises again some

2   questions about ultimate effect of the drug and

3   ultimate mechanism of that effect.

4   Any other specifics that people would like

5   to add to that brief summary?

6   (No response.)

7   DR. R. SMITH: Okay. So let's go to

8   discussion question 2. I've been advised that it's

9   2:30, and we should take a break. So let's take a

10 15-minute break, and then we'll address question 2.

11 Thank you. Again, there should be no discussion of

12 the issues before the committee by panel members

13 with each other or with members of the audience

14 during the break.

15   (Whereupon, at 2:27 p.m., a brief recess was

16 taken.)

17   DR. R. SMITH: If people would please take

18 their seats. We're going to proceed to discussion

19 question number 2. And I'm going to ask Brendan

20 Everett to read the question because I choked on a

21 piece of hazelnut, and I intend to get my voice

22 back within the next 5 minutes.

1   (Laughter.)

2   DR. EVERETT: Okay. I think I'm up to the

3   task. So question number 2, for discussion.

4   Multiple subgroup analyses of the primary

5   composite endpoint were specified in the

6   statistical analysis plan. The most notable

7   differences in treatment effect were observed in

8   subgroups defined by diabetes status or age, using

9   a threshold at 75 years, as summarized in the table

10   below. And you all can read the table. Provide

11   your interpretation of these subgroup findings.

12   DR. R. SMITH: Thank you, Brendan. So this

13   is open for discussion. Yes, Debra McCall?

14   MS. MCCALL: Debra McCall. If it's all

15   right, I'd like to ask the clinicians a non-math

16   question, and it's really for context for me.

17   On the handy-dandy handout from the FDA, on

18   page 11, they said they defined new onset diabetes

19   as "two consecutive fasting glucoses of greater

20   than or equal to 126." In your clinical practice,

21   would you diagnose someone with new onset diabetes

22   based on that lab value, or would you use more than

1   that, or a hemoglobin A1C?

2   DR. R. SMITH: That's one of the key

3   recommended thresholds by various professional

4   groups like the American Diabetes Association and

5   others, European groups as well. So it's sort of

6   an agreed-upon threshold in what is recognized as a

7   continuum in deterioration of glucose tolerance.

8   There are other measures as well, but that's

9   a common and accepted measure. One could add

10   complexity, but I don't think we need to do that.

11   MS. MCCALL: Thank you.

12   DR. R. SMITH: Yes?

13   DR. PROSCHAN: I think other people were in

14   front of me.

15   DR. R. SMITH: Okay. I thought you were

16   higher up on that list.

17   Dr. Blaha?

18   DR. BLAHA: I appreciate this interesting

19   discussion. So provide my interpretations of the

20   subgroup findings.

21   I do agree with the notion that one has to

22   be very careful with secondary analysis of

1   subgroups, particularly when we were looking at so

2   many. That being said, what I find in common about

3   diabetics and those with age greater than 75, I

4   find higher risk status.

5   So to me, one thing that's common is higher-

6   risk patients might observe more of a benefit from

7   therapy, which is not an uncommon notion in

8   clinical practice. And I think especially when

9   effect size is small, like we've seen, we think

10   about higher-risk groups might be able to discern

11   the most clear benefit.

12   Now, I still think that diabetics might have

13   worse residual dyslipidemia and higher atherogenic

14   lipoprotein, though it is a potential explanatory

15   cause of why diabetics might get more benefit.

16   Therefore, I think we need to be very

17   cautious about secondary analysis from this trial.

18   And I think that the notion that I take away is to

19   not over-read into this, and that perhaps higher-

20   risk groups get more benefit.

21   DR. R. SMITH: Dr. Wilson?

22   DR. WILSON: I support the same concept of

1   being careful about subgroup analyses. Diabetics

2   were around 25 to 30 percent, and so they were

3   slightly over-sampled, partly, I'm sure, because of

4   the higher event rates. But that really adds a lot

5   of robustness to the trials, to have included the

6   diabetics.

7   The one thing I find a little concerning is

8   that diabetics, number one, are behaving more like

9   what I might have expected a priori in the trial.

10   It's the nondiabetics who weren't.

11   The second thing is although this is a major

12   subgroup, this is perhaps one of the largest

13   diabetic-included trials in the history of

14   preventive cardiology. We have 5,000 diabetic

15   patients. So it's not just a small subgroup. It's

16   a very significant subgroup.

17   DR. R. SMITH: Dr. Heckbert?

18   DR. HECKBERT: Yes. This is Dr. Heckbert,

19   Susan Heckbert. I'd like to agree with the two

20   previous speakers that, in general, we shouldn't be

21   using these subgroup findings as a basis for making

22   FDA recommendations. But the subgroup findings are

1   interesting and are fodder for discussion. But I

2   would conclude that we shouldn't be using these

3   subgroup findings as a basis for FDA

4   recommendations.

5   DR. R. SMITH: Dr. Budnitz?

6   CAPT BUDNITZ: Yes. Dan Budnitz from CDC.

7   I come from this as a public health surveillance

8   epidemiologist and not a clinical trialist. So I'm

9   just going to look at this table and provide my

10   interpretation of these subgroup findings.

11   If I saw this as -- I'll take the

12   perspective from it I'm more familiar with, a

13   cohort study. If I saw these findings in a cohort

14   study, I'd look and say, there's no way I'm making

15   a summary estimate of a hazard ratio here. We have

16   a positive interaction term. We have this group,

17   age less than 75, nondiabetic, whose hazard ratio

18   is above 1, and these other groups where it's all

19   significantly below 1. It doesn't make any sense

20   whatsoever to combine these groups and have a

21   summary conclusion about all patients.

22   I appreciate that this is a clinical trial

1   and we don't want to break the clinical trial

2   design, and we've cautioned about using subgroup

3   analysis in clinical trials. But that's typically,

4   as I understand it, when the overall result is no

5   difference, and we should be cautious about finding

6   an effect in a subgroup; in other words, rejecting

7   the null hypothesis.

8   But my interpretation here is the opposite.

9   It's if anything is happening by chance, it would

10   be this -- if we accept the rejection of the null

11   hypothesis, if we reject the null hypothesis, the

12   group that's giving us a result, the subgroup

13   that's giving us a result by chance is 60 percent,

14   this group of age less than 75, nondiabetics, with

15   11,000 people in them. And that seems to be

16   unusual, that the subgroup analysis that is

17   contrary to the overall finding is 60 percent of

18   the patients.

19   Now, I do want to hear the discussion here

20   because I'm not a clinical trialist. I want to

21   understand it better. But I also put on my general

22   internist hat and think about if I saw a general

1   indication for all patients, and then I saw this

2   table here, I wouldn't know what to do with that

3   with my under-75 nondiabetic patient. As a general

4   internist, how do I interpret that?

5   DR. R. SMITH: Dr. Hiatt?

6   DR. HIATT: I'm reluctant to combine the

7   subgroups. When you take them individually, I

8   think the 75 threshold falls apart when you look at

9   under 65. And so in my mind, that's probably not a

10   credible subgroup finding.

11   Perhaps more interesting in the diabetic

12   subgroup. And I think I would defer to Colin

13   Baigent's discussion of that point and recognize

14   that while there are a lot of diabetics in this

15   trial, the larger findings in the overall statin

16   meta-analysis would suggest not a big difference.

17   However, as Sanjay Kaul has pointed out,

18   well, maybe you have a specific drug effect here

19   that's somehow different. And I just don't think

20   we have enough data to do that.

21   So if we're thinking about how to interpret

22   these data, I think these will certainly appear in

1   the clinical summary of a label. But I wouldn't

2   dissect the trial any further and try and draw

3   actually separate conclusions from these two

4   subgroups. Thank you.

5   DR. R. SMITH: Thank you. Dr. Proschan?

6   DR. PROSCHAN: Yes. I basically agree that

7   I think it's overreaching when you start looking at

8   under-75 diabetics. Richard Peto had a great

9   chapter in a cancer book talking about even if you

10   only are looking at one subgroup, men and women,

11   and you see a marginally significant result

12   overall, it's not that unlikely that you'll see a

13   pretty striking difference in one of the groups and

14   not much difference in the other group.

15   So I think when you look at 23 of these, I

16   agree that I think it's easy to overreach.

17   DR. R. SMITH: And Dr. Packer?

18   DR. PACKER: Well, taking the point of view

19   for a clinical trialist, I really look at these

20   subgroups as providing entertainment value as

21   opposed to something that is closer to the truth.

22   We see subgroup interactions in large trials

1   all the time. And what makes it really awful is

2   that we're underpowered to see them. The

3   interaction test is a low-powered test, so a lot of

4   relevant interactions, we're not going to pick up.

5   And we do so many subgroups that we're going to get

6   one or two by chance alone.

7   Here's the most important point. What is

8   the likelihood? I asked Chris if he wanted to do

9   this trial again, and he hasn't answered, but I'm

10   going to assume no. But if he did it again, would

11   he see these subgroups again? And my sense is, no

12   way is he ever going to see these subgroups again

13   in a second trial.

14   DR. R. SMITH: And Dr. Kaul?

15   DR. KAUL: Yes. I pretty much agree with

16   what has been said. In the words of Janet Wittes,

17   "Subgroup analyses are tempting, but they can be

18   treacherous." But providing advice like "be

19   careful" is good enough for academic discussion. I

20   think the regulatory agencies have to

21   operationalize it.

22   There are many examples in the recent past

1 where there were subgroup analyses where the

2 decision to approve drugs were delayed because of

3 heterogeneity of treatment effect. The most famous

4 example I can cite is PLATO, U.S. interaction.

5   The U.S. cohort was only 8 percent. North

6 American cohort was only about 10 percent, much

7 smaller than the 27 percent diabetic cohort. The

8 unadjusted p-value was 0.009. The adjusted p-

9 value, if they had adjusted for all the multiple

10 comparisons, would be 0.24.

11   Yet, the agency deliberated over this and

12 delayed approval until disparity was documented to

13 be related to an aspirin dose, which personally I

14 don't agree with. And no such explanation is

15 discernible, at least from what I have seen, for

16 the diabetic subgroup. I don't think it has been

17 systemically explored. I think some suggestions

18 offered by Dr. Blaha are on target.

19   So is it a prospectively defined hypothesis?

20 Yes, it was prespecified. Was it a biologically

21 plausible subgroup classification? Maybe. High

22 risk, but there are other high-risk categories that

1   we don't see this interaction for.

2   Is it a proper pre-randomization subgroup?

3   Yes, it is. Is there a significant treatment

4   effect in overall analysis? Yes, quite modest. Is

5   there a significant interaction o treatment with

6   subgroup variable? Yes, nominally.

7   It's quantitative in nature. If you were to

8   believe in subgroup analyses, quantitative, meaning

9   difference in magnitude rather than difference in

10   direction where the point estimates go on the

11   opposite sides of the unity, they're much more

12   credible, reliable, and replicable. But if you

13   adjust for multiple comparisons, then it doesn't

14   meet the 0.05 threshold, but subgroup analyses are

15   inadequately powered.

16   So I would say that at this point, it is

17   hard to ignore that 27 percent of the cohort is

18   where most of the treatment benefit is observed.

19   And the regulatory agencies will have a difficult

20   time, it will be quite challenging for them to

21   operationalize this, given previous precedents.

22   DR. R. SMITH: I might follow that up.

1   Another way that subgroup analyses are often viewed

2   is as hypothesis-generating but never hypothesis-

3   resolving. And it's so easy to understand that,

4   and yet to fall into a trap.

5   So the subgroup analyses that are

6   illustrated in this table are a product of multiple

7   subgroup analyses. These are the ones that are

8   really hot to look at. So I feel that in terms of

9   hypothesis generation, the observation in the

10   diabetic versus the nondiabetic population is

11   extremely interesting and leads one to, I think, a

12   very interesting hypothesis, that this drug has an

13   effect in that population in the diabetic that's

14   different than the nondiabetic.

15   That is nothing but a hypothesis. And as

16   Dr. Kaul has already stated, we can generate some

17   mechanistic ideas about why that might be observed,

18   but we don't really have a very compelling basis

19   for that.

20   So I think it's a very nice example of

21   hypothesis generation, and I think it's important

22   to keep in mind the context in which these findings

1   in this table are observed. So that's again

2   another way of approaching, I think, the same

3   conclusion I've been hearing, which is a lot of

4   caution about subgroups. And stated a little more

5   bluntly, the subgroup data does not rival the

6   primary endpoint data in this study in what it can

7   tell us and what we can conclude.

8   Dr. Kaul, you would like to respond?

9   DR. KAUL: Yes. I think there's also

10   regulatory precedence where subgroups have been

11   utilized post-fact in order to optimize the

12   benefit/ risk balance of treatments. Usually it's

13   the safety concerns in certain subgroups that play

14   into that. That's something that the regulatory

15   agencies should be keen in exploring. Is there any

16   way you can optimize the benefit/risk of this drug?

17   Here, the challenge is that it will be driven by

18   efficacy, not by safety.

19   We had another cardio-renal panel a couple

20   years ago on vorapaxar. The original cohort

21   included individuals with coronary artery disease,

22   recently stabilized MI, peripheral arterial

1   disease, and patients with a history of stroke.

2   The overall treatment effect was positive in

3   the overall cohort, but there was a prohibitive

4   increase in the risk of intracranial hemorrhage in

5   individuals that had an underlying history of

6   stroke. And the FDA utilized this post hoc to

7   eliminate the stroke cohort and only focus on the

8   PAD and the stabilized MI cohort in order to

9   enhance the benefit/risk balance of the drug.

10   But the key criteria there is that the

11   treatment effect has to be significant in the

12   overall cohort. You can't pick a group post hoc

13   and identify it, which is what is driving the

14   treatment benefit. And that potentially could

15   apply to this scenario.

16   DR. R. SMITH: But again, even from

17   regulatory considerations, in my opinion, these are

18   subgroup data that came out, a massive subgroup

19   data, and there will always be subgroup data. And

20   so it will always have that limitation.

21   Dr. Fleming?

22   DR. FLEMING: Glad to follow you. I very

1 much concur with the sense of how you view this,

2 and my colleagues. It's delightful to have such an

3 enlightened discussion, recognizing that there is

4 obviously an inherent interest in understanding not

5 just whether our therapies have favorable benefit

6 to risk, but in whom.

7   There is in all likelihood a difference in

8 those patients that are most likely to have the

9 greatest benefit to risk. The problem is that we

10 are struggling here to get the global answer, much

11 less to be able to understand it within subgroups,

12 although we have a really huge trial here, so it's

13 tempting to say maybe we can glean something.

14   But I think the sponsor was on target. I

15 think the overall discussion here has been on

16 target, that you have to be, however, incredibly

17 cautious. I always say there are three fundamental

18 things I want to look at: what is the strength of

19 evidence? What is the biological plausibility?

20 And is there confirmation?

21   By strength of evidence, I don't mean

22 two-sided 0.05 or even two-sided 0.001. I mean

1 something that really takes into account the

2 multiplicity here. And we've heard there are like

3 23 subgroups, if not more, and age itself is one

4 covariate; it could be split at 65, at 75, or at

5 any other array.

6   Just because there is in fact an indication

7 that this is one of many subgroups we're going to

8 look for, that's not really prespecification.

9 Prespecification is when you say up front, there's

10 something biologically really compelling here, and

11 we think there'll be a global effect, but we think

12 this genetic subgroup will be, in particular,

13 benefitted. And it's specified in that way.

14   So the issue of strength of evidence in

15 terms of multiplicity, one has to adjust. And as

16 you've said, when you do, it's not compelling,

17 although I have to say statistical tests for

18 interaction are notoriously underpowered. So if

19 you really do have an interaction, you're fortunate

20 to be able to see it. And then when you do the

21 alpha adjustment, it's going to be completely

22 insensitive.

1   So biological plausibility. I always say

2   you can come up with something favorable, and the

3   best way is subgroups. Statisticians are skilled.

4   They can get you whatever p-value you want. Let

5   them do enough analyses. Enough subgroups is the

6   best way. And then when you find them, clinicians

7   are skilled, too. They'll be able to tell you

8   biologically why it's plausible.

9   So biological plausibility doesn't mean

10   after the fact; it means, what did you predict? So

11   I look in the SAP, and the SAP here didn't have

12   these as elevated to a high level. These were one

13   of many, s so I view that with concern.

14   I tried to get my own biological

15   plausibility. I explored the data here, and I

16   thought maybe we could do another PLATO with

17   ticagrelor and clopidogrel, where we were able to

18   explain that based on aspirin use. So I looked in

19   those people that were by age, and those less than

20   75, 87 percent were on an ACE inhibitor and ARB,

21   and only 40 percent older. And I thought, well,

22   maybe it's when you're not giving the ACE inhibitor

1   or ARB, you're getting more benefit.

2   So then I went to the interaction by

3   diabetic status, and where there is benefit there

4   in those nondiabetics, they're more likely on ACE

5   inhibitors or ARBs. So my little theory was

6   completely incapable of explaining the interaction.

7   So biological plausibility has got to be

8   something that is compelling and ideally

9   prespecified, and not something we explore in the

10   data. So the bottom line is the confirmation, and

11   it's as you stated it, then. This is hypothesis-

12   generating. And unless it's just enormously

13   compelling, it's something that we need an

14   independent source for.

15   But there is a take-home message here, and

16   that is, I don't ignore this. While I'm not

17   willing to say this is actionable, this is

18   concerning to me. And my view of the way that the

19   subgroups were explored in this SAP were laid out,

20   which was logical, wasn't that they were expecting

21   there to be an interaction that they wanted to

22   establish, but rather, as regulatory authorities

1   often say, when you have a single trial, what makes

2   it registrational?

3   It's got to be pristinely conducted, robust,

4   and compelling, and internally consistent, meaning

5   lack of indications of factors that make treatment

6   effect different because then I'm not only worried

7   about whether to approve but in whom to approve.

8   So the fact that there are these

9   interactions don't lead me to conclude that these

10   are reliable guidances of who to treat. It makes

11   me even more uncertain, not only about whether to

12   approve, but who are the people? Is it in fact

13   specifically the older people and the diabetics?

14   Maybe this is not irrelevant. This is

15   suggestive. It's just not reliable. And it leaves

16   me now even more uncertain.

17   DR. R. SMITH: Dr. Packer?

18   DR. PACKER: I mentioned entertainment

19   value, and I just want to enhance that a little

20   bit. One of the most remarkable things when Chris

21   Cannon presented the results of this trial was not

22   what people said about ezetimibe but what people

1   said about the LDL hypothesis.

2   Basically -- and, Chris, correct me if I'm

3   wrong -- there was a world where there were statins

4   that lowered LDL and had an effect on morbidity and

5   mortality. And people said, well, maybe it's a

6   statin-specific event and it's not LDL. And Chris'

7   ability to put a dot on the regression line led

8   people to rise up in joy that the LDL hypothesis

9   had been proven.

10   Well, gee, if you go to subgroups, there's a

11   lowering of LDL in the diabetes group, which is

12   just like the nondiabetes group. And there's a

13   lowering of LDL in the elderly, just like in the

14   non-elderly. So if we believe in the LDL

15   hypothesis, and I don't know whether it should be a

16   religious belief or not, it's totally inconsistent

17   with the subgroup effects.

18   We're seeing LDL lowering in the

19   nondiabetics and in the younger people, but not the

20   effect on morbidity and mortality. I'm really

21   sorry, but it just -- it doesn't hang together.

22   DR. R. SMITH: So I could push you on that a

1   little bit and ask whether your point is that you

2   question based on the data the LDL hypothesis or

3   whether you question subgroup analyses as a means

4   to draw conclusions about the LDL hypothesis?

5   DR. PACKER: My skepticism, does it have to

6   be confined to one, or can I be skeptical about

7   both?

8   DR. R. SMITH: I think that's your choice.

9   Dr. Shamburek?

10   DR. SHAMBUREK: Yes. I agree with a lot of

11   what was said. The big points of age and diabetes

12   were drawn out of the big subgroup analysis. I

13   think the FDA, and we don't need to see it, had

14   figure 9 on page 88 where they showed some of the

15   comparisons. And then the sponsor on page 48 and

16   49 had figure 4, and we actually saw it, I think,

17   just after the break, where I think -- being a

18   nonstatistician, I always look on those which favor

19   the combination to the left of the 1.0 line.

20   If you look at that, you're seeing females

21   greater than 65, nonsmokers, hypertension,

22   Caucasian, not having had a stroke, lower CRP,

1   baseline LDL, and several others -- elevated CRP,

2   excuse me, and a lower baseline LDL.

3   But I think there's great limitation in

4   looking at that. But I think this also has to come

5   back that this is somewhat consistent with the

6   primary endpoint, that there are a lot of things

7   favoring it, but I would never take one or probably

8   even the total where it's substantially conclusive.

9   But I would say we heard a little bit about

10   the biological plausibility. And as a clinician, I

11   think if Dr. Cannon repeated his study, he would

12   find the elderly at the highest risk. And I would

13   say -- I would bet a lot that the diabetics are, so

14   much so that most guidelines say that a diabetic is

15   a CAD risk factor regardless of LDL.

16   So I'm very happy with that result, and I

17   think it would be reproducible. I don't know the

18   duration of diabetes in these subjects. I don't

19   know if the elderly are very different, and they

20   probably are. And many have probably been treated

21   on a higher statin, so I wouldn't want to go in

22   there.

1   But I think if I had to bet that, the

2   elderly who've had the longest exposure to the

3   increased LDL are likely going to be impacted, you

4   might say the LDL hypothesis. And diabetic

5   patients, I think that is a pretty good,

6   concrete -- although I don't know a whole lot about

7   this group.

8   So I have major reservations on subgroup

9   analysis. The two mentioned do jump out and are

10   provocative, but I think we have to stick with the

11   primary composite endpoint.

12   DR. R. SMITH: Dr. Packer, you had a

13   follow-up on that?

14   DR. PACKER: Just very briefly. I just want

15   to make sure that I understand. I'm totally

16   convinced that if Chris were going to do this

17   again, the diabetics would be at higher risk and

18   the elderly would be at higher risk. But do you

19   think that the interaction --

20   DR. SHAMBUREK: No.

21   DR. PACKER: No? Good. Thank you.

22   DR. SHAMBUREK: Yes. Those two I think we

1   would win on.

2   DR. R. SMITH: Dr. Fleming?

3   DR. FLEMING: Or in the terminology we often

4   use, a prognostic factor does not an effect

5   modifier make. So we have a wealth of data to tell

6   us what groups are at high risk. That doesn't tell

7   us which groups benefit from therapy because

8   prognostic factors aren't necessarily effect

9   modifiers.

10   DR. PACKER: Just to make sure, you have

11   that saying in the statistical community, what you

12   just said? It sounds ancient, and it's --

13   DR. FLEMING: It does, doesn't it?

14   (Laughter.)

15   DR. PACKER: It sounds like it's been around

16   for 500 years.

17   DR. PROSCHAN: That one's pretty old.

18   (Laughter.)

19   DR. FLEMING: Yes. That's true.

20   DR. R. SMITH: Dr. Kaul?

21   DR. KAUL: Yes. I think it might be

22   helpful, although the numbers are very small, do we

1 see a similar trend in the newly diabetic

2 individuals within the trial? Do we see a similar

3 pattern emerge? Because there are about 720 versus

4 694, and that perhaps might make it a little more

5 clear if this is real or not.

6   DR. R. SMITH: Does anybody have data

7 immediately available on that? Sponsor says no.

8 FDA says no. So we just -- interesting question.

9   DR. KAUL: Right. And so I just would like

10 to respond to that LDL hypothesis entertainment

11 factor that Dr. Packer brought up. I remain

12 skeptical also of the LDL hypothesis.

13   If you look at the recent four trials that

14 are relevant, if you look at the FIELD trial of

15 fenofibrate done in the diabetics -- and again,

16 this is a sort of fishing expedition -- total

17 cardiovascular disease events that were closer to

18 the primary endpoint in IMPROVE-IT, there was a

19 risk reduction that was 11 percent. Bear in mind

20 that the primary endpoint was not significant. And

21 the delta in the LDL was around 12 percent, percent

22 reduction in LDL relative to control LDL.

1   In the Heart Protection Study 3, the

2   patients with vascular diseases are all high-risk

3   patients. The major vascular event, which

4   approximates the IMPROVE-IT primary endpoint, the

5   risk reduction was 4 percent despite a 16 percent

6   relative reduction in LDL. It translates into an

7   absolute LDL difference of 10 milligrams.

8   In the IMPROVE-IT, we have a 16.7 or 12 or

9   24 percent relative LDL reduction, and the hazard

10   ratio is 0.94. This is a post-ACS. Of course, the

11   baseline LDL levels are different. Therefore, what

12   I'd consider relevant is the percent LDL reduction.

13   Then we have the PROVE-IT, 16 percent treatment

14   effect, with a 35 percent LDL reduction.

15   If you would just simply look at these four

16   trials, I really can't make sense of any

17   relationship between LDL lowering, whether it's

18   absolute LDL difference or percent LDL reduction

19   relative to treatment intervention.

20   Of course, the treatment intervention in

21   IMPROVE-IT, Heart Protection Study 3, and FIELD was

22   in addition to -- a nonstatin in addition to a

1   statin. So perhaps a relationship when you add a

2   nonstatin to reduce LDL may perhaps not be similar

3   to what you see when you add a statin on top of a

4   placebo or a more intensive LDL lowering relative

5   to a less intensive LDL lowering. So I remain

6   skeptical about the LDL hypothesis.

7   DR. R. SMITH: Speaking of LDL and non-LDL,

8   that reminds me that the sponsor had mentioned

9   having some data in accordance with Dr. Blaha's

10   question earlier, and I apologize for not bringing

11   that forth. If you could just briefly show us

12   those data.

13   DR. TERSHAKOVEC: Yes. We have looked

14   at -- Dr. Blaha's question was asking about, in the

15   diabetes subgroup, if there are any differences on

16   ApoB and non-HDL. So we looked at one-year

17   achieved ApoB and non-HDL levels in subdiabetic and

18   nondiabetic and don't see any substantive

19   differences that would explain a benefit or

20   difference on the hazard ratio between those two

21   groups.

22   I did want to also address the issue that

1 has been raised about the expected treatment

2 effect. The IMPROVE-IT showed, based on CTT, and

3 we've done a very careful analysis with Dr.

4 Baigent, reached out to CTSU to make sure that we

5 use the exact methodology that they used. And the

6 hazard ratio that we achieved in IMPROVE-IT was

7 0.8, and the CTT analysis is 0.78. And that's per

8 millimole per liter.

9   So it's very, very similar. And that effect

10 size is -- if you want a bigger effect size, then

11 you're expecting the drug to do more than it's

12 supposed to do, and you're expecting the drug to do

13 more than what you'd expect to see from a statin.

14   If I could get slide up? Based on what we

15 know about both the ezetimibe and statins, this is

16 a slide that shows LDL levels on the baseline, and

17 the arrows show if you've got the same proportional

18 reduction, 25 percent, as you're going down the LDL

19 line, you're going to get smaller LDL change. On

20 the Y-axis, you see the expected benefit you would

21 get based on that.

22   IMPROVE-IT was down at the very bottom on

1   the left hand of the X-axis between 50 and 67. So

2   if you'd gone up higher on that axis, if we were

3   different patients or a different study population,

4   you would have a larger expected benefit.

5   So again, the benefit is exactly what we'd

6   expect based on the broad information we have on

7   CTT and lipid lowering, exactly what you would have

8   been expected from a statin in the same clinical

9   situation.

10   DR. R. SMITH: Dr. Proschan?

11   DR. PROSCHAN: Yes. I don't agree with that

12   because it's not consistent with slide 10 in terms

13   of the reduction in LDL. From slide 10, it

14   suggests you should have about a 9.4 percent

15   reduction in events, and you've got a 6 percent,

16   roughly, reduction in events. So I don't agree

17   that that's consistent with what was hypothesized.

18   Now, the point about, well, if you had

19   targeted people with higher LDL, you would have

20   seen a bigger reduction, I don't doubt that. I

21   think that probably makes sense, because it makes

22   sense to me that there's some point at which

1   additional lowering is not going to be beneficial.

2   You don't want to lower someone to zero, for

3   example.

4   So there's some point at which it stops

5   being beneficial. So I can accept the fact that if

6   you take people with really low LDLs, you're

7   probably not going to get as much of a benefit.

8   But you knew that going into this trial, and you're

9   dealing with people with low LDLs in this trial.

10   DR. ROTHMANN: I just need to add one thing

11 about the LDL that you misunderstand.

12   DR. R. SMITH: If you'd go to the

13 microphone. Yes, thanks.

14   DR. ROTHMANN: So the LDL that was reported

15 in the paper is the LDL that was measured, which

16 was the LDL on the people who came in to visit. So

17 all of the people off study who had events, okay,

18 who diluted everything, also had an LDL at baseline

19 and during some point in the study, which may or

20 may not have been included in that 1-year value.

21   So we then corrected that 1-year value to

22 include what they would have been. That's why it

1   came down.

2   DR. PROSCHAN: Right. But my understanding

3   is that to make that correction, you assume that

4   there was zero difference among the people who

5   didn't come back. You don't know that. Right?

6   Unless you took their last LDL value or something,

7   you really don't know that there's a zero

8   difference among the people who stopped coming

9   back. So I still think that that's problematic.

10   DR. R. SMITH: Yes. Another comment from

11   the sponsor?

12   DR. BAIGENT: If a person goes off the

13   study, he stops taking study treatment, and they're

14   blinded, remember, they don't get unblinded when

15   they come off -- you would expect them perhaps to

16   go to their cardiologist or their local physician,

17   and they may go back onto the treatment they were

18   on before they went into the trial -- you'd expect

19   that to be randomly distributed between the two

20   arms.

21   So I think the hypothesis that there is zero

22   difference between the two in those circumstances

1   is reasonable.

2   DR. PROSCHAN: I don't think it's reasonable

3   because the reason you're going off could very well

4   be different in the two arms. So randomization

5   does not protect you in that setting.

6   DR. BAIGENT: We'll have to agree to

7   disagree on that.

8   DR. R. SMITH: So again, the discussion

9   question before us has to do with subgroups. This

10 is all a really useful and interesting discussion,

11 but any more comments related to this discussion

12 question 2 on subgroups? Yes?

13   DR. PROSCHAN: Sorry.

14   DR. R. SMITH: That's okay.

15   DR. PROSCHAN: But one thing, the plots, the

16 forest plots that were made, they are excellent.

17 An excellent tool, and I think they do show general

18 consistency. However, when you show forest plots

19 like that, you should do it on a log scale because

20 a hazard ratio of one-half is as good in favor of

21 treatment as a hazard ratio of 2 is against

22 treatment.

1   Yet, when you don't use a log scale, it

2   looks like one-half is a lot closer to the null

3   value of 1 than 2 is. So I think plots are really

4   helpful. I do think it should have been on a log

5   scale.

6   Another possible plot that I think could be

7   helpful, and I'm not sure about this, but if you

8   had independent groups, if you had completely

9   independent people, then you could look at the

10   smallest p-value of the different subgroups and

11   plot it against what you would expect the smallest

12   p-value, what you expect the next smallest p-value

13   to be. And here, you don't have independent

14   groups, but I'm wondering if there might be some

15   way to try and approach that by adjusting for the

16   other covariates.

17   So it might be possible to look at another

18   plot that would help trying to figure out whether

19   this subgroup thing is real or not.

20   DR. R. SMITH: I will again briefly, not

21   completely in detail, summarize.

22   The various members of the panel have most

1 consistently agreed in discussing this question on

2 the limitations and hazards of evaluating

3 subgroups. And perhaps that was, by way of direct

4 example, best illustrated by the point Dr. Hiatt

5 raised, that whereas there seems to be an

6 intriguing difference between individuals above and

7 below age 75, that finding doesn't or a similar

8 finding doesn't occur with individuals above and

9 below age 65. And that maybe illustrates the

10 problem with selected subgroups out of a large

11 group of subgroups in terms of interpreting those

12 data.

13   Nevertheless, there is interest in the

14 findings, and substantial interest in the findings,

15 within these subgroups. And there's interest in

16 hypotheses that perhaps the subgroups are providing

17 some insight into a greater effect of drug with

18 more severe or more rapidly progressive disease.

19 Perhaps there is a specific effect within a

20 diabetes population that would be of interest.

21   So there is interest in the subgroups, but I

22 haven't heard members of the panel suggest that

1   this information is useful in addressing the

2   question -- is definitively useful in addressing

3   the question of the effects on the primary

4   endpoint, as we discussed under discussion

5   question 1, or in defining with confidence how to

6   handle the subgroup data in terms of making a

7   decision on recommendations for use at this point.

8   Fair enough? Modifications? Dr. Budnitz?

9   CAPT BUDNITZ: I would just make two points.

10   One is that I think there might be a hint of a dose

11   response by age. We don't have the data in detail

12   enough, but on page 48 of the sponsor's background

13   materials, figure 4, there is a stronger effect in

14   folks greater than 65, a lesser effect -- I'm

15   sorry -- a stronger effect for folks greater than

16   75, a lesser effect in those greater than 65. So I

17   think there's potential for a dose effect there.

18   That is a hypothesis-generating exploratory.

19   Then I do want to still make the point

20   that -- I don't know if I can clearly articulate

21   it. But the difference between subgroup analysis

22   when you're finding a subgroup that has -- well,

1   when the overall result rejects a null hypothesis

2   versus a subgroup analysis when the overall result

3   doesn't.

4   I think that's what we have to think about a

5   little bit more carefully here when we assess how

6   the subgroups might affect our final decision, and

7   if the IMPROVE-IT trial does have a positive

8   result.

9   DR. R. SMITH: Okay. So we'll go on to

10   discussion question 3. I'll read this.

11   "The applicant has proposed that the results

12   from IMPROVE-IT, which tested the addition of

13   ezetimibe to simvastatin among patients with very

14   recent acute coronary syndrome, can be extrapolated

15   to other clinical situations, such as adding

16   ezetimibe onto any statin among patients with

17   stable coronary heart disease. Discuss the extent

18   to which such extrapolation is reasonable."

19   That's open for comment. Dr. Kaul?

20   DR. KAUL: If I did not read incorrectly,

21   both the FDA and the sponsor cautioned us on

22   interpreting the landmark analysis. The treatment

1   effect emerged after 6 to 12 months, during

2   arguably a chronic disease phase, and they said it

3   is a nonrandomized comparison subject to bias. And

4   I agree with that interpretation.

5   So based on the trial data set, I don't

6   think that evidence of benefit emerging during

7   chronic disease phase is actionable. Absent that,

8   I look for external evidence. Is there any

9   evidence supporting the role of this combination

10   therapy?

11   There are two trials. The SEAS study,

12   essentially no treatment effect was discernible on

13   cardiovascular events. It's very difficult to

14   interpret a secondary endpoint if your primary

15   endpoint is negative. And then the SHARP study, a

16   15 percent reduction in major vascular events

17   compared with placebo, but the treatment effect of

18   Zetia versus simvastatin could not be

19   differentiated.

20   That's the interpretation of the FDA, hence

21   their decision to reject the claim for the SHARP

22   results that were presented, even though 31 percent

1   of the LDL lowering with the combination therapy

2   was attributable to Zetia. But the FDA rejected

3   that and denied that claim.

4   So we have no reason to draw the inference

5   based on the trial itself, and we don't have any

6   supportive external evidence.

7   DR. R. SMITH: Dr. Heckbert?

8   DR. HECKBERT: Yes. This is Susan Heckbert.

9   Yes, I agree with Dr. Kaul that these trial results

10   don't provide direct evidence that allow us to

11   extrapolate the effects seen here to other clinical

12   situations, such as adding ezetimibe to other

13   statins.

14   It may be an interpretation that clinicians

15   may want to make, but the trial doesn't provide us

16   that direct evidence. And in particular, we don't

17   have information about its use in combination with

18   higher potency statins, which is an important

19   question.

20   DR. R. SMITH: Dr. Teerlink?

21   DR. TEERLINK: Sure. This is John Teerlink.

22   I also agree with what's been said before. I think

1   it's also interesting to see the evolution of this

2   in the publications, actually, from IMPROVE-IT

3   itself.

4   So the first design paper says, this is

5   designed to reduce cardiovascular outcomes in

6   patients with acute coronary syndromes in the

7   title. That's 2008. And then 2014 is to reduce

8   outcomes, improve outcomes, in patients after

9   coronary syndromes. And now we've moved towards

10   inpatients who have coronary heart disease. So the

11   creep has continued throughout this program.

12   I think when you have a selection criteria,

13   a patient population that's selected to test a

14   hypothesis in general, the application of that

15   therapy should be done in the selected population

16   unless, of course, the only reason you picked that

17   population was to enrich and invest.

18   If that's the case, then you might make a

19   persuasive argument why you think the patients who

20   have had acute coronary syndrome are actually

21   identical to the patients who have chronic heart

22   disease and chronic coronary disease. And I don't

1   think that that case could be made convincingly

2   here. So I would suggest that, unfortunately, we

3   cannot extrapolate to these other clinical

4   situations based on that.

5   DR. R. SMITH: Dr. Hiatt?

6   DR. HIATT: I agree with everything that's

7   been said. I think broadening the label beyond the

8   population actually studied is an overreach. And

9   the definition of the study population based on

10   inclusion criteria really is the population the

11   data applied to, not the patients who were enrolled

12   with coronary disease.

13   So like the other comments, I completely

14   agree. I think the label should reflect the

15   enrollment criteria for the patients who were

16   actually studied and should be limited to those

17   patients. Thank you.

18   DR. R. SMITH: Dr. Wilson?

19   DR. WILSON: I support that, and just two

20   other comments. One is I believe the experience of

21   this trial is largely in the usual troponin levels,

22   not the high-sensitivity troponins. So in the

1   future, this might be open to misinterpretation in

2   who has coronary disease. That's number one.

3   Then number two, because my colleagues

4   haven't said it, is many of our patients who have

5   coronary disease really expect a survival benefit.

6   And we don't have evidence here for a survival

7   benefit, and I think that needs to be front and

8   center. It's been reduction in nonfatal events,

9   for the most part, and not improved survival.

10   DR. R. SMITH: Dr. Everett?

11   DR. EVERETT: Thanks. When does an acute

12   coronary syndrome become chronic coronary disease?

13   Thirty days? Sixty days? Ninety days? Never?

14   It's not clear to me.

15   But in that context, I actually think that

16   the disease process is the disease process. In

17   fact, the pathologic mechanisms driving an acute

18   coronary syndrome might actually be different than

19   the ones that are impacted by LDL reduction.

20   That perhaps -- not to go down the subgroup

21   rabbit hole with the Kaplan-Meier curves, but that

22   might be why there's a difference in the Kaplan-

1 Meier curves after a year, because whatever process

2 is driving the acute coronary syndrome has passed,

3 and now you're in the context of a chronic coronary

4 disease, and you're better able to impact that

5 disease process with LDL reduction.

6   So I can tell I'm swimming a little bit

7 upstream here. But I think it's reasonable to

8 consider the addition of ezetimibe to statins in

9 the secondary prevention of chronic coronary

10 disease, not just in the immediate aftermath of an

11 acute coronary syndrome, with the caveat that the

12 absolute benefit is going to be less substantial

13 than we even saw in this trial when patients are on

14 more potent statins and potentially start ezetimibe

15 with an LDL cholesterol of 70, let's say, or 65

16 because they're on rosuva 40 or atorva 80.

17   But nonetheless, I think that from my

18 perspective, that's where the biology is most

19 persuasive. And I guess in that sense, I

20 would -- support might be the wrong word, but I

21 think it's reasonable to consider expanding the

22 label to include all secondary prevention patients.

1   DR. R. SMITH: Dr. Fleming?

2   DR. FLEMING: I interpreted this question

3 with two components. One was, what would be the

4 acceptability of adding ezetimibe to another statin

5 in this clinical setting? And then secondly,

6 expanding to patients with stable coronary heart

7 disease.

8   So taking the first question, it's of

9 interest to say we have high-potency statins like

10 atorvastatin, rosuvastatin, could we add ezetimibe

11 to those? And if I follow the sponsor's logic, the

12 lower we're getting the overall cholesterol here,

13 LDL, the lesser return we might expect in terms of

14 the relative risk reductions.

15   So there is some logic to asking whether we

16 could add this to those other high-potency statins.

17 My worry is, this really modest effect that we've

18 seen in adding it to simvastatin logically would

19 seemingly be the same or less in those settings.

20   The other question is, what about

21 generalizing to patients with stable coronary heart

22 disease? And I worry greatly about extrapolating

1   in that type of setting. Many of my colleagues

2   have said the same. We don't know.

3   I know Dr. Blaha and Dr. Shamburek had both

4   said, as we were answering question 2, that may be

5   it's true that we do have a somewhat better effect

6   in patients that have more advanced disease or

7   higher risk. And there's some logic to thinking

8   that, and that logic would say maybe the fact that

9   you have more effect in the people above 75 is

10   real.

11   I don't know if it's real or not. But there

12   are other examples that go in the other direction.

13   Oncology, for example, our biggest effects are in

14   minimal disease settings. People in the adjuvant

15   setting get huge benefit versus people with solid

16   tumors.

17   Then there are a whole array of different

18   examples that I could give where it's better in a

19   more advanced patient or better in a less advanced.

20   I'm just very concerned that if the results are

21   really difficult to even show here in a high-risk

22   setting, why should we be able to conclude that

1   there'd be a clinically meaningful effect and

2   lesser risk?

3   It might be true, but I'd like to have

4   direct evidence to show that. And so this is a

5   great question. The answer should be based on rich

6   evidence beyond IMPROVE-IT to tell us the extent to

7   which this result extrapolates to other settings.

8   DR. R. SMITH: Dr. Proschan?

9   DR. PROSCHAN: Yes. Many years ago, there

10   were meta-analyses done that seemed to suggest that

11   the relative benefit in people with high LDL was

12   not all that different in primary prevention,

13   secondary prevention, all these different

14   subgroups. The absolute difference was highly

15   dependent on those other factors, but the relative

16   effect was not.

17   I think once you get down to a really pretty

18   darn low LDL that was seen in this trial, I do

19   expect there to be a difference -- not as great a

20   benefit, but I guess I wouldn't be surprised if you

21   took other similar populations and you get about

22   the same reduction if their LDL is starting at the

1   same level as the people in this trial.

2   I wouldn't find that surprising at all. In

3   fact, I would expect that. I think, to me, the big

4   factors are the LDL reduction and the starting LDL.

5   DR. R. SMITH: So just to follow up on that

6   with my own thoughts about that, I think we only

7   have data on simvastatin. That's going to remain a

8   fact. But there's nothing in these data that would

9   lead us to strongly suspect that this is a

10   simvastatin-specific co-action of this agent.

11   So the issue is not so much another statin,

12   where we acknowledge there's a lack of data but we

13   don't see a reason for concern that this would be

14   specific to simvastatin. But more it's the issue

15   of what we speculate about and don't know about the

16   role of where a given patient is in their starting

17   LDL level at the time that this therapy might be

18   introduced.

19   Is that a fair addition to the points that

20   people made about statins?

21   (Dr. Proschan nods head affirmatively.)

22   DR. R. SMITH: Okay. Dr. Blaha?

1   DR. BLAHA: Great. I want to articulate a

2   point, I think, in between some of the comments of

3   Dr. Everett and others. And Dr. Everett very

4   wisely mused on what the difference between an

5   acute coronary syndrome and a secondary prevention

6   is. That's not exactly clear to me.

7   But I want to also look at the words "very

8   recent," before very recent acute coronary

9   syndrome. Also, it was very interesting to me. I

10   guess to me very recent means in the hospital or

11   something like that, before someone is discharged.

12   I think it's very reasonable to me to think

13   that someone who has a coronary syndrome who

14   follows up for secondary prevention therapy in the

15   clinic who's had a recent, but not very recent,

16   acute coronary syndrome has similar biology as was

17   articulated of coronary artery disease that has a

18   rupture of plaque. It's very reasonable to think

19   that those patients might get a benefit out of

20   further LDL lowering.

21   Now, patients with what I would chronic

22   secondary prevention, let's say years apart from

1   their acute coronary syndrome, that are very

2   stable -- I think we'd all agree with what I'm

3   talking about here -- these data may not at all

4   apply to those patients. I agree.

5   But I think there's something about some

6   difference between a very recent acute coronary

7   syndrome and a recent coronary syndrome, maybe

8   transitioning into the outpatient setting. But

9   it's not a chronic coronary disease patient to me

10 where I can see applying this data.

11   DR. R. SMITH: Dr. Packer?

12   DR. PACKER: I made this point before, and

13 it may be relevant here. The proposed indication

14 by the sponsor is not linked to any cholesterol

15 measurement or cholesterol criteria. Basically,

16 the proposed indication is, if you have coronary

17 heart disease, you should get this drug. That's

18 what it says.

19   Coronary heart disease means you have

20 coronary disease and you have something wrong with

21 the heart. It could be a past MI or it could be

22 something else. It could be someone who has a

1   segmental wall abnormality and no history of an MI.

2   It's just an incredibly ambitious proposal

3   based on the patients enrolled in IMPROVE-IT.

4   Basically, based on the proposed indication, you go

5   out and every patient you see who has coronary

6   artery disease and something wrong with their

7   hearts, you get the drug. Forget about

8   cholesterol. Forget about measuring it. Forget

9   about recent MI. I don't know. I don't understand

10   the sponsor's thinking process.

11   DR. R. SMITH: Other comments? Yes?

12   DR. KAUL: So with respect to adding a high-

13   potency statin, assuming you start off with a

14   baseline LDL post-stabilized ACS of around about

15   95, and you push your LDL to, let's say, 55 with a

16   high-potency statin, and you add Zetia on top of it

17   and you get an incremental 22 percent reduction,

18   which would get us to about 45, are we suggesting

19   that the delta from 55 to 45 is going to be

20   associated with a similar or reduced effect size?

21   I mean, we had difficulty going, in the

22   PROVE-IT, from 95 to 62, we got a treatment effect.

1   And then we're pushing from 69 and 54; we got a

2   very modest effect. And now we're going from 55 to

3   45; are we going to get a treatment effect? So

4   without having the direct evidence, I don't think

5   that that question is answerable.

6   DR. R. SMITH: Dr. Kewalramani?

7   DR. KEWALRAMANI: I read this question to

8   ask two different points. One, can it be combined

9   with any statin as opposed to simvastatin, which

10   was directly studied. And then the issue of the

11   stable coronary heart disease versus ACS, the

12   inclusion population.

13   I'll leave the second point alone; I think

14   that's been well-addressed. But going back to any

15   statin, I think the distinct mechanism of actions

16   between the statins versus Zetia, the clinical

17   development program in which Zetia has been studied

18   with other statins and has had comparable LDL

19   reductions, and the fact that the magnitude of the

20   treatment effect in this instance is what had been

21   predicted as we've talked a lot about with regard

22   to CTT, I don't see a reason that this would -- I

1   don't see any convincing evidence that this

2   wouldn't be something we would consider for

3   combination with other statins.

4   DR. R. SMITH: Okay. So again, I'm just

5   going to briefly summarize the discussion. Oh,

6   yes, Dr. Shamburek?

7   DR. SHAMBUREK: No. I was just going to

8   say, once again reiterate, the population here is a

9   little different. And I think the population

10   here -- it's not the genetic one -- is more

11   representative of chronic coronary heart disease.

12   Yes, ACS is a different part of it. But

13   with patients with high LDL, they get MIs. They

14   get strokes. They get acute coronary syndrome.

15   It's part of the natural history. And the

16   combination of these drugs are -- we've heard a lot

17   about operating in the common pathway.

18   When I looked at the biological plausibility

19   of comparing them, I couldn't really find how a

20   different statin would likely be behaving

21   differently. And in fact, the sponsor, I think

22   their slide 13 showed a study from Pearson from

1   Mayo Clinic. But I would say, go right back to the

2   package insert, where they take the data from the

3   STELLAR trial, and Zetia plus simvastatin -- again,

4   this is looking at the combination -- had a

5   56 percent reduction in LDL.

6   If you look at the package insert, Zetia

7   plus atorvastatin 40 milligram gives you also a

8   56 percent. I can't see, based on any of the data

9   here, yes, we would have to be extrapolating, but I

10   also don't see why that extrapolation wouldn't be

11   valid.

12   If we believe the effect is based on LDL

13   lowering, then this would -- there's never going to

14   be a trial about this. But if you halve the dose

15   of atorvastatin to 20, you're only going from a 56

16   to a 54 percent. And if you even go down to a

17   quarter of the dose, to 10 milligram, you're going

18   from 56 to 53.

19   Now, what does this mean to clinicians?

20   Well, statin intolerance is a big effect, and we

21   would really like to be reassured that we could

22   reduce cardiovascular events. Yes, we would love a

1   clinical trial. I don't think we're ever going to

2   see that.

3   But I think what the panel and/or the FDA is

4   going to have to decide is an equivalent reduction

5   in LDL, or even more -- what if you went to

6   atorvastatin 80 or rosuvastatin -- would you see

7   differently?

8   I don't see them behaving differently. The

9   mechanism is identical. We're seeing the same LDL

10   reduction. But I think you could have a major

11   impact with muscle aches and symptoms on patients

12   who might not be able to tolerate high doses.

13   So yes, the pure trialist wants a

14   randomized, controlled trial. We're not going to

15   see one with each of the statins. We're not likely

16   going to see one with other doses. But I think we

17   have to think about if we believe it's the LDL

18   reduction and we believe that the results are

19   correct, that it's biologically positive.

20   DR. R. SMITH: So I'll summarize. Again, I

21   think, in regard to this question, the most

22   consistent position communicated by the group was

1   that there is a lack of evidence to support an

2   extrapolation from this trial to other clinical

3   situations.

4   There's a variation of views after making

5   that simple statement, and it has been argued that

6   there's a lack of convincing evidence that groups

7   that may have stable coronary heart disease are

8   comparable to the acute coronary syndrome group

9   that was studied in the IMPROVE-IT trial.

10   On the other hand, the point was made that

11   the way the courses of individuals and the events

12   actually occurred within that trial, where the

13   differences were observed, that in fact it raises

14   at least the possibility that something closer to

15   stable coronary disease was in fact where

16   substantial effect was observed, and noted that the

17   biology of the process may, one could argue, be

18   similar between acute and more chronic coronary

19   events. Again, these are speculative arguments

20   presented by the group.

21   In terms of other statins, there seems to be

22   a general view that there's not a reason for

1   concern about other statins individually other than

2   the question about what the starting LDL level

3   might be at the time that ezetimibe were

4   introduced..

5   That became a major point of discussion

6   without complete resolution, which is the

7   possibility that the effectiveness, on the one

8   hand, of ezetimibe may be very much dependent on

9   the starting LDL level and the potential to lower

10   that. But it was also noted that there could be a

11   role potentially in the real clinical world for an

12   agent like ezetimibe, which lowers LDL levels,

13   where patients may be on limited doses of whatever

14   the statin is because of the ability to tolerate

15   that.

16   Would anybody like to add anything to that

17   summary?

18   (No response.)

19   DR. R. SMITH: Okay. We'll go to

20   question 4, which also is a discussion question.

21   Discuss the safety findings of the IMPROVE-IT

22   trial.

1   So this is open for comment. I think the

2   things that one might want to comment on that

3   context would be the discussions about hemorrhagic

4   stroke. It might be issues of liver disease. And

5   it might be issues of other general concern,

6   perhaps, that's been addressed in some of the

7   safety data we've heard.

8   Anyone want to pick that up besides me?

9   Dr. Blaha?

10   DR. BLAHA: Just, I guess, a simple comment.

11   I think that the safety findings look similarly

12   safe to what you see in some other studies in

13   ezetimibe and ezetimibe/simvastatin combinations.

14   I think the hemorrhagic stroke signal, we've seen

15   that in other studies, as we saw in the CTT meta-

16   analysis.

17   So we should be mindful of that. It's a

18   relatively rare outcome, but it's notable.

19   Otherwise, I find the safety database from this

20   long trial convincing.

21   DR. R. SMITH: Any other comments? Yes?

22   DR. PROSCHAN: Yes. I certainly have some

1   concern about hemorrhagic stroke. And I think you

2   have to take that in the context of the benefit

3   that you're seeing. You can never look at one

4   thing and not the other.

5   Given that you're seeing a relatively small

6   benefit, that raises the concern level about seeing

7   things go the wrong direction for hemorrhagic

8   stroke. So yes, I definitely have some concerns

9   about that.

10   DR. R. SMITH: Dr. Heckbert?

11   DR. HECKBERT: Yes. I agree with these

12   comments, and basically I think the study showed

13   that the addition of ezetimibe to simvastatin,

14   basically the safety was really quite good. There

15   was the hemorrhagic stroke, which is of concern,

16   particularly when the benefit is not large, but it

17   was a known -- I felt that the sponsor explained

18   that it was a known association with hemorrhagic

19   stroke, and its not a new finding here.

20   So its certainly something to take into

21   consideration, but I don't think the trial

22   uncovered new safety signals that we didn't already

1   know about.

2   DR. R. SMITH: I might add to that that,

3   again, we've talked about the scale of this trial

4   and the quality of this trial. And actually,

5   safety issues were looked at very carefully. There

6   was a host of endpoints that we're not commenting

7   on because, in fact, there were not alarming

8   signals observed.

9   So one is always left with safety concerns

10   at the end of any study or clinical experience.

11   But a lot was looked at without generating alarm

12   except for what's been measured.

13   Dr. Proschan, you have another comment?

14   DR. PROSCHAN: Yes. I neglected to mention

15   in my earlier comment that I don't know if -- let's

16   say that that's real; there's an increased risk of

17   hemorrhagic stroke, and everyone believes it. I

18   don't know whether that's because of ezetimibe or

19   just because of additional cholesterol lowering. A

20   hypothesis was put forward earlier. It may be just

21   that if you lower cholesterol enough in people with

22   very low cholesterol, that in itself might be

1   harmful.

2   But I think its impossible to separate those

3   two things because, on the one hand, this trial is

4   testing a particular combination. But it also is

5   intimately linked to this idea of, is it good to

6   continue to lower, lower, lower, going below 70 or

7   below 60.

8   So I think that raises concern. Even if

9   it's not because of ezetimibe but it's just because

10   you shouldn't lower cholesterol too low, then I

11   think that's still a concern.

12   DR. R. SMITH: Dr. Kaul?

13   DR. KAUL: Yes. I agree. I have no major

14   safety concern. But I find it interesting that if

15   you lump hemorrhagic stroke as an efficacy

16   endpoint, they get penalized, but if you then go

17   back and include it as a safety endpoint.

18   So I would feel more comfortable if I had

19   lack of double counting in the benefit/risk

20   assessment. So they clearly are going to win with

21   respect to efficacy if they exclude the hemorrhagic

22   stroke, but they're going to lose in terms of

1   safety because quite a few people die as a result

2   of hemorrhagic stroke.

3   So I'd like to see those kind of analyses to

4   help frame the benefit/risk profile.

5   DR. R. SMITH: One question I might ask the

6   group, then, would be, other than the comments I've

7   heard, if there's anything more specific that panel

8   members might want to communicate to the FDA in

9   terms of how to proceed with this hemorrhagic

10   stroke data in hand. Yes, Dr. Teerlink?

11   DR. TEERLINK: John Teerlink. I think one

12   of the things we've mentioned, one of the ways you

13   can explain it is there may be too low of a

14   cholesterol, that you don't want to go below a

15   certain number. And I don't think any of us really

16   know what that number is.

17   But this has impact for if you're going to

18   say, well, we're just going to prove this and it

19   should be just done regardless of what cholesterol

20   is. I don't know what the risk/benefit of adding

21   ezetimibe on top of rosuvastatin with somebody who

22   has an LDL of 30 is going to be, and that's of

1   concern.

2   So if you get to the point of thinking about

3   how to think about labeling things, that is

4   something that I'd be concerned about.

5   DR. R. SMITH: Dr. Everett, were you wanting

6   to follow up on that?

7   DR. EVERETT: Yes, just quickly. It's

8   possible that the hemorrhagic stroke is related to

9   the enrollment criteria for the trial because

10 patients had to have an ACS to come in, and

11 immediately after an ACS, you're often on dual

12 antiplatelet therapy.

13   So the timing of those events -- and the

14 sponsor may have explored this -- might actually be

15 relevant. In other words, we're talking about an

16 ACS treatment population. If the patients had the

17 hemorrhagic strokes, there weren't that many. But

18 if they tended to have them in the first year or

19 two, when they tended to be on dual antiplatelet

20 therapy, plus the low LDL, that might be

21 illustrative.

22   DR. KAUL: That can be easily addressed with

1   a Kaplan-Meier plot. Look at hemorrhagic stroke.

2   DR. EVERETT: I don't know that I've -- at

3   least I haven't seen those data, but I think it's

4   worth looking.

5   DR. KAUL: I'm looking. Did you do the

6   Kaplan-Meier plot on that?

7   DR. CANNON: Excellent points. As we've all

8   noted, no one with the statins or any of these

9   agents knows why hemorrhagic stroke seems to be

10   higher. Slide up. These are the Kaplan-Meier

11   curves that have nonhemorrhagic stroke on top, and

12   the pointed question is hemorrhagic stroke on the

13   bottom, the hazard of 1.38, p-value of 0.11.

14   So it looks more linear over the plot here

15   of 7 years of follow-up. But I guess to the

16   overall point, this is hemorrhagic fatal or

17   nonfatal, so it's the total hemorrhagic stroke.

18   It's obviously balanced by the nonhemorrhagic.

19   If we could also have up the Giugliano less

20   than 30. We did explore the very appropriate

21   question, because we asked the same thing; is it

22   that we're getting people super-duper low? So this

1   is a plot. All the way on the left is hemorrhagic

2   stroke. And in the green color -- oh, slide up,

3   sorry.

4   So this breaks out the patient population by

5   the achieved LDL at 1 month and looks at subsequent

6   events to try and explore this question of if you

7   got the LDL very low. And so the group in green

8   has an achieved LDL of less than 30, and this

9   combines the two groups, so statin or statin and

10   ezetimibe.

11   The vast majority are in the combination in

12   that less than 30. There's just under a thousand

13   patients, so this is definitely the largest

14   experience. This was presented at the European

15   Society of Cardiology.

16   So then 40 to 50 is the achieved group, and

17   50 to 70 and greater. And you can see there's no

18   pattern of the bottom left corner in terms of event

19   rates. If anything, it's the lowest one in the

20   less than 30.

21   This is the plotted or the unadjusted rates,

22   but when we adjust, there's no difference adjusting

1   for the large number of different baseline

2   characteristics of those who achieve less than 30.

3   So we couldn't in this database identify very, very

4   low LDL as a risk factor.

5   So we come back to what all of us in the

6   various lipid trials have come to. So hopefully

7   that's helpful.

8   DR. R. SMITH: Thank you. Any -- well,

9   let's go to Dr. Fleming next.

10   DR. FLEMING: Just wanted to discuss a

11   separate safety issue, and that is to come back

12   once again to the issue about cancer risk and what

13   we've learned now from the collective experience.

14   SEAS, as we know, created a signal, and that

15   signal indicated that there were in excess of

16   diagnoses of new cancer, incidence as well as

17   cancer deaths. And in particular, the cancer

18   deaths excess was 37 against 20. Nominal

19   significance because the confidence interval

20   excluded equality.

21   Again, should raise another example about

22   how careful we have to be; when you explore data

1   and you find things, you may be finding something

2   that's a signal that's real. You may readily,

3   though, be finding something that's spurious. And

4   almost certainly you're overestimating it.

5   There'll be random high bias.

6   The sponsor at that time, or someone at that

7   time, went back in 2008 and did a look on an

8   interim basis of what was evolving from SHARP and

9   IMPROVE-IT, and very fairly estimates for the

10 cancer incidence. Cancer deaths, though, I think

11 the relative risk was still in the neighborhood of

12 about 1.3, 1.35.

13   My perspective and argument, I believe, once

14 you find a cancer signal, you do need to do what

15 was done here, and that is to look independently at

16 a different data set and find out, in a manner

17 independent, as to whether that's real.

18   The point estimate matters. But in essence,

19 safety isn't established by having a lower limit

20 that includes equality, meaning safety isn't

21 established by failure to show significant

22 increases. Safety is established by the upper

1   limit, by what you can rule out.

2   Do you have sufficiently favorable estimates

3   and precision in that? You can rule out an upper

4   limit that would be ruling out everything that's

5   unacceptable. So surely that conclusion didn't

6   come from that interim analysis in 2008.

7   In 2011, we had the revelation of SHARP, and

8   we got some more good news, I think. And that is,

9   SHARP said the cancer excess risk for cancer deaths

10   is 1.15, with an upper limit that's around 1.45.

11   So while that is moving in the right direction, it

12   still was suggesting a 15 percent increase with as

13   much as a 45 percent increase.

14   By the way, to be truthful, did anyone

15   actually think that we really had a 70, 80 percent

16   increase in cancer deaths? That would have been

17   totally unacceptable. But quite frankly, a 20 to

18   30 percent increase would be, I would view in most

19   settings, very, very unacceptable as well.

20   So the most reassuring evidence to date then

21   is IMPROVE-IT. And while I believe its overpowered

22   on its primary endpoint, hence statistical

1   significance is not enough on the primary endpoint,

2   one of the effects of that overpowered experience

3   in 88,000 person-years is to begin to get more

4   insight that's more reliable about some of these

5   other issues, such as cancer deaths.

6   So in this setting, we have a point estimate

7   of 1.03, which is, I think, the most favorable

8   evidence to date. Upper limit of 1.22. And so

9   it's still consistent with as much as a 22 percent

10   increase.

11   So I do call back a comment that the sponsor

12   had made when they were defending the fact that the

13   hazard ratio for overall mortality is 1. They were

14   pointing out how it would take 60,000 person-years

15   and 4- or 5,000 events to detect a 1 versus a 1.10.

16   They're right. It's also true for cancer deaths,

17   that it would take 4,628 deaths to distinguish 1

18   from 1.1. It would take 1,264 deaths to

19   distinguish 1 from 1.2.

20   So we're beginning to get toward that. We

21   have, between SHARP and SEAS, about 800 deaths. We

22   have an estimate that's 1.03 and 1.15. Put them

together, it's 1.07. Somebody put them together in

2008, so I put them together now.

So in essence, my view of what we know from

the totality of the data, is really encouraging.

But from an evidence-based perspective, the fact

that we don't have a significant increase doesn't

mean we've at this point totally nailed down the

cancer death issue.

Does it matter? Maybe not, because

everything's benefit to risk. And if we are in

fact seeing major benefits, we might accept a 10 or

maybe a 20 percent increase in cancer deaths,

maybe. The issue that I have of concern here is

overall deaths are neutral. In the trial here,

they're neutral even though there's only 8 excess

cancer deaths.

If my best sense of truth comes from all of

the data, from SHARP and from SEAS, I would say

that's my estimate of the meta-analysis. That's a

7 and a half percent increase, upper limit of 1.22,

which would mean you'd expect to see 20 excess

deaths.

1   If the upper limit of 1.22 is the truth,

2   there would be 60 excess cancer deaths. So the

3   totality of the data makes me confident that in

4   this type of setting where we saw an excess of 8,

5   it's very inconsistent. The truth would be more

6   than 60. But the point estimate from all the data

7   would say the truth should have been more like 20,

8   and we saw 8.

9   So I come away from this feeling broadly

10   reassured, saying, thank goodness for IMPROVE-IT.

11   It's given us the best sense yet, and it's the most

12   favorable sense yet, although it hasn't completely

13   eliminated the issue, particularly in a setting

14   where the on-target effects are not leading to any

15   reduction in overall deaths.

16   So again, the fundamental issue is, you've

17   resolved a safety issue not when you've failed to

18   show there's an excess but when you've successfully

19   ruled out any excess which, if real, would be

20   unacceptable. And when the on-target effects are

21   so limited, it makes a very low threshold for what

22   would still be of some relevance.

1   DR. R. SMITH: Dr. Hiatt, I think you had a

2   comment?

3   DR. HIATT: Yes. Can you hear me?

4   DR. R. SMITH: Yes, we can.

5   DR. HIATT: I lost the audio feed on the

6   WebEx. But I'd like to make a comment on the

7   hemorrhagic stroke risk. I would simply note that

8   on page 95 of 178 in the FDA briefing document, the

9   on-treatment analysis had presented 32 hemorrhagic

10   strokes in the combined group, 34 in the

11   simvastatin alone group, which has been commented

12   on previously.

13   I just would note that. I think there are a

14   lot of ways to look at safety. I do think safety

15   may be best assessed when you're actually exposed

16   to the agent, and so this maybe helped me a little

17   bit. But I still have a concern about hemorrhagic

18   strokes because in most settings, in most trials,

19   hemorrhagic strokes are highly associated with

20   death. And so that doesn't completely erase that

21   concern.

22   Another comment would be on the muscle side

1   effects, and I think that what's helpful from

2   IMPROVE-IT is that the muscle effects looked at

3   numerous ways that were fairly balanced between

4   groups, and continue to support, really, the

5   clinical trial evidence that true muscle side

6   effects are quite uncommon, in sharp contrast to

7   what many of our patients actually report to us on

8   a daily basis when they see us in clinic.

9   Lastly, I think Tom Fleming said better than

10   anyone what the cancer exposure was like and how

11   helpful that was. Thank you.

12   DR. R. SMITH: Other comments?

13   (No response.)

14   DR. R. SMITH: So to briefly summarize, the

15   overall opinion of the group, as I hear it, is that

16   the safety findings generally are encouraging and

17   favorable and not concerning. To comment a little

18   further on the cancer risk, the new data added to

19   prior data on cancer risk are reassuring and are

20   encouraging, although not adequate to completely

21   rule out an increased risk of cancer with this

22   agent. That's a common situation with clinical

1   data.

2   In terms of hemorrhagic stroke, the most

3   discussion was generated and the most concern, and

4   it's felt that it's important to note the numbers

5   on hemorrhagic stroke. It raises some concerns

6   about the potential relationship between degree of

7   cholesterol lowering and extreme degrees of

8   cholesterol lowering and that possible link to the

9   occurrence of hemorrhagic stroke.

10   Some data were presented from the IMPROVE-IT

11   trial that aren't consistent with that, although

12   with very small numbers. So the thought from the

13   committee was that that's something the FDA needs

14   to keep in mind, perhaps not just for this trial

15   but in general, this issue of potential hazards of

16   very low cholesterol levels in response to various

17   treatments.

18   Any additions to that? Dr. Kaul?

19   DR. KAUL: Yes. I think we have to provide

20   advice to the clinicians. How do we mitigate this

21   risk for hemorrhagic stroke? And we need to

22   understand that better before we provide that

1 advice. You'll have to have some further

2 exploratory analysis to figure that out.

3   Is it the on-treatment LDL level? Is it

4 concomitant therapies? Is it prior history? All

5 of that needs to be done because in terms of the

6 weight, most clinicians and most patients are

7 fearful of hemorrhagic stroke.

8   The case fatality rate with hemorrhagic

9 stroke is three- to fourfold higher than ischemic

10 stroke. And so I think additional effort needs to

11 be made to explore that so that we can provide

12 advice to the clinicians to mitigate that risk.

13   DR. R. SMITH: Okay. So I'm going to

14 progress to the final question, which is a voting

15 question, and before reading it and opening the

16 discussion, just mention we're going to be using an

17 electronic voting system.

18   Once we get to the stage of voting and not

19 just the discussion, on your microphone the buttons

20 will start flashing and they'll continue to flash

21 even after you've entered your vote. So you should

22 press the button that corresponds to your vote.

1   You can press it more than once if you want. You

2   can change your vote until the voting is complete.

3   At the end of the voting, the vote will be

4   displayed on the screen. The DFO will read the

5   vote from the screen into the record. And then

6   we're going to go around the room, and each

7   individual who voted will state their name and

8   their vote into the record, and at that point, can

9   comment on why you voted as you did if you want to.

10   And it's helpful if you do that.

11   So I think we'll proceed next to the -- I'll

12   read this question, and then if there's any needed

13   clarification, we can talk about that.

14   So the voting question is, do the efficacy

15   and safety data from the IMPROVE-IT trial provide

16   substantial evidence to support approval of a claim

17   that adding ezetimibe to statin therapy reduces the

18   risk of cardiovascular events?

19   If your vote is yes, please comment on your

20   rationale and whether such claim should carry any

21   limits; for example, whether the data support use

22   in only certain clinical situations or subgroups.

1   If your answer is no, please provide your rationale

2   and comment on what additional data would be needed

3   to support approval.

4   First of all, I'd just like to ask if any of

5   the committee members have points for clarification

6   on the question, because then I think we're going

7   to progress to the vote.

8   DR. TEERLINK: One quick question. Do you

9   want to define for us what "substantial" is?

10   (Laughter.)

11   DR. J. SMITH: Just a quick, easy question.

12   Thank you. So substantial evidence -- and I don't

13   have the statute in front of me, but to paraphrase.

14   Substantial evidence is evidence that consists of

15   adequate and well-controlled investigations on the

16   basis of which it can be concluded that the drug

17   will have the effect it purports to have.

18   That is often interpreted, the plural

19   "investigations," as two or more trials, as many of

20   you know. The statute also allows for one trial to

21   provide substantial evidence. The agency has

22   described that in guidance.

1   In general, for a single trial to provide

2   substantial evidence, one would expect the trial to

3   be of excellent design, very well conducted, to

4   have a highly reliable and statistically

5   significant, strongly statistically significant,

6   evidence of an important clinical benefit.

7   But ultimately, the guidance also says that

8   whether to rely on a single adequate and well-

9   controlled study is inevitably a matter of

10   judgment, and you are here to provide some

11   judgment.

12   Dr. Kaul, you have a follow-up question?

13   DR. KAUL: Yes. And you faithfully

14   represented the statute. The difference here is,

15   does that still apply to a drug or a biologic

16   that's already approved?

17   DR. J. SMITH: Yes.

18   DR. KAUL: Okay. Thank you.

19   DR. R. SMITH: Any other questions,

20   comments, related to this question itself?

21   (No response.)

22   DR. R. SMITH: So if your microphone is like

1   mine, the lights are flashing and the voting is

2   open.

3   (Vote taken.)

4   LCDR BEGANSKY: The vote was 5 yes, 10 no,

5   zero abstain.

6   DR. R. SMITH: So what we would like to do

7   at this point is, for each of the voting members,

8   I'd like to just go around the room in order. I

9   think we'll start over on my right.

10   We need you to activate your

11   microphone -- starting on the end, yes -- you need

12   to activate your microphone, state your name for

13   the record, state your vote, and then you can make

14   any comments that you wish to make about the basis

15   for your vote.

16   DR. TEERLINK: Surely. John Teerlink, and I

17   voted no. I think this trial actually meets a lot

18   of the criteria in terms of being excellently

19   designed, wonderfully executed, and rigorously

20   performed. So that's the good news.

21   I do not believe it provided, however, the

22   substantial evidence in terms of supporting the

1 approval claim, for two reasons. First of all, I

2 don't think it was substantial in terms of

3 statistical and clinical meaningfulness in terms of

4 the endpoints. And also in terms of the claim

5 specifically, the claim was much too broad for me

6 in terms of the population that was studied. I

7 think that's probably a reasonable summary.

8 　　　　　DR. PROSCHAN: I'm Mike Proschan. I also

9 voted no. I agree with what Dr. Teerlink said,

10 that to me it wasn't substantial. And if you're

11 thinking in terms of two trials being significant,

12 that's a pretty high degree of evidence, and I

13 don't think that was met.

14 　　　　　I'm definitely concerned about missing data.

15 I completely disagree that randomization is going

16 to somehow protect you. I think the fact that

17 there was such a big imbalance in missingness in

18 that first year tells you that randomization is not

19 protecting you because you shouldn't see an

20 imbalance if you think it's all the same,

21 randomization would protect you.

22 　　　　　So to me, that's a big issue, the missing

1   data. And I also had concerns about the

2   hemorrhagic stroke. But ultimately, I think it

3   comes down to, was it substantial when you look at

4   the benefits versus the risk, and I don't think it

5   was.

6   DR. R. SMITH: Again, for no votes, it would

7   be helpful if you might comment on what additional

8   data you would need or want to see. And again -- I

9   apologize -- state your name again.

10   DR. TEERLINK: I'm still John Teerlink. It

11   hasn't changed.

12   DR. R. SMITH: The recording doesn't know

13   that.

14   DR. TEERLINK: I know. So in terms of

15   additional data, I think it would have been

16   interesting to have seen what would have happened

17   had the sponsor gone for an indication for post-

18   ACS. So that's the question in terms of patient

19   population. I think they were way too broad in

20   their request in terms of patient populations.

21   Otherwise, I'm not sure that there's

22   anything additional that could be done except

1   another huge trial, and I'm not sure it would be

2   done.

3   DR. PROSCHAN: One thing that occurs to me

4   is you could stratify it by the baseline LDL level

5   because it's possible that in those with high

6   enough LDL, there is a good, favorable benefit to

7   risk profile. So that would be what I would

8   recommend.

9   DR. KAUL: My name is Sanjay Kaul, and I

10   voted no. The two key reasons why I voted no was

11   that although the treatment effect was modest,

12   along expected treatment effect, I didn't think it

13   was statistically persuasive, going by the

14   regulatory statute. And I had questions about the

15   clinical meaningfulness of the treatment effect.

16   With regards to the subgroups and missing

17   data, that added additional concern, but by

18   themselves they were not deal-breakers for me.

19   The most robust treatment effect is seen in

20   an endpoint, which unfortunately was an exploratory

21   endpoint; hence, cannot be used for a claim, which

22   is the cardiovascular death, nonfatal MI, and

1　nonfatal stroke. We see a 10 percent risk

2　reduction with a p-value that 0.003, quite robust.

3　But unfortunately, we cannot use that. It's not

4　approvable for a claim.

5　　　　What would I like to see in addition? I

6　agree with Dr. Proschan. If I had to redesign this

7　trial, I would have included patients with a higher

8　baseline LDL, so that I would get a larger delta

9　and I would have seen a bigger treatment effect.

10　　　　Buried within the data set, I think there

11　are individuals where the baseline LDL might be a

12　little higher. If we can do that stratified

13　analysis, perhaps that might be informative. I'll

14　stop there. Thank you.

15　　　　MS. MCCALL: Debra McCall, and I voted no,

16　for some of the reasons that have already been

17　noted. The missingness stands out.

18　　　　As a patient representative, my job is to

19　really look at risk versus benefit. And when I

20　read these, I always think, well, would I take it?

21　Would I recommend it to family and friends that I

22　care about? And the risk versus benefit on this

1   was almost neutral until I looked at the

2   hemorrhagic stroke. I've cared for family and

3   friends who've had hemorrhagic strokes. And I

4   really did not like this data, and I would not be

5   comfortable saying, oh, I think this is a good

6   idea, because of that.

7   What the sponsor did really right about

8   this, which I was really tickled to see, was that

9   you had a younger population. You started at 50,

10   not 65. You had 25 percent female, which is higher

11   than most of the data ones that I see for trials.

12   You also added highly sensitive CRP, which I

13   don't see very often in anything cardiovascular.

14   And I'm glad to see that was included this time.

15   This was a nice, big, long study with lots of juicy

16   data. So that was really wonderful.

17   Like Dr. Kaul mentioned, if they were ever

18   going to do this again, I would like them to start

19   off or include patients with a higher LDL than the

20   70 than they had set as the target. And I would

21   also ask that they specifically target more

22   minorities in here.

1   DR. R. SMITH: Dr. Fleming, you're up.

2   DR. FLEMING: Tom Fleming. I voted no,

3   although I hate the voting process, as I've said

4   many times in advisory committees. What does

5   "advisory" mean?

6   So this has been a fabulous discussion. I

7   think our role is to give you a sense of what we

8   think the strengths are and the concerns are. And

9   I think the people on the committee have done a

10 marvelous job on that. The vote to me isn't the

11 essence.

12   My sense about this is benefit to risk. My

13 sense about this is very much, what is the

14 statistical persuasiveness of whether or not we

15 have a clinically relevant effect? And missingness

16 plays a role in this. The effects on components

17 play a role.

18   I think my main rationale comes from my

19 answers to questions 1 and 2. My belief -- by the

20 way, I would endorse what Michael Proschan has

21 said, and his randomization absolutely does not

22 allow us to believe that missingness is an issue

1   that could not be differentially influential.

2   Randomization only protects you for factors

3   up to the time you begin therapy. Therapies'

4   administration can clearly impact patients,

5   circumstances and other factors that influence

6   missingness.

7   When we take into account missingness, which

8   isn't a huge issue here but it becomes important

9   because the effect is so frail in terms of its

10   magnitude, my sense of the truth is that we have an

11   estimate of a 5 percent reduction with a confidence

12   interval from 0.9 to 1.0.

13   So the 0.9 is as important as the 1.0 here.

14   We're ruling out as much as a 10 percent reduction,

15   which is along the lines of what we had hoped the

16   truth would be when we designed the trial.

17   The 1.0 is marginally ruled out, but it is

18   not robust from the perspective of a single

19   stand-alone trial, where we would expect more than

20   just 0.025. And there's no single magical p-value.

21   But certainly, .025 itself in a single trial, one

22   such as this where there was plenty of opportunity

1 for having a highly robust p-value if the estimates

2 had been anything close to what we had hoped to

3 see, it isn't robust.

4   In terms of clinical relevance, I am most

5 impressed with mortality, with strokes without

6 recovery, with STEMI MIs. And we're estimating a

7 reduction, but it's a reduction of about 1.5 events

8 per thousand person-years. If we count all the

9 events in the primary endpoint, it becomes closer

10 to 4.5 events per thousand person-years.

11   It's interesting to put that into context

12 because we do cardiovascular non-inferiority trials

13 frequently now. We do them to rule out what would

14 be unacceptable increases. We do them in obesity

15 and type 2 diabetes. We do them COX-2 inhibitors

16 in OARA patients.

17   The calculations that we're using for those

18 margins, those upper limits that we're using in

19 that setting that are typically in the range of 1.3

20 to 1.4, are essentially ruling out an increase in

21 MACE events that would be in the range of 3 to 6

22 excess events per thousand person-years.

1   To have a basis for accepting that, that

2   means that it's okay to have that much. You just

3   can't have more. Well, if it's okay to have that

4   much just so you don't have more in a

5   cardiovascular safety trial, then why is it okay to

6   have 1.5 to 4.5 as something that really matters?

7   So you've got to be consistent with your

8   non-inferiority margins. If something matters in a

9   superiority setting, then it should matter in a

10   non-inferiority setting. And we've spoken for a

11   long time about what we'd accept in

12   non-inferiority.

13   So the 1.5 to maybe 4.5 events per thousand

14   person-years is certainly very controversial as to

15   whether or not it's enough. But that together with

16   the fact that a p-value in a single stand-alone

17   trial of 18,000 people with 2500 deaths and

18   5,000 primary endpoints, achieving something that

19   is in the fragile range of a 0.039 p-value is

20   surely not a robust evidence of benefit.

21   DR. BLAHA: Michael Blaha. I voted yes.

22   And I voted yes for what I would consider a

1   modified claim, which I'll come back to.

2   I want to state that I think there is a

3   modest unmet need for add-on therapy, LDL-lowering

4   therapy, in patients with coronary disease,

5   particularly patients with coronary syndrome. So I

6   think this is an important space we're talking

7   about, where clinicians have a hard time treating

8   patients to low LDL cholesterol levels because of

9   statin intolerance or for other reasons.

10   So in my view, the IMPROVE-IT study, which

11 was large, 18,000 patients over 7 years, showed

12 that lowering LDL-C with ezetimibe add-on therapy

13 works. That is, it lowered the primary endpoint,

14 stated in the trial, in patients with recent ACS,

15 consistent with the CTT analysis.

16   But of course, this effect is modest. But

17 the trial was positive. The effect is modest, and

18 that's not something that clinicians are uncommon

19 dealing with, is an effect size that's small.

20   In my view, we waited for a long time for

21 evidence that a drug added onto a statin therapy

22 works. And we have it, actually interesting here.

1   This was a positive study for this drug, not for

2   any drug added onto a statin but for this drug.

3   It appears that this drug lowered the

4   primary endpoint. That's the first time we've seen

5   that on top of a statin, and that's clinically

6   relevant, and there's an unmet need in this area.

7   Now, of course, once again, I'm going to come back

8   to say over and over, the effect was small.

9   I worry we're missing some of the key

10   elements of this study. I guess I'd come back to

11   the biology a little bit here. The idea that lower

12   is better is really an important concept that the

13   IMPROVE-IT study showed. There are lots of other

14   elements that are all very important that we've

15   discussed. But IMPROVE-IT was extremely important,

16   I think, for showing the scientific community that

17   lower is better.

18   I think we've talked sometimes about not

19   looking at individual endpoints, and we talked a

20   lot about individual endpoints since some of us

21   talked about mortality a lot. Once again, of

22   course, statins in primary prevention don't reduce

1   mortality. We've all had this discussion before

2   about reducing mortality, and statins in primary

3   prevention also don't reduce mortality. I think

4   all of us use those drugs and find them highly

5   indicated.

6   A lot of variable opinions about clinical

7   relevance. I actually find the results mildly

8   clinically relevant because patients who've had an

9   acute coronary syndrome want to avoid heart attacks

10 and strokes. That's what my patients most of the

11 time want to avoid.

12   So I think there's a difference in the room

13 amongst those who treat patients a lot or treat

14 patients less about clinical relevance, and I think

15 that's a reasonable discussion.

16   So what do I do when the effect size is

17 small in clinical practice? I do risk

18 stratification. SO I would imagine that patients

19 in clinical practice who might be treated with

20 ezetimibe on top of a statin might be those that

21 are at higher risk.

22   That could include older patients or

1   patients with diabetes or more advanced coronary

2   disease to reduce the number needed to treat. And

3   in patients who are lower risk, I wouldn't

4   anticipate using the drug.

5   So I voted yes consistent with the way that

6   I would use this drug in clinical practice. And I

7   actually would recommend it to a family member who

8   has had an acute coronary syndrome who had LDL

9   levels that were, let's just say, above 70 on a

10   maximally targeted statin. We'll come back to that

11   phrase in a second.

12   So I would have advocated for a label

13   endorsing modest cardiovascular risk lowering in

14   high-risk patients with recent ACS -- let's call it

15   maybe within 6 to 12 months of an ACS -- on top of

16   maximally tolerated statin, with using the

17   phraseology consistent with what we use when we

18   talked about PCSK9 inhibitors.

19   Once again, I said modest cardiovascular

20   risk lowering in high-risk patients with recent ACS

21   on top of maximally tolerated statin.

22   DR. WILSON: Peter Wilson. I voted yes. I

1   will not repeat the same issues that Mike Blaha

2   just iterated. But to build on a couple of the

3   aspects, one is, I see the data that was put

4   forward.

5   This is one of the highest quality trials

6   that any of us have reviewed, and it was twice the

7   size and one and a half times the typical length.

8   So I think that it meets certainly more than one

9   trial; it's almost two trials all by itself, number

10   one.

11   Number two is, a low LDL starting point is

12   a particularly difficult point. We haven't had a

13   positive trial yet that's really caught our

14   attention until this result came along. And in

15   fact, I was glad there was some clarification on

16   what "substantial" is, but from my perspective, I

17   think we think of substantial for primary

18   prevention and from a different starting point.

19   This is much more difficult from my

20   perspective, a secondary prevention trial with a

21   low starting point for a sponsor that did work with

22   the agency to put together a really well-done trial

1   that essentially ran over 10 years until we get the

2   results.

3   Then it's a positive study, and then to say

4   it's not something that's going to change us. It's

5   going to change us. We certainly know that this is

6   a positive result even with the limitations that we

7   discussed a lot today.

8   I echo also, anticipating Brendan Everett's

9   and Mike Blaha's, is a narrow viewpoint. This is

10   an ACS trial, and I'm not sure it really can be

11   extended to all patients with chronic, stable

12   disease.

13   So in summary, I think it's great that for

14   those of us who are clinicians, we have a positive

15   trial at the lower level, and it's an evidence-

16   driven result.

17   DR. HECKBERT: This is Susan Heckbert, and I

18   voted no. Although I felt IMPROVE-IT had an

19   excellent design and was very well conducted -- it

20   was obviously huge, lasted a long time, and gave us

21   a lot of good information about safety -- I don't

22   feel that it met the requirement that it provide

1   strongly statistically significant evidence of an

2   important clinical benefit. And the details of my

3   thinking on that have already been very well

4   described by Drs. Teerlink, Proschan, Kaul, and

5   Fleming.

6   DR. EVERETT: Brendan Everett. I voted yes.

7   I think it's important to emphasize, as many people

8   have, that in this case the perfect is the enemy of

9   the extremely, very, very good. And it's just not

10   possible to do a perfect trial and get the perfect

11   answer to the clinical question.

12   So in that sense, I think the practicalities

13   mean that from my standpoint, this represents

14   substantial evidence to support approval. And

15   that's my own judgment, obviously.

16   I think it's important that the IMPROVE-IT

17   trial included patients with ACS. But patients

18   with ACS then transitioned into chronic, stable

19   coronary disease. And not all patients with

20   chronic, stable coronary disease start with an ACS.

21   Many, many patients are diagnosed with stable

22   angina or don't have an acute coronary syndrome,

1   and yet nonetheless require adjunctive therapy for

2   LDL cholesterol levels that are not optimal.

3   So while expressing clearly that the data

4   from IMPROVE-IT don't necessarily directly apply to

5   these patients, I'm comfortable that those are

6   patients similar enough to those enrolled in

7   IMPROVE-IT they are likely to derive benefit, and

8   maybe are even more likely to derive benefit than

9   those immediately post-ACS.

10   So while I have qualms then about

11   potentially considering extending or broadening the

12   label, it also seems to me like those patients

13   ought to be the real target of this particular

14   drug.

15   I want to emphasize, as others have, that

16   the benefit is really pretty modest, which I think

17   we all agree. Nonetheless, it's likely. And it is

18   likely to be even more modest or less substantial,

19   if you will, in patients who were to start

20   ezetimibe with even lower LDL cholesterol levels.

21   But the problem I have in my clinic is not

22   that. It's the converse, which is that typically

1   patients have LDL cholesterol levels that are too

2   high on the maximum tolerated statin dose or statin

3   intensity. And so that's a patient population who

4   actually might derive more substantial benefit than

5   what we saw in the trial. So I think for that

6   reason, among the others I've expressed, I voted

7   yes.

8   DR. R. SMITH: This is Robert Smith. I

9   voted no. It was a difficult vote, which I

10 ultimately based on the narrow reading of the

11 question as posed by the FDA, as Dr. Heckbert

12 stated, whether there was strongly statistically

13 significant evidence of a substantial clinical

14 benefit.

15   I feel that there are some questions that

16 have been raised about the statistical analysis and

17 the strength, supporting the conclusion. They

18 don't bother me as much as the very modest clinical

19 effect in making that vote.

20   Now, putting that aside, I think this is a

21 positive trial. The effect is modest. I don't

22 think that it communicates that this is a drug that

1   is not effective in lowering risk. And I think

2   that remains as a question.

3   So my no vote is really geared to the

4   specific question and not whether or not there is a

5   role there for the drug. I in fact suspect that it

6   is effective, and I think we just don't know that.

7   That is again not a criticism of the design

8   of this trial, which was wonderfully designed and

9   conducted, even though I would sure like to know

10   what would be observed in some different patient

11   populations, as has been discussed by others, with

12   perhaps higher LDL levels, where there might be

13   both lowering from a higher starting level and

14   perhaps a greater magnitude of effect on LDL

15   levels.

16   So I'm not unenthusiastic about the drug.

17   But in answering this question, I don't see

18   substantial clinical benefit, and I have some

19   questions about the strength of the conclusion that

20   this is a statistically significant effect.

21   DR. HIATT: This is William Hiatt. I voted

22   yes. I would comment that I was actually a little

1   surprised by the committee vote, with the majority

2   voting no. I was surprised because the IMPROVE-IT

3   trial was a positive trial on cardiovascular

4   events, demonstrating the combination of ezetimibe

5   plus simvastatin was better than simvastatin alone.

6   As I think back over many years previously

7   serving on the cardio-renal advisory committee and

8   now EMDAC, that this discussion of statistical

9   significance versus clinical relevance has come up

10   a number of times.

11   It seems that the history has been that the

12   FDA's role is to decide if a study is positive or

13   not, and it's other bodies that decide what's

14   clinically significant, relevant, and applicable.

15   And that can be the payers. It can be the

16   guidelines. It can be a number of mechanisms to do

17   that. And I think back on examples such as carotid

18   stenting that follow that line of reasoning.

19   So I was surprised. I think that in

20   addition to it being a positive trial, it offers an

21   alternative that may not be applicable to many

22   patients, but certainly to some. And I think

1   having something that helps guide an alternative is

2   useful, although the evidence speaks for itself and

3   certainly clinicians can use this off-label.

4   But overall, I think that it makes me a

5   little uncomfortable to take a positive trial on

6   the primary endpoint and disclaim that based on

7   what is substantial and what is not because I don't

8   think that's clearly defined.

9   Tom, I do agree with you that if we're going

10   to apply something -- we set arbitrary thresholds

11   for ruling out cardiovascular harm for obesity and

12   diabetes drugs -- maybe we should think on the

13   other side of the spectrum. But we haven't really

14   cleanly done that.

15   I too am uncomfortable about the upper bound

16   on safety trials, and then maybe what should be the

17   lower bound on efficacy trials. So overall, I do

18   think the evidence supports this.

19   If it were to move forward at some level, I

20   would encourage the FDA in its labeling to

21   emphasize what the number needed to treat per year,

22   which in my calculation was around 350. So it took

1   a lot of exposure to prevent one event. I'll leave

2   it at that. Thank you.

3   MS. HALLARE: Diana Hallare. I voted no.

4   The results were modest, as my peers have -- I

5   mean, those who voted no have indicated. And also,

6   I found the question to be rather broad, actually a

7   bit broader than discussion number 3. For

8   instance, with regards to the statin therapy, I

9   found it to be a broad category, and also the

10   populations with the risk of cardiovascular events.

11   I also found that the missing data and the

12   stroke data were concerning. And if I were to ask

13   for additional data, that would be what would be

14   the safety and treatment effect results with

15   regards to the combination of the ezetimibe and

16   also the other statins, and also how other

17   populations would be affected.

18   I understand that we are not necessarily

19   looking at subgroups right now, but what if you're

20   going to consider people with hypertension and/or

21   high cholesterol and/or diabetes who may or who may

22   not have had prior cardiovascular events? So this

1   concludes why I voted no and what I believe should

2   be added.

3   DR. SHAMBUREK: This is Bob Shamburek, and I

4   voted yes. I want to first say that the group who

5   performed the study should really be complimented

6   for their persistence. I wasn't sure the study

7   could get done with all the setbacks, with the

8   cancer risk in the SEAS trial, the changes of

9   simvastatin going from 80 to 40 and everything.

10   And they really should be complimented.

11   This study was in lower LDL patients at

12   entry who had ACS, but part of a very long natural

13   history of atherosclerosis. This is a clinically

14   important trial. There is an unmet need in this

15   population, which is typically not studied. It

16   showed lowering LDL to less than 70 is important

17   for clinical events. Treatment with the

18   combination ezetimibe and simvastatin resulted in

19   somewhere between 5 and 6.4 percent relative risk

20   cardiovascular events, which over a lifetime has a

21   major impact.

22   It was driven by the elderly, age over 75,

1 and diabetes. But this is certainly a biologically

2 plausible group. This is clinically important for

3 endpoints and a clinically logical group that would

4 benefit the most.

5   The events were driven by nonfatal MI and

6 nonfatal stroke, which is important to my patients.

7 There were no safety issues other than what we

8 talked about with the hemorrhagic stroke and no

9 concern for prespecified safety endpoints. I think

10 the results are consistent with the CTT meta-

11 analysis, which included data from 26 statin

12 trials.

13   I think the findings of reduced risk, which

14 were not the primary endpoint of the SEAS and SHARP

15 trial, were supported. I'm not completely

16 reassured, with the missing data, how to deal with

17 that or the hemorrhagic stroke, but that did not

18 sway my vote.

19   I believe the data supports the claim, and I

20 have no suggested limits. I think it could be

21 extrapolated to other statins of comparable LDL

22 cholesterol lowering to levels that were seen in

1   IMPROVE-IT. And that's my explanation.

2   CAPT BUDNITZ: Dan Budnitz. I voted no. I

3   thought either the impact on clinically significant

4   outcomes is small but distributed across a broad

5   population, or maybe it's a stronger benefit among

6   a subgroup of patients.

7   But I don't know what that subgroup is, and

8   so I don't know what a label would say. Maybe it's

9   older folks. Maybe it's patients with diabetes.

10   And maybe these are just proxies for some other

11   biological mechanism yet to be determined.

12   So what would need to be done would be a

13   trial of that targeted population, if there truly

14   is a stronger benefit among that smaller group.

15   And the hope would be that a smaller trial would be

16   sufficient because there'd be a stronger benefit in

17   that group; but concern that I don't know how to

18   label this for a broad population.

19   DR. PACKER: This is Milton Packer. I voted

20   no. The purpose of this committee is not to

21   determine whether a trial is positive or negative.

22   I don't really like those terms. I don't know what

1 a positive trial is. I don't know what a negative

2 trial is.

3   I'd like to find out whether a trial is

4 informative or not informative, whether it's

5 interpretable or not interpretable, whether it

6 helps or whether it confuses. There's no binary

7 concept of a positive versus a negative trial.

8   The second point I'd like to make is

9 everyone who wants to use this drug for risk

10 reduction in cardiovascular disease can do that

11 right now, based on the current labeling. If you

12 think that the LDL hypothesis is valid, and I won't

13 dare challenge that today, you have a label right

14 now for this drug that says that you can use it for

15 cholesterol lowering.

16   If you believe that that cholesterol

17 lowering lowers cardiovascular risk, then IMPROVE-

18 IT supports that, and you can do it, and you don't

19 need a label change to do that. The label change

20 here is -- if you believe that this drug lowers the

21 LDL cholesterol, and LDL cholesterol determines

22 cardiovascular risk, you don't need any additional

1   help from this committee.

2   However, there is something I'd like to

3   suggest that would be perhaps unexpected. The

4   current label for this drug says that there is no

5   evidence that the effects of this drug change

6   cardiovascular outcomes. Is that correct?

7   DR. CLARK: There's a limitation of use.

8   DR. PACKER: Okay. I might suggest that we

9   have enough evidence to take that line out.

10   DR. J. SMITH: Just to clarify the point

11   that you might want to make, the current Zetia

12   label says, "The effect of Zetia on cardiovascular

13   morbidity and mortality has not been determined."

14   DR. PACKER: I think that we have enough

15   data right now not for a claim, but, gee,

16   18,000 patients followed for 6, 7 years, I think

17   that deserves a description in the clinical trial

18   section. And if you describe it in the clinical

19   trial section with appropriate caveats and all the

20   concerns that this committee has expressed, why

21   would that not be a useful addition to the label?

22   It's not a claim. It is a piece of

1 information in the clinical trial section, and it

2 could be substituted for the current language that

3 says that the effect of this drug on cardiovascular

4 events is unknown.

5 Well, that to me is the kind of thing that

6 you say when the sponsor hasn't even tried to look

7 for the effect on cardiovascular risk. Here, the

8 sponsor has made an enormous effort to try to

9 define that. And it actually has done that with

10 confidence intervals that are narrow, and

11 unimpressive in terms of an effect.

12 But gee, to keep that line in the package

13 label is to say that this trial didn't teach us

14 anything. And that's not fair. This trial taught

15 us something. We may not think it's enough for a

16 claim, but the trial was informative.

17 DR. R. SMITH: Thank you. Dr. Kewalramani,

18 would you like to make any comment? I know you're

19 not a voting member, but --

20 DR. KEWALRAMANI: I'm sorry. My voice is

21 giving way. But I think the important points

22 have been covered. I will say that it has been

1   acknowledged, but I will just underline the

2   challenges of doing a trial of this size, of this

3   duration, in the population that was studies to

4   both study an important question but also do what

5   is felt to be appropriate for patients who are

6   post-ACS and at high risk to maintain them in a

7   certain LDL range, which may be on the lower side.

8   Given the practical limitations of what is

9   possible for this kind of question, I think that

10   the data are sufficient to teach us that there is a

11   reduction in LDL along the lines that were

12   purported based on the CTT examination, and the

13   outcomes benefit are modest but not absent.

14   DR. R. SMITH: Thank you.

15   FDA, would you like to make any final

16   comments?

17   DR. J. SMITH: I think, as always, you have

18   blessed us with a very rich and thoughtful

19   discussion, and we thank you very much for your

20   time and all of your comments. And with that, I

21   would just like to thank you all very much for

22   being here.

1   DR. R. SMITH: Okay. I, too, would like to

2   thank the sponsor for your presentations and your

3   help in probing questions and finding data for

4   questions that came up, and the FDA for all your

5   help, and the panel members for a really

6   informative, thoughtful discussion. Thanks for all

7   the time, and thanks to the people in the audience

8   for being here.

9   This meeting is now adjourned. Please

10   remember to take your belongings with you, and I

11   think you're supposed to drop off your name badges

12   also.

13   DR. PACKER: And thank you for the chair.

14   Thank you.

15   **Adjournment**

16   DR. R. SMITH: So we're adjourned.

17   (Whereupon, at 4:54 p.m., the meeting was

18   adjourned.)

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