FOOD AND DRUG ADMINISTRATION

NINETY-SIXTH MEETING OF THE

CARDIOVASCULAR AND RENAL DRUG ADVISORY COMMITTEE

8:37 a.m.

Friday, April 12, 2002

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

ATTENDEES

COMMITTEE MEMBERS:

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ATTENDEES (Continued)

COMMITTEE MEMBERS: (Continued)

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SPECIAL GOVERNMENT EMPLOYEES:

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ATTENDEES   (Continued)

SPECIAL GOVERNMENT EMPLOYEES: (Continued)

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SPONSOR REPRESENTATIVES:

RAY BAIN, PH.D.
BARRY BRENNER, M.D.
MICHAEL C. ELIA, PH.D.
JONATHAN FOX, M.D.
BONNIE GOLDMAN, M.D.
STEVEN HAFFNER, M.D.
WILLIAM KEANE, M.D.
MARVIN KONSTAM, M.D.
PETER KOWEY, M.D.
SHAHNAZ SHAHINFAR, M.D.
SCOTT ZEGER, M.D.

C O N T E N T S

NDA 20-386/S028, Cozaar (losartan potassium)
Merck and Company, Inc.
Proposed Indication: For the Treatment of
Type II Diabetic Patients with Nephropathy

* * *

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

2   (8:37 a.m.)

3   DR. BORER: We will call the meeting to order.

4   This is the 96th meeting of the Cardiovascular and Renal

5   Drugs Advisory Committee.

6   The agenda consists of consideration of one NDA

7   for losartan potassium for the indication of treatment of

8   diabetic patients with type II diabetes with nephropathy.

9   We have no applicants for public discussion

10   this morning.

11   I need to announce that Dr. Michael Artman, who

12   made every effort to be here, was unable to get here

13   because of a last minute problem, so the committee will be

14   without Dr. Artman today.

15   I also want to announce prophylactically that I

16   have been importuned to provide a break at 9:45. We didn't

17   do that the last time, and so we will. So, don't worry.

18   Now, we will begin then with the conflict of

19   interest statement. Dr. Peterson, do we have one?

20   DR. PETERSON: Yes. Before we go on I just

21   want to caution the committee that if you are going to

22   speak you need to push the center button to turn the mikes

23   on.

24   DR. BORER: Yes, I'm sorry. I should have

25   mentioned as well that as for the committee, as well as for

1   anybody among the presenters or among the audience, if you

2   are recognized, we do need you to state your name before

3   you start talking so that the transcription can be as

4   accurate as possible. Thank you.

5   DR. PETERSON: I'll read the conflict of

6   interest statement now. The following announcement

7   addresses the issue of conflict of issue with regard to

8   this meeting and is made a part of this record to preclude

9   even the appearance of such at this meeting.

10   Based on the submitted agenda for the meeting

11   and all the financial interests reported by the committee

12   participants, it has been determined that all interests in

13   firms regulated by the Center for Drug Evaluation and

14   Research, which have been reported by the participants

15   present, present no potential for an appearance of a

16   conflict of interest at this meeting with the following

17   exceptions.

18   Dr. Susanna Cunningham has been granted waivers

19   under 18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an

20   amendment of Section 505 of the Food and Drug

21   Administration Act, for ownership of stock in the sponsor

22   valued between $25,001 and $50,000.

23   Dr. Andrew Brem has been granted waivers under

24   18 U.S.C. 208(b)(3) and under 21 U.S.C. 355(n)(4), an

25   amendment of Section 505(a) of the Food and Drug

1 Administration Modernization Act, for ownership of stock in

2 the sponsor valued between $5,001 and $25,000.

3 Dr. Alan Hirsch has been granted a waiver under

4 18 U.S.C. 208(b)(3) for his participation on a sponsor's

5 bureau supported by firms that have a financial interest in

6 the product at issue and the competing product. He

7 receives less than $10,001 per year.

8 Dr. Steven Nissen has been granted a waiver

9 under 18 U.S.C. 208(b)(3) for his consulting with the

10 sponsor on unrelated matters. He received less than

11 $10,001 over the past year.

12 A copy of these waiver statements may be

13 obtained by submitting a written request to the agency's

14 Freedom of Information Office, room 12A-30 of the Parklawn

15 Building.

16 In the event that the discussions involve any

17 other products and firms not already on the agenda, for

18 which an FDA participant has a financial interest, the

19 participants are aware of the need to exclude themselves

20 from such involvement, and their exclusion will be noted

21 for the record.

22 With respect to all other participants, we ask

23 in the interest of fairness that they address any current

24 or previous financial involvement with any firm whose

25 products they may wish to comment upon. Thank you.

1   Dr. Borer?

2   DR. BORER: Thank you. We will begin with the

3   sponsor's presentation. Dr. Elia.

4   DR. ELIA: Good morning Mr. Chairman, members

5   of the advisory committee, FDA, ladies and gentlemen. My

6   name is Michael Elia from the Department of Regulatory

7   Affairs at Merck Research Laboratories.

8   I would like to thank the Advisory Committee

9   and the FDA for the opportunity to present Merck's data on

10   the efficacy and safety of losartan in providing renal

11   protection in type II diabetic patients with nephropathy.

12   I am going to provide an introduction today to

13   our presentation that will focus on the results of Merck's

14   renal outcome study RENAAL, which stands for reduction in

15   endpoints in non-insulin dependent diabetes mellitus with

16   the angiotensin II receptor antagonist losartan.

17   RENAAL is a multicenter international, double-

18   blind, randomized, placebo-controlled trial to evaluate the

19   protective effects of losartan in patients with type II

20   diabetes and proteinuria.

21   Just to remind you, as we stated in our

22   briefing document, we will use the words "nephropathy" and

23   "proteinuria" interchangeably today.

24   Prior to initiating RENAAL, no convincing long-

25   term renal protection outcomes data were available in type

1   II diabetic patients with nephropathy.

2   To address this, RENAAL was designed as a long

3   term renal protection outcome study. In RENAAL the primary

4   endpoint was a time to event analysis of a the composite of

5   doubling of serum creatinine, end-stage renal disease,

6   defined as the need for chronic dialysis or

7   transplantation, or death.

8   As we will show you today, this study provides

9   persuasive evidence that losartan delays the progression of

10   renal disease in type II diabetic patients with

11   nephropathy.

12   Complete data on the hard endpoints of end-

13   stage renal disease and death were collected on all

14   randomized patients. No patients were lost to follow-up.

15   The results of RENAAL confirm that the safety and

16   tolerability profile of losartan is these patients is

17   consistent with that in the currently approved U.S. product

18   circular for Cozaar.

19   Furthermore, RENAAL demonstrated that the

20   benefit of losartan treatment in these patients exceeds

21   that attributable to blood pressure reduction alone. We

22   believe that these results merit modification of our

23   product label, with the following new indication. Under

24   the heading of renal protection in type II diabetic

25   patients with proteinuria, Cozaar is indicated to delay the

1   progression of renal disease, as measured by a reduction in

2   the combined incidence of doubling of serum creatinine,

3   end-stage renal disease, or death.

4   It's important to note that at present there

5   are no drugs approved in the United States for renal

6   protection in type II diabetic patients with proteinuria.

7   While we believe that the RENAAL study provides

8   compelling evidence to support our proposed indication, it

9   is a single study. In an earlier meeting this year, this

10   committee and the FDA discussed the evidence needed to

11   support a new claim for renal protection in type II

12   diabetic patients with proteinuria. In considering the

13   questions before the committee today, it's useful to review

14   the evidentiary standard needed to support a new claim for

15   an approved drug. This is especially important when the

16   basis for the proposed claim rests largely on the results

17   of a single study such as RENAAL.

18   Although the FDA has relied on data from a

19   single study to support a new indication, their views on

20   the matter had not been fully delineated prior to the

21   issuance of a guidance document.

22   In 1998 the FDA issued a guidance document

23   entitled "Providing Clinical Evidence of Effectiveness for

24   Human Drug and Biological Products", that gives the agency

25   its current thinking on the approval of new claims based on

1   data from a single trial.

2   When regulatory decisions are based primarily

3   on a single study it is important to determine the level of

4   confidence one can have in the results of that study. Are

5   the data scientifically convincing or simply due to chance?

6   FDA's guidance document provides several points to

7   consider in evaluating whether one has sufficient

8   confidence in the results of a single study to support a

9   new effectiveness claim.

10   As you will see you a few minutes in Dr.

11 Shahinfar's presentation, the RENAAL study satisfies

12 several of the key features of a single study that can be

13 used to support an effectiveness claim. For example,

14 RENAAL is a large, multicenter study conducted at 250

15 clinical sites in 28 countries, and it provides persuasive

16 evidence that losartan delays the progression of renal

17 disease in type II diabetic patients with proteinuria.

18   The consistent and significant benefits of

19 losartan across multiple endpoints and multiple subgroups

20 in the RENAAL study promote confidence in its findings and

21 provide strong support for our proposed indication.

22   Furthermore, as described in the advisory

23 committee's background package, several separate smaller

24 clinical studies and preclinical studies have demonstrated

25 the beneficial effect of losartan therapy on renal

1 endpoints. These latter studies support the biological

2 plausibility of renal protective effects of losartan

3 observed in RENAAL.

4   In summary, we will show you today that the

5 efficacy and safety of losartan in patients with type II

6 diabetes and proteinuria support our proposed indication.

7   Finally, the agenda for today's Merck

8 presentation is as follows. After discussing the natural

9 history of type II diabetes and current treatments, Dr.

10 Shahnaz Shahinfar from Merck's Department of Cardiovascular

11 Clinical Research will describe the efficacy and safety

12 results from the RENAAL study.   Next, Dr. William

13 Keane, Vice President of Clinical Development in Merck's

14 U.S. Human Health Division, will summarize the evidence

15 that supports and confirms the RENAAL results, and end our

16 presentation with our overall conclusions.

17   The advisory committee members have previously

18 received a briefing document from Merck that provides more

19 detailed information than time allows us to present here

20 this morning.

21   In addition, Merck has brought several

22 consultants to the meeting. These experts are available to

23 facilitate the Advisory Committee's discussions and

24 deliberations.

25   Here today are Dr. Barry Brenner from the

1 Harvard Medical School, who served as Chair of the RENAAL

2 Steering Committee; Dr. Steven Haffner from the University

3 of Texas, who chaired the RENAAL Endpoint Adjudication

4 Committee; Dr. Carl Erik Mogensen from Aarhus

5 Kommunehospital in Denmark, who chaired the Data and Safety

6 Monitoring Committee; Dr. Peter Kowey from Jefferson

7 Medical College, who was a member of the Data and Safety

8 Monitoring Committee for RENAAL; Dr. Marvin Konstam from

9 the Tufts New England Medical Center: and Dr. Scott Zeger

10 from the Johns Hopkins University.

11   I would now like to turn the podium over to Dr.

12 Shahinfar.

13   DR. SHAHINFAR: Good morning. I'm Shahnaz

14 Shahinfar of Cardiovascular Clinical Research of Merck

15 Research Laboratory. I was the clinical monitor for the

16 RENAAL study, which I have the pleasure of presenting to

17 you.

18   Today I will be reviewing the background and

19 rationale for the RENAAL study, followed by a presentation

20 of demographics, efficacy results, and safety results. Dr.

21 William Keane will conclude our presentation with a review

22 of the evidence and our conclusion regarding the renal

23 protective effect of losartan in type II diabetes.

24   Diabetes mellitus is a major public health

25 issue worldwide. The most common type of diabetes is type

1 II diabetes, which is the focus of our discussion today.

2 Up to 40 percent of type II diabetic patients develop

3 kidney disease. End-stage renal disease is a devastating

4 complication of diabetes mellitus. Studies have shown that

5 the incidence of end-stage renal disease is increasing

6 worldwide. In the United States diabetic nephropathy is

7 the leading cause of end-stage renal disease.

8   It should be noted that end-stage renal disease

9 is an irreversible condition, and dialysis is a life-

10 support system to prevent death in these patients. Even

11 with dialysis, up to 40 percent of diabetic patients die

12 within 2 years of its initiation, a mortality rate

13 comparable to that of end-stage heart failure.

14   No treatment has shown conclusively to delay

15 end-stage renal disease in type II diabetic patients with

16 nephropathy. It is extremely important to identify a

17 therapeutic intervention for this unmet medical need.

18   In the search for a therapeutic intervention to

19 reduce end-stage renal disease, it should be remembered

20 that diabetic nephropathy is primarily a glomerular

21 disease. The exact mechanism of progression of diabetic

22 nephropathies are known, but many factors, both hemodynamic

23 and nonhemodynamic, may contribute to the development of

24 this glomerular injury. Angiotensin II has been

25 hypothesized to play a role in the progressive nature of

1   this glomerular injury.

2   The proposed mechanisms by which angiotensin II

3   is involved in diabetic glomerular injury are shown

4   pictorially on this slide. The glomerulus is the site of

5   the original injury in diabetic nephropathy. As a result

6   of the original insult to the glomerulus and the loss of

7   the nephrons, there is a remarkable adaptation within the

8   kidney to compensate for this nephron loss.   The

9   remaining nephrons increase the workload through a state of

10 hyperfiltration in order to maintain overall glomerular

11 filtration rate.

12   Angiotensin II plays an important role in this

13 adaption by increasing resistance in post-glomerular vessel

14 or efferent arteriole. In addition, in diabetic patients,

15 resistant in preglomerular vessel or afferent arteriole is

16 reduced. This combination of increased efferent arteriolar

17 resistance, mediated by angiotensin II, and decreased

18 efferent arteriolar resistance results in an increase in

19 intraglomerular pressure or glomerular hypertension.

20   This glomerular hypertension, while favorable

21 in the short term, has long-term detrimental effects on the

22 nephron. This increasing glomerular pressure initiates an

23 up-regulation of a series of nonhemodynamic factors. These

24 factors include increased permeability of the filtering

25 membrane, which may result in proteinuria and activation of

1 fibrotic and inflammatory processes, in which angiotensin

2 II also plays a role. The end result is glomerulosclerosis

3 and death of the nephron. This cycle of nephron death

4 continues until all nephrons are lost, and that's when end-

5 stage renal disease occurs.

6   Since angiotensin II appears to be play an

7 central role in many of the hemodynamic and nonhemodynamic

8 mechanisms of the progression of diabetic nephropathy, it

9 has been hypothesized that the blockade of angiotensin II

10 will provide renal protection in this disease.

11   This hypothesis has been tested repeatedly with

12 both losartan and ACE inhibitors in animal models of

13 diabetic nephropathy. There is no perfect experimental

14 model for type II diabetic nephropathy. However, the

15 streptozotocin-induced diabetic rats have been used for

16 this purpose. It has been demonstrated that the blockade

17 of angiotensin II in this model is associated with a

18 reduction in glomerulosclerosis and proteinuria.

19   Furthermore, in an animal model of non-diabetic

20 renal disease, blockade of angiotensin II reduced

21 proteinuria and glomerulosclerosis. In the same studies,

22 other antihypertensive agents did not confirm these renal

23 protective effects. These findings support the biological

24 plausibility of the effect of angiotensin II blockade in

25 renal protection.

1   This hypothesis was tested clinically with

2   captopril in type I diabetic patients with nephropathy,

3   approximately a decade ago. In this study, in 409 type I

4   diabetic patients with proteinuria and retinopathy, with a

5   mean age of approximately 35, captopril significantly

6   reduced end-stage renal disease or death. However, until

7   now, conclusive clinical data on end-stage renal disease

8   have not been available in patients with type II diabetic

9   nephropathy, which is the most common type of diabetes. It

10   is important to note that type I and type II diabetic

11   patients represent two different populations, and it is

12   difficult to extrapolate data from type I to type II and

13   vice versa.

14   Patients with type II diabetes are typically

15   older, obese, and have insulin resistance, advanced

16   atherosclerosis, and long-standing hypertension. Many of

17   these patients are hypertensive even before the onset of

18   nephropathy. The kidney of a patient with type II

19   diabetes, in addition to the glomerular injury of diabetic

20   nephropathy, also has other morphological changes, which

21   may be a reflection of long-standing hypertension, older

22   age and macrovascular disease. Only a portion of this

23   disease burden may be susceptible to the blockade of the

24   renin-angiotensin system.

25   In evaluating a therapeutic intervention,

1   especially the magnitude of benefit, these differences

2   between type I and type II diabetes should be taken into

3   consideration.

4   In the absence of definitive data, current

5   therapeutic approaches among clinicians for renal

6   protection in type II diabetic nephropathy have focused on

7   metabolic control and blood pressure control. Valuable

8   amounts of data are available for each strategy. However,

9   there is no conclusive clinical evidence that these

10   therapeutic approaches are associated with a reduction in

11   end-stage renal disease in type II diabetic patients with

12   nephropathy.

13   Prior to the initiation of RENAAL, the question

14   remained. In patients with type II diabetes and

15   nephropathy does angiotensin II blockade with losartan

16   offer renal protection? The RENAAL study was designed to

17   answer that question.

18   RENAAL, reduction of endpoints in non-insulin

19   dependent diabetes with the AII antagonist losartan, was a

20   multicenter, multinational, double-blind, randomized,

21   placebo-controlled study to evaluate the renal protective

22   effects of losartan in patients with type II diabetes and

23   nephropathy.

24   There were three oversight committees in

25   RENAAL: the Steering Committee, the Data and Safety

1 Monitoring Committee, and the Endpoint Adjudication

2 Committee.

3   The Steering Committee, chaired by Dr. Barry

4 Brenner, was blinded to the study results and oversaw the

5 overall conduct of the study.

6   The Data and Safety Monitoring Committee was

7 chaired by Dr. Carl Erik Mogensen. This committee was

8 unblinded to the results of RENAAL, and oversaw the safety

9 of the patients in the study.

10   An Endpoint Adjudication Committee, chaired by

11 Dr. Steven Haffner, included two cardiologists, three

12 nephrologists and one endocrinologist, who were blinded to

13 the results, and adjudicated all the primary renal and

14 secondary cardiovascular endpoints in RENAAL.

15   Merck functioned as the coordinating and data

16 management center, with national and regional coordinators.

17 There were 250 centers from 28 countries worldwide.

18   The primary hypothesis in RENAAL was, in type

19 II diabetic patients with nephropathy, losartan compared to

20 placebo would increase the time to the first event of the

21 composite endpoint of doubling of serum creatinine, which

22 represented more than 50 percent loss of renal function,

23 end-stage renal disease, defined as need for chronic

24 dialysis or transplantation, or death, defined as all-cause

25 mortality.

1   These components of the primary endpoints were

2   selected based on the natural course of nephropathy in type

3   II diabetic patients. Serum creatinine progressively

4   rises, leading to a doubling of this biochemical marker,

5   which represents approximately 50 percent loss of renal

6   function, followed eventually by the clinically

7   irreversible condition of end-stage renal disease.

8   In patients who reach end-stage renal disease,

9   dialysis or transplantation is necessary to sustain life.

10   Thus, death and dialysis are competing events. Despite

11   dialysis, mortality remains high in these patients. Of

12   course, death from any cause can occur at any time.

13   There were three secondary hypotheses in

14   RENAAL. The first two were renal hypotheses. Losartan

15   would reduce the rate of progression of renal disease as

16   measured by the slope of reciprocal of serum creatinine

17   compared to placebo. Second, losartan would reduce

18   proteinuria, compared to placebo, during the course of this

19   study.

20   Another secondary hypothesis was a

21   cardiovascular hypothesis. It should be noted that RENAAL

22   was specifically designed as a renal protection study.

23   However, since cardiovascular events are common in these

24   type II diabetic patients, we made cardiovascular morbidity

25   and mortality a secondary hypothesis and adjudicated all

1 cardiovascular events.

2   The cardiovascular hypothesis was that in type

3 II diabetic patients with nephropathy losartan, compared to

4 placebo, would increase the time to first event of the

5 composite endpoint of cardiovascular morbidity and

6 mortality. This cardiovascular composite endpoint included

7 cardiovascular death, myocardial infarction, stroke, first

8 hospitalization for heart failure, first hospitalization

9 for angina and revascularization, both coronary and

10 peripheral revascularization.

11   The major inclusion and exclusion criteria in

12 RENAAL are noted on this slide. Since RENAAL was a renal

13 protection study, we enriched our population with patients

14 who had risk of progression of renal disease.

15   Important inclusion criteria were that these

16 patients were required to have type II diabetes and had to

17 be between the ages of 31 and 70 years, with proteinuria

18 defined as an albumin-to-creatinine ratio of more than 300

19 milligrams per gram on a first morning void, which

20 demonstrate macroalbuminuria, or greater than 500

21 milligrams protein in a 24-hour urine. Serum creatinine

22 was required to be between 1.3 and 3 milligrams per

23 deciliter.

24   Important exclusion criteria included patients

25 with known non-diabetic renal disease, such as patients

1 with renal artery stenosis and polycystic kidney were

2 excluded. Patients with uncontrolled diabetes, defined as

3 hemoglobin A1C greater than 12 percent, were excluded.

4 Patients with a history of myocardial infarction or CABG

5 within a month, stroke or PTCA within 6 months, and TIA

6 within a year of randomization, were excluded. Patients

7 with a history of heart failure were excluded. A heart

8 failure exclusion criterion was added shortly after the

9 initiation of the study.

10   The RENAAL study design is shown on the next

11 few slides.

12   RENAAL was a double-blind, randomized, placebo-

13 controlled, multicenter study. Because of the known effect

14 of proteinuria on the progression of renal disease in type

15 I diabetics and in non-diabetic patients with renal

16 disease, patients were stratified, based on an urinary

17 albumin-to-creatinine ratio, less than 2,000 or greater

18 than or equal to 2,000 milligrams per gram.

19   During the follow-up, clinic and laboratory

20 evaluations were performed every 3 months. We planned for

21 1-year enrollment and 5 years maximum follow-up.

22   This is a schematic diagram of the study

23 design. Qualified patients with type II diabetes were

24 screened by urine protein dipstick, and were placed in a

25 run-in period for 6 weeks. During this period, prior

1   antihypertensive therapy was maintained, except for

2   angiotensin converting enzyme inhibitors or angiotensin II

3   receptor antagonists, which were stopped 6 weeks prior to

4   randomization, and were replaced by other antihypertensive

5   drugs if needed.

6   To qualify patients at baseline, they first

7   were stratified, based on urinary albumin-to-creatinine

8   ratio, less than 2,000 or greater than 2,000 milligrams per

9   gram. Within each stratum, patients were randomized to

10 receive either 50 milligrams losartan or matching placebo

11 once daily, on the background of the run-in period

12 antihypertensive therapy. The goal was a trough blood

13 pressure of systolic less than 140 millimeters of mercury

14 and diastolic less than 90, which was the WHO-recommended

15 guideline for diabetics at the time of initiation of the

16 study.

17   If this goal blood pressure was not achieved

18 within 4 weeks, the study drug could be increased to 100

19 milligrams losartan once daily or matching placebo. If the

20 goal blood pressure was still not achieved, other open-

21 label antihypertensives, except angiotensin II antagonists

22 or ACE inhibitors, could be added, or the dose of the

23 existing drug could be adjusted.

24   Comprehensive patient follow-up was an

25 important feature of RENAAL, to ensure that doubling of

1   serum creatinine, end-stage renal disease, and death events

2   were collected in all patients.

3   Importantly, in RENAAL patients were required

4   to remain on a study therapy, regardless of nonfatal events

5   until the completion of the study. For example, if

6   patients doubled their serum creatinine, they were to

7   remain on therapy until the end of the study unless the

8   patient died. If patients experienced end-stage renal

9   disease, they were to remain on a study drug until the end

10   of the study, unless the patient died.

11   We collected end-stage renal disease and death

12   data in all patients, regardless of doubling of serum

13   creatinine events. This permitted the independent

14   assessment of treatment on the clinical endpoints of end-

15   stage renal disease in all patients. For all patients,

16   including those who discontinued the study drug, clinic

17   visits were to continue every 3 months to capture renal and

18   cardiovascular endpoint information.

19   After discontinuation of the study drug, if

20   clinic visits were not feasible, telephone follow-up was

21   done to capture end-stage renal disease and death

22   information. Whereas doubling of serum creatinine and

23   cardiovascular morbidity information were not captured in

24   telephone follow-up, data on end-stage renal disease and

25   death were collected for all patients randomized.

1   On February 10, 2001, the Steering Committee,

2   while blinded to the study results, voted unanimously to

3   end RENAAL prior to its planned termination date of March

4   2002, because of concerns of continuing the placebo group

5   without the blockade of the renin-angiotensin system. This

6   decision was based on increasing evidence that ACE

7   inhibitors may be effective in reducing cardiovascular

8   events in patients with cardiovascular risk factors. These

9   data were from the Heart Outcome Prevention Evaluation

10   study, HOPE, and a subpopulation of patients with renal

11   impairment, which was reported by Mann, et al. in Annals of

12   Internal Medicine, April 2001.

13   I would now like to discuss the RENAAL

14   demographics and efficacy results. In discussing the

15   efficacy results, I will first present the information

16   under primary and secondary renal data, followed by the

17   secondary cardiovascular data.

18   This slide summarizes the patient disposition

19   in RENAAL. In RENAAL, 3,893 patients were screened, 1,513

20   patients were randomized, 751 patients were allocated to

21   losartan, 762 patients were allocated to placebo.

22   The breakdown of patients who completed on the

23   study drug and the number of patients who discontinued the

24   study drug after reaching a primary event or prior to

25   reaching a primary event are shown in these boxes. There

1   are no patients lost to follow-up in RENAAL. Outcome data

2   on end-stage renal disease and death are available for all

3   patients randomized.

4   The next 4 slides provide the baseline

5   demographic data in RENAAL.

6   Patients were equally distributed with respect

7   to baseline demographics between losartan and placebo arms

8   of the study. With respect to gender, age, blood pressure

9   and body mass index, the two treatment groups were

10 comparable.

11   The two treatment groups were also comparable

12 with respect to race and region. The RENAAL study achieved

13 an excellent representation from diverse ethnic groups.

14 Among the patients in RENAAL, about 17 percent were Asian,

15 15 percent were Black, 49 percent were Caucasian, and 18

16 percent were Hispanic.

17   The treatment groups were comparable with

18 respect to past medical history at baseline. As

19 anticipated, the majority of patients in RENAAL were

20 hypertensive at the beginning of the study and were treated

21 with antihypertensive drugs. At baseline, the number of

22 patients with cardiovascular history of angina, myocardial

23 infarction, and stroke was relatively low in our study.

24   This slide provides selected mean laboratory

25 values at baseline in RENAAL. The two treatment groups

1   were comparable with respect to mean serum creatinine,

2   serum potassium, hemoglobin, and hemoglobin A1C. I will

3   discuss the differences baseline proteinuria later in my

4   presentation.

5   As a reminder, the primary hypothesis of RENAAL

6   was that losartan compared to placebo would increase the

7   time to the first event of the composite endpoint of

8   doubling of serum creatinine, end-stage renal disease, or

9   death. The analytical approach to the primary composite

10 endpoint was the time to each patient's first event. In

11 the next two slides I will illustrate how patients

12 contributed to this time-to-event analysis.

13   In the left column, we have 5 hypothetical

14 patients, A through E. In the next 3 columns, we show

15 three endpoints that contributed to the primary composite

16 endpoint. As you can see, patient A doubled his serum

17 creatinine, developed end-stage renal disease, and died.

18 Compare this patient to patient D, who died without

19 doubling of serum creatinine or developing end-stage renal

20 disease.

21   On this slide we have circled the endpoint that

22 occurred first for each patient. Each of these values were

23 used as the first event in the analysis of the primary

24 composite endpoint. Thus, for patient A, doubling of serum

25 creatinine was the first event captured, and this event was

1 used in the analysis of the primary composite endpoint.

2   For patient D, death was the first event, and

3 this event was used in the analysis of the primary

4 composite endpoint. Note that also 4 of the 5 patients in

5 this example died. Only the death of patient D would

6 contribute to the primary composite endpoint.

7   The next slide will illustrate the results of

8 our analysis on the primary composite endpoint.

9   DR. BORER: Dr. Shahinfar, can you just stop

10 for a moment? Before you actually show the outcome data, I

11 would like a clarification that sounds like you won't get

12 to later.

13   In the book that you sent us, it suggests that

14 there was a distinct difference in the average years of

15 patient follow-up. It says here on your page 12 that you

16 had an average of 173 patient-years of follow-up in the

17 losartan group and 234 years of patient follow-up in the

18 placebo group. That is clinic follow-up. And with regard

19 to telephone follow-up, there was the same discrepancy.

20   Now, in the FDA analysis, however -- and this

21 was looked at in a different way -- the conclusion was that

22 exposure to drug in the placebo group and the losartan

23 group was approximately equivalent.

24   Before you actually go on and present the data,

25 I'd like to understand why this apparent discrepancy

1   exists, or is not a discrepancy, or do I not understand

2   these data correctly?

3   DR. SHAHINFAR: Thank you very much for your

4   question. The numbers that you are referring to in the

5   background refer to the patients who were discontinued and

6   they went to some kind of follow-up.

7   Basically, after patients were discontinued

8   from the study, we tried to keep them in the clinic

9   regardless of whether they were on drug or were not on

10 drug. So, in those patients, some of them couldn't come

11 back for subsequent clinic visits, but we followed these

12 patients in telephone follow-up. Does that answer your

13 question?

14   DR. BORER: Yes, it does indeed. What we are

15 seeing here is that people stayed on losartan longer.

16 That's why there were presumably fewer patient years of

17 follow-up in the losartan group. I understand. Thank you.

18   DR. SHAHINFAR: The next slide will illustrate

19 the results of our analysis on the primary composite

20 endpoint. In all the slides that you will see today,

21 losartan is depicted in yellow and placebo in white.

22 Unless otherwise noted, all efficacy analyses are based on

23 intention to treat.

24   The primary composite endpoint results of

25 RENAAL are demonstrated in this Kaplan-Meier curve. In

1   this slide, the y axis is the percentage of patients with

2   events. The x axis is the duration of follow-up. The

3   number below the x axis represents the number of patients

4   at risk at each time point.

5   As this slide illustrates, RENAAL began with

6   762 patients in the placebo group and 751 patients in the

7   losartan group. By 36 months in this study, year 3, there

8   still remained 296 patients at risk in the placebo group,

9   and 300 patients in the losartan group. As anticipated, by

10 month 48 a relatively small number of patients at risk is

11 available in each treatment group.

12   The risk reduction for losartan was calculated

13 using the Cox proportional hazard regression model. The

14 results demonstrate that losartan significantly reduced the

15 risk of the primary composite endpoint of time to first

16 event of doubling of serum creatinine, end-stage renal

17 disease, or death by 16.1 percent; p equals .022.

18   In RENAAL, there were prespecified analyses of

19 the irreversible clinical endpoints, collectively referred

20 to as end-stage renal disease, death, and a composite of

21 end-stage renal disease or death. Since patients were

22 followed after the occurrence of a nonfatal primary

23 endpoint, many patients experienced multiple clinical

24 endpoints. In these cases the key principles applied were

25 that a patient counted as having had an endpoint in all

1 relevant analyses and that a patient counted only once in

2 any analysis.

3   This slide summarizes the analytical approach

4 taken for the irreversible clinical endpoints. For end-

5 stage renal disease, the analytical approach included all

6 patients who reached end-stage renal disease, regardless of

7 whether doubling of serum creatinine occurred first.

8   For death, the analytical approach included all

9 patients who died, regardless of whether doubling of serum

10 creatinine or end-stage renal disease occurred first.

11   For end-stage renal disease or death, the

12 analytical approach included patients who reached a first

13 event of end-stage renal disease or death, regardless of

14 whether doubling of serum creatinine occurred first.

15   These analyses were performed on the entire

16 patient cohort, because all patients were followed for the

17 occurrence of end-stage renal disease and death for the

18 entire study.

19   The next slide illustrates how these events

20 would be captured for separate analysis of ESRD, death, and

21 the composite of ESRD or death.

22   This slide illustrates the same 5 hypothetical

23 patients that we showed you earlier. For each patient, the

24 first occurring primary event is circled. Now, let me show

25 you how these events in these patients would be captured in

1   each of the analyses of the irreversible clinical endpoints

2   of ESRD, death, and the composite of ESRD or death.

3   The three columns on the right-hand side of the

4   slide illustrate the analysis of end-stage renal disease,

5   death, and the composite of ESRD or death, and the

6   contribution of each patient's event to each analysis.

7   Patient A contributes to all three analyses,

8   whereas patient D contributes to the analysis of death and

9   to the analysis of ESRD or death.

10   Please note that although a patient can

11   experience each of the three endpoints of doubling of serum

12   creatinine, end-stage renal disease, and death, a patient

13   is only counted once in each analysis.

14   For the prespecified analysis of end-stage

15   renal disease, defined as need for chronic dialysis or

16   transplantation, the y axis shows the percentage of

17   patients with events. The x axis demonstrates duration of

18   follow-up.

19   Losartan treatment reduced the risk of end-

20   stage renal disease by 28.6 percent; p equals .002. As you

21   see in this Kaplan-Meier curve, the effect of therapy is

22   observed about 18 months after the initiation of losartan,

23   as demonstrated by the separation of the curve at this time

24   point.

25   This is the first time that a therapeutic

1   intervention has shown a beneficial effect on end-stage

2   renal disease in type II diabetic patients with

3   nephropathy.

4   For the prespecified analysis of all-cause

5   mortality, there was no significant difference in this

6   endpoint between losartan and placebo; p equals .884.

7   End-stage renal disease and death are competing

8   events in type II diabetic patients with proteinuria

9   because these patients may die before reaching end-stage

10   renal disease or die as a result of requiring but not

11   receiving dialysis, which is a life support therapy in

12   these patients. Therefore, we evaluated the effect of

13   losartan on the risk of experiencing either of these two

14   endpoints. The prespecified analysis of the composite

15   endpoint of end-stage renal disease or death demonstrated

16   that losartan significantly reduced the risk of this

17   outcome by 19.9 percent; p equals .009.

18   To summarize the results of the RENAAL primary

19   hypothesis and prespecified analysis of irreversible

20   clinical endpoints, this chart displays the percent risk

21   reduction and its 95 percent confidence interval.

22   Note that the horizontal scale is a logarithmic

23   scale from plus 50 percent on the left, corresponding to a

24   reduction risk due to losartan, to minus 50 percent on the

25   right, corresponding to an increase in risk with losartan.

1   The confidence intervals are symmetric on this logarithmic

2   scale. Losartan significantly reduced the risk of the

3   primary composite endpoint and the irreversible clinical

4   endpoint of end-stage renal disease and end-stage renal

5   disease or death.

6   Before the initiation of RENAAL, we recognized

7   the overall importance of proteinuria on the progression of

8   renal disease, but the precise nature of this relationship

9   in type II diabetes was unknown. Therefore, RENAAL

10 patients were stratified at baseline, based on a level of

11 proteinuria less than 2,000 or greater than 2,000 albumin-

12 to-creatinine ratio.

13   As a result of the stratification, within each

14 stratum an equal number of patients were randomized to each

15 treatment group. However, there was an imbalance in the

16 distribution of baseline proteinuria within the higher

17 stratum of greater than 2,000. Specifically, more patients

18 with baseline proteinuria above 4,000, the highest level of

19 proteinuria, were randomized to the losartan arm compared

20 to placebo. I will now illustrate these two points in each

21 of the next two slides.

22   This slide demonstrates the patient randomized

23 to losartan or placebo in each stratum. The x axis

24 demonstrates categories baseline proteinuria and the y axis

25 is the percentage of patients in each category. The two

1 strata are noted: the lower stratum below 2,000 on the

2 left, and the higher stratum above 2,000 on the right.

3   As you see from this slide, stratification

4 ensured that overall there was an equal number of patients

5 on losartan and placebo in each stratum. But such a

6 stratification does not eliminate the possibility of an

7 imbalance of distribution of patients within each stratum.

8 As I will show you next, that occurred in RENAAL.

9   As demonstrated on this slide, there is a

10 statistically significant imbalance in the distribution of

11 patients between losartan and placebo with respect to

12 baseline proteinuria within the higher stratum. This

13 imbalance is especially pronounced in the category of

14 greater than 4,000 patients where we have more losartan

15 than placebo patients. I will show you later that these

16 patients are at the highest risk of progression of renal

17 disease, and that 80 percent of these patients had a

18 primary endpoint during the study.

19   In RENAAL, we demonstrated that in type II

20 diabetic patients there is a strong relationship between

21 baseline proteinuria and the risk of the primary composite

22 endpoint as shown on this slide. In this analysis we

23 pooled the losartan and placebo groups. On the x axis,

24 different levels of baseline proteinuria are listed. On

25 the y axis is the hazards ratio for the primary composite

1   endpoint, which is the hazard rate for each level of

2   proteinuria relative to 300 milligrams albumin-to-

3   creatinine ratio, which was the entry criterion for

4   proteinuria in our study. The larger the hazard ratio

5   represents the higher risk for primary event. As it is

6   shown, the risk for primary events increases substantially

7   as baseline proteinuria increased.

8   For example, in a patient at baseline

9   proteinuria of 2,000 albumin-to-creatinine ratio, the

10   hazard rate for the primary outcome is approximately 3

11   times higher than a patient with 300 milligrams albumin-to-

12   creatinine ratio. In a patient with 4,000 albumin-to-

13   creatinine ratio at baseline, the hazard rate is about 8

14   times higher than a patient with 300 milligrams albumin-to-

15   creatinine ratio.

16   Because of the important role of proteinuria

17   and the risk of the progression of renal disease, and since

18   prespecified primary analysis did not adjust for imbalances

19   within strata, it was reasonable to adjust for imbalances

20   in baseline proteinuria for RENAAL. The results of this

21   analysis are shown in the next two slides.

22   Using the baseline proteinuria as a continuous

23   covariate, in the Cox proportional hazard regression model,

24   the risk reduction with losartan on the primary composite

25   endpoint increases from 16.1 percent to 22.2 percent; p

1   equals .001.

2   Adjustment for baseline proteinuria also

3   results in an increase in treatment effect on irreversible

4   clinical endpoints of end-stage renal disease and a

5   composite of end-stage renal disease or death. This slide

6   demonstrates the risk reduction with losartan for the

7   primary composite endpoint, end-stage renal disease, death,

8   and end-stage renal disease or death. The solid line with

9   a circle represent the prespecified analysis, and the

10 dotted line with the square represents the adjusted value,

11 using baseline proteinuria as a continuous covariate. As

12 you can see, the dotted line with the square moves toward

13 the left of the 0 line in favor of losartan.

14   DR. BORER: Before you go on, Dr. Shahinfar,

15 this is Jeff Borer for the microphone for the tape there.

16 Those adjustments are very interesting, and intuitively

17 they seem reasonable and I don't want to suggest that there

18 isn't an effect here and that the proteinuria isn't

19 important. But I have some concern about accepting

20 adjustments and numbers based on adjustments per se because

21 my understanding is that to make an adjustment you have to

22 assume that you know the relationship quantitatively

23 between the variable for which you are adjusting and the

24 dependent variable, the outcome variable. I don't think we

25 know that. So, you're assuming a model.

1   I am going to ask Tom Fleming and the FDA

2   statistician, if we have him or her here, to comment on

3   that. But, what I would like to see, if you have the data

4   -- and you may not have them this minute, so you can pull

5   them out -- is an analysis of absolute numbers for the

6   outcome in people above 4,000, understanding that there's

7   an imbalance in favor of more on losartan, and for 2,000 to

8   4,000, which are the patients where there was an imbalance

9   in favor of placebo, still above your prespecified cut

10 point.

11   I would like to know that, and, Tom, I would

12 like to have some comment from you about the validity of

13 this kind of adjustment, if you would.

14   DR. FLEMING: I would be happy to look at the

15 results as you have asked for them, and then I can comment.

16   You have asked, since in particular what we are seeing is

17 a breakdown of imbalances in those above 4,000, it would be

18 interesting to see the results in that stratum above 4,000,

19 and then in the complement.

20   DR. BORER: I was also asking about the generic

21 issue of making imbalances based on models when we don't

22 really know the relation between the variables that we are

23 adjusting for.

24   DR. FLEMING: Okay, I'll go ahead a comment now

25 then.

1   The approach that is being used is a very

2   standard approach to address any potential confounding that

3   can exist, and a confounder arises, as you know, when you

4   have a very predictive variable that is imbalanced between

5   the two arms.

6   What we are seeing here is a recognition that

7   baseline proteinuria in advance is obviously a very

8   important predicted variable. The structure that was

9   imposed was to balance for those below 2,000 and above

10   2,000.

11   What we're seeing here -- and I would like to

12   probe a little bit later, at exactly how this functional

13   form was derived -- I think it is in slide 54, which is

14   certainly very informative and relevant. Taking that as

15   the truth, what it is showing is that there's a striking

16   monotonic trend toward increasing risk of the outcome as

17   you increase that baseline proteinuria level, such that

18   there could readily be emerging imbalances in the cohort

19   above 2,000 because there was no structure imposed beyond

20   what randomization does itself to assure a balance in those

21   people who were above 2,000.

22   What emerged in the data was an excess of 92

23   versus 71 people with values above 4,000. So, there was a

24   confounding that emerged in spite of the structure imposed

25   at randomization, and that confounding certainly has the

1 potential of biasing the results.

2   If you use a Cox regression or a stratified log

3 rank analysis, you get a very appropriate and legitimate

4 adjustment for that balance. You don't have to assume you

5 know the functional form. If it's a highly predictive

6 covariate and it's imbalanced, we don't have to assume we

7 know that to do a Cox regression analysis or a stratified

8 log rank.

9   The problem that we run into in interpreting

10 this, though, is post hoc analyses that are adjusting for

11 imbalances that can occur even in a random way in a

12 randomized stratified trial require some careful

13 interpretation because one could do these analyses in

14 numerous ways; i.e., you could form innumerable different

15 types of covariate adjustments. And I'd like to come back

16 to this discussion later on. That's the issue that I think

17 we have to be a bit cautious about how we interpret.

18   But it is certainly very appropriate in a

19 supportive analysis to look for what might be profound or

20 very substantial evidence of confounding and in a

21 supportive analysis to look to see whether that strengthens

22 or weakens our sense of association.

23   DR. BORER: Thank you.

24   Dr. Temple?

25   DR. TEMPLE: So, I think the first thing

1 Jeffrey asked was where did you get those numbers. How did

2 you decide how to make the adjustment? And, your answer,

3 if I understand it was, they looked at the relationship

4 between proteinuria in both the untreated and treated

5 people and found that relationship in these data. The risk

6 in there is that you can find it even if it's not true as a

7 matter of chance sometimes. So, you have to judge its

8 degree of plausibility. If it were extremely plausible, of

9 course it would have been prospectively defined. This

10 comes up all the time. People are smarter after the fact

11 than before.

12   The other point I guess is that looking at the

13 two groups, people over 4,000 and under 4,000 is sort of

14 the poor man nonstatistician covariate analysis, and it's

15 very helpful for people who don't quite understand what

16 covariate analyses are, like me. So, that's always very

17 helpful.

18   DR. FLEMING: In this discussion, I think if

19 you could put slide 54 up as well, which I think is your

20 slide that showed what I call the functional form. This is

21 very important.

22   For a covariate to be a confounder you need to

23 have an imbalance. Okay, we've seen that, 92 against 71.

24 It has to be imbalanced in a way that matters, i.e. those

25 people, i.e., the 92/71, or the people who are at 4,000 or

1   to the right, and those people are at much higher risk than

2   people who were to the left. Two questions.

3   I'm always a little skeptical about a curve

4   that is so smooth. That probably is what nature really is,

5   but our data usually has much more noise. So, how did this

6   function form? Was it derived from this study or other

7   data? That's question 1.

8   Question 2 is, is this the relationship of

9   baseline proteinuria with a triple endpoint, and if so, I

10 might speculate the relationship with what I care more

11 about, which is the double endpoint. End-stage renal

12 disease/death would be even a more striking gradient.

13   Can you answer those two questions?

14   DR. BAIN: Yes. Ray Bain, clinical

15 biostatistics, Merck Research Lab.

16   You're correct. This slide here was based on

17 the pooled groups from the RENAAL study, the 15/13

18 patients. You are also right that this particular

19 analysis, this hazard ratio of increasing baseline

20 proteinuria, relative to a patient who has 300 milligrams

21 per gram, is based on our primary triple endpoint,

22 doubling, death, or dialysis.

23   Now, Dr. Temple is also correct that sometimes

24 if we were more intelligent we would have probably

25 introduced this correction way back when we were designing

1   the protocol. It turns out that we were half intelligent.

2   We did recognize the importance of baseline protein and

3   therefore prestratified. Now, unfortunately we only

4   prestratified by less than 2 and greater than 2, but we

5   recognize that it was a very important baseline risk

6   factor.

7   In addition to that -- and we can go into this

8   later -- we also prespecified in our data analysis plan to

9   do a risk score analysis, which looked at a number of

10   different baseline risk factors. It turns out 1 of the

11   risk factors that we included as potentially being a risk

12   factor for our triple endpoint was, again, baseline

13   proteinuria. We can go into that later if you like.

14   Dr. Borer, did we answer your question?

15   DR. BORER: Reasonably.

16   DR. TEMPLE: Do you have that curve for the

17   renal endpoint alone?

18   DR. BAIN: Yes, we do.

19   DR. LINDENFELD: Jeff, may I ask?

20   DR. BORER: Yes.

21   DR. LINDENFELD: I wonder if we could back to

22   the last slide. Can you just show us that same data on

23   slide 54 when the endpoint is end-stage renal disease or

24   death?

25   The reason I ask this -- and everyone can help

1   me with this -- is I think all of us who see these patients

2   recognize as the proteinuria goes up and up the diuretics

3   go up and up. And while in the past we have considered a

4   doubling of creatinine a real endpoint -- that is, it

5   reflects loss of renal function -- when we start to add

6   those diuretics, we have all seen the creatinine double.

7   We withdraw diuretics and it goes back down. So, I wonder

8   if this same endpoint holds when we don't use the doubling

9   of creatinine.

10   DR. BAIN: We do not have that particular

11 graph, but we could probably get it.

12   DR. FLEMING: The second question that I was

13 intending to ask was that I wanted to see that same curve

14 not for the triple endpoint, but what I call the double

15 endpoint. I think of the double endpoint as end-stage

16 renal disease/death, where my speculation is the gradient

17 or the slope I would expect would be even greater, but I'd

18 like to see that.

19   DR. BAIN: Okay, we'll work on that.

20   But, as you can see here, this is again one of

21 these curves where now on the x axis here is hazard ratio,

22 so the .5 is that 50 percent reduction. You can see the

23 doubling of serum creatinine if you look at that line. I'm

24 sorry. The primary composite outcome is at the top there.

25   At the very top, the solid line is our primary outcome,

1   the .022. The next line below that is what Dr. Shahinfar

2   already discussed. When you adjust for baseline

3   proteinuria, it moves the effect to the left and you get a

4   p value of .001 that she showed.

5   Now, we haven't shown you that curve for

6   baseline proteinuria as a prediction of ESRD or death, but

7   you can see the same type of effect here when you look at

8   the ESRD. We haven't gotten there yet I think, but you'll

9   see that endpoint of ESRD or death, and then you'll also

10 see that when you adjust again for continuous baseline

11 proteinuria it moves the treatment effect to the left.

12   DR. FLEMING: Let me just clarify a little bit.

13   Put that slide back up.

14   I guess to provide the most precise statement,

15 where I'd expect the biggest gradient is end-stage renal

16 disease as a single endpoint, because certainly what we are

17 seeing is an effect on end-stage renal disease much more so

18 than death, doubling in serum creatinine for reasons we can

19 discuss later. It doesn't strike me as an endpoint that

20 should be as strongly affected by baseline proteinuria as

21 end-stage renal disease itself. In fact, if we look at the

22 adjustment here, the adjustment is in fact visually the

23 greatest for end-stage renal disease.

24   So, my speculation is if we show that gradient

25 curve that you were showing on slide 54, it would be very

1 interesting to show what the relationship is of baseline

2 proteinuria not just with the triple endpoint, but with the

3 double endpoint and with end-stage renal disease itself.

4   DR. BAIN: Okay, so your request is to look at

5 slide 54 for the single endpoint of ESRD and then the

6 double endpoint of ESRD or death. Will do.

7   DR. TEMPLE: And end-stage renal disease or

8 doubling, just for me.

9   DR. BAIN: And end-stage renal disease or

10 doubling. Okay.

11   DR. SHAHINFAR: In RENAAL, we prespecified

12 several sensitivity analyses for the primary composite

13 endpoint, using hemoglobin A1C and mean arterial pressure

14 as time varying covariates. We also performed analyses of

15 baseline subgroups. Hemoglobin A1C, as mentioned in your

16 background, was comparable between the two treatment

17 groups. In the next several slides, I will discuss the

18 sensitivity analysis for mean arterial pressure and

19 baseline subgroups.

20   Blood pressure control was an important

21 treatment goal in the RENAAL study. Blood pressure was

22 aggressively treated in both treatment groups in order to

23 get to equal blood pressure levels between losartan and

24 placebo, a trough systolic less than 140 and diastolic less

25 than 90 millimeters of mercury.

1   The goal blood pressure was achieved by

2   titrating losartan or matching placebo from 50 to 100

3   milligrams first and then titrating other open-label

4   antihypertensives from different classes, with the

5   exception of ACE inhibitors and AII receptor antagonists.

6   The next slide shows concomitant

7   antihypertensive drugs used during the study. As you see

8   from this slide, many drugs from different classes of

9   antihypertensives had to be used in order to control blood

10 pressure in these patients.

11   It should be noted that in addition to study

12 drug, patients in both treatment groups took an average of

13 3-and-a-half antihypertensive drugs from different classes.

14   The use of each class of antihypertensive agents was

15 comparable between the losartan and the placebo group.

16   This slide demonstrates the mean systolic and

17 diastolic blood pressure in each treatment group during the

18 study. The y axis is blood pressure in millimeters of

19 mercury, and the x axis is duration of follow-up. Overall,

20 the mean systolic and diastolic blood pressure were reduced

21 throughout the study. In the losartan group blood pressure

22 declined from 152 systolic and 82 diastolic at baseline to

23 140 systolic and 75 millimeters of mercury diastolic at the

24 study end, while in the placebo group, blood pressure

25 declined from 153 systolic and 82 millimeters of mercury

1 diastolic to 142 systolic and 75 diastolic at the study

2 end.

3   Since both systolic and diastolic blood

4 pressure were aggressively treated, the best approach would

5 be evaluation of mean arterial pressure, which reflects

6 both.

7   This slide demonstrates by percentile the

8 distribution of mean arterial pressure. The y axis is the

9 mean arterial pressure in millimeters of mercury, and the x

10 axis is duration of follow-up. The line in the middle of

11 each box represents the 50th percentile of mean arterial

12 pressure. The bottom of the box is the 25th percentile,

13 and the top of the box is the 75th percentile of mean

14 arterial pressure. The whiskers represent the 5th and 95th

15 percentile of mean arterial pressure in all patients.

16   As you can see, we were successful in reducing

17 blood pressure in these patients. Mean arterial pressure

18 decreased in all patients throughout the study. Overall,

19 except for the first year of the study, the mean arterial

20 pressure was comparable between the losartan and the

21 placebo group. On the average there was a 2 millimeter of

22 mercury difference in mean arterial pressure, with the

23 losartan group having lower blood pressure. This

24 difference, although small, did achieve a statistical

25 significance.

1   Adjusting for differences in mean arterial

2   pressure, using a predefined analysis of a time varying

3   covariate, demonstrated that the losartan effect on the

4   primary composite endpoint and on the irreversible clinical

5   endpoints of end-stage renal disease, death, and a

6   composite of end-stage renal disease or death, were

7   minimally affected by this adjustment.

8   As is demonstrated on this slide, the dotted

9   lines with squares shows the treatment effect after

10   adjustment for mean arterial pressure, using mean arterial

11   pressure as a time varying covariate.

12   This supports the conclusion that the renal

13   protective effects of losartan on the primary composite

14   endpoint and on irreversible clinical endpoints of end-

15   stage renal disease, and end-stage renal disease or death,

16   is over and above the antihypertensive effect of losartan.

17   DR. BORER: Excuse me, Dr. Shahinfar, two

18   things. First, because I always keep my word, it's 30

19   seconds short of 9:45, and we've been importuned to have a

20   break at 9:45 for about 10 minutes, which we will. This

21   seems like a reasonable break point.

22   At this point I want to just take my 30 seconds

23   to ask you about these data, because to me these are

24   particularly important in judging the independent effect of

25   losartan for this indication.

1   Here I am even more concerned about the

2   relation of the model to the conclusion, because, in fact,

3   the adjustment makes the drug appear to be somewhat less

4   effective. I don't care about the p values and all because

5   it's hard for me to interpret those in this setting when

6   we're talking about adjustments.

7   But, did you do anything with blood pressure

8   that was analogous to what you did with protein? For

9   example, you found 4,000, after the fact, that there was an

10 imbalance above 4,000. Wasn't there an imbalance above 160

11 or 180 in favor of placebo, and is that where most of the

12 events lay in the placebo group? I don't know.

13   The other question I would ask is why, and we

14 don't need a prolonged answer here, and maybe one of your

15 consultants wants to get up and talk about this, because

16 they know more than I do. You looked at mean pressure and

17 you said that really was the best integrator, and I would

18 wonder about that.

19   As data emerged it appears that systolic

20 pressure and pulse pressure, particularly in the population

21 that you studied, might be more important, and mean blood

22 pressure would tend to minimize the effect of the widening

23 pulse pressure that you see when you look at the difference

24 in the systolic and diastolic blood pressure curves on drug

25 and on placebo. There is a wider pulse pressure on average

1 throughout the course of the study in the patients on

2 placebo than on losartan. You tend to lose that when you

3 define a mean blood pressure.

4   So, I would like some quick answers to those

5 questions, and if one of them is going to be long, we'll

6 wait until after the break. But first, how about the cut

7 points for blood pressure?

8   DR. SHAHINFAR: We didn't do exactly what we

9 did for proteinuria. It's not exactly the same picture.

10 It was to see where are the outliers.

11   One important factor is that we saw events in

12 all different levels of blood pressure control. But the

13 important finding is that the better the blood pressure is

14 controlled, so even in the placebo group, when blood

15 pressure is controlled absolutely great, we have better

16 treatment effect with losartan, which basically proved that

17 this is not just blood pressure.

18   The answer to your next question, I think is

19 very important, and I agree with you. In looking at the

20 pulse pressure and systolic and diastolic in these

21 patients, we look at all of those factors. Mean arterial

22 pressure was predefined. What I presented today is the

23 predefined analysis and the correction that we did. Did I

24 answer your question?

25   DR. BORER: Pretty much. But it looks like we

1   have an additional answer here.

2   DR. KEANE: Thank you. I'm Bill Keane. I'm

3   the last presenter this morning, but maybe I could just

4   quickly come in here and talk to the issue before we do

5   break. I'm Vice President for Clinical Development in U.S.

6   Human Health.

7   Let me give you some numbers, and if we want to

8   discuss these more -- we did look at the prespecified, as

9   Dr. Shahinfar has indicated, the mean arterial pressure --

10   and you've already seen that data.

11   We've also looked at obviously each of the

12   components, the systolic, the diastolic, as well as the

13   pulse pressure, to see the influence on our risk reduction.

14   In essence, the risk reduction all was approximately 16

15   percent. For the mean arterial pressure, it was 15

16   percent. For the diastolic pressure alone, it was a 17

17   percent risk reduction. For the systolic blood pressure

18   alone, there was a 13 percent risk reduction, and for the

19   pulse pressure, there was a 13 percent risk reduction. So,

20   this basically I think answers the issue that you are

21   raising.

22   I think that this is an important point because

23   overall, as Dr. Shahinfar has said, we did aggressively

24   lower blood pressure in the trial. We came from about 150

25   over 80 at the start. We brought it down to about 140 over

1 about 75 at the end. Blood pressure changed, and these

2 were our adjustments as we looked at them.

3   DR. BORER: We may want to come back to this,

4 but I wonder if anybody, before the break, has any other

5 comments they want to make on the committee about this

6 issue. Otherwise, we can come back to it in later

7 discussion. Tom?

8   DR. FLEMING: Just very briefly, if that slide

9 can go back up. It confirms what your sense was, Jeff.

10 Basically the imbalance seems to be more with systolic than

11 with diastolic, and so when you adjust for systolic rather

12 than the mean you do see the bigger effect of the

13 confounding.

14   DR. BORER: Okay. Thank you very much. We may

15 come back to this later.

16   Let's take a short break now and reconvene at

17 10 o'clock.

18   (Recess.)

19   DR. BORER: Okay. Dr. Bain.

20   DR. BAIN: Dr. Borer, your original question

21 was, was there a difference in baseline blood pressure?

22 Actually you were interested in some of the upper

23 distributions. We looked at the distribution of blood

24 pressure at baseline and there was no difference in the

25 distribution, if you look at the percentiles over time.

1   Now, this morning already we've talked about

2   two different adjustments, and what I want to do is make

3   sure that everybody understands the two different

4   adjustments we've talked about so far.

5   The first one we introduced was the adjustment

6   because we observed this difference in baseline

7   proteinuria. As we showed, there were higher levels of

8   proteinuria in our upper stratum, the greater than 2 grams.

9   The rate was higher in the losartan group. Because of

10 that baseline imbalance we showed you, when we adjusted the

11 treatment effect, the treatment effect got stronger because

12 of the losartan group having the higher baseline protein.

13 So, that's the first one we talked about.

14   Then we introduced another adjustment when Dr.

15 Shahinfar was talking about the difference that we observed

16 in mean arterial pressure over the course of the trial.

17 Okay. So, now we're not talking about baseline anymore.

18 Now we're talking about adjusting for that difference in

19 mean arterial pressure during the study. And what we

20 showed there was, when you adjust for the mean arterial

21 pressure as a time varying covariate, is it had minimal

22 impact on that same treatment affect that we observed on

23 our primary composite endpoint. Okay?

24   DR. BORER: Okay. Thank you.

25   DR. KOPP: Could I ask a blood pressure

1   question? You have blood pressures out to 48 months. Were

2   patients censored for collection of that data when they

3   went on dialysis?

4   DR. SHAHINFAR: No. All patients were included

5   in the analysis, so that included all of them.

6   DR. BAIN: Let me clarify that. If you are

7   talking about the blood pressures that we were using to

8   adjust for the primary composite endpoint, in that

9   adjustment we were only adjusting up to the time they had

10   the event. We continued to collect blood pressures after

11   that, but the adjustment is only in effect up to the time

12   of the event.

13   DR. BORER: Dr. Hirsch?

14   DR. HIRSCH: Thank you. Alan Hirsch.

15   I want to talk about a little bit of physiology

16   and the pre hoc hypothesis for the adjustments. As a non-

17   nephrologist, for me, I am still a little bewildered by

18   what I would have anticipated the adjustment would have

19   accomplished. In other words, in a patient with greater

20   than 4 grams of urinary protein excretion, was it

21   anticipated that losartan would have a greater impact or a

22   lesser impact on the primary outcome, based on the time to

23   the first event? In other words, if we adjust for those

24   patients who are sicker, would we have anticipated a lesser

25   or a greater effect of the drug?

1   DR. BAIN: I think the question was, in

2   patients that entered -- we're back to baseline proteinuria

3   -- with relatively high levels of protein, we were

4   adjusting for that imbalance, because that's mainly where

5   the imbalance was. It turns out that, as Dr. Shahinfar has

6   already indicated, in those patients that have high

7   baseline protein -- like, say, greater than 4 milligrams

8   per gram -- 80 percent of them had an event. And when you

9   adjust for that baseline difference, that's what's having

10   the effect to push the treatment effect to be larger than

11   what we observe when we don't adjust for that imbalance in

12   the high levels of baseline protein.

13   DR. BORER: Does that satisfy you, Alan?

14   DR. HIRSCH: Well, I'll come back to this later

15   then. I'm not entirely satisfied.

16   DR. BORER: Before you start the next section,

17   we've been talking about nephropathy and proteinuria, and

18   Dr. Elia said that the terms are going to be used

19   interchangeably. I would just like to hear from the

20   nephrology members of the panel about that equivalence and

21   how we should interpret these data based on definitions and

22   what have you. Dr. Brem?

23   DR. BREM: Andrew Brem.

24   I was a little bit troubled I guess by the

25   opening remarks, stating something to the effect that

1   proteinuria will equal nephropathy. Proteinuria is a sign

2   of the nephropathy perhaps, and biopsy is the gold standard

3   to establish what the nephropathy is and to make that

4   diagnosis.

5   I certainly realize that one is not going to

6   biopsy 1,500 patients, so that's not a possibility, but I

7   think it's important to recognize that we are using

8   proteinuria as a surrogate for the nephropathy, not as the

9   nephropathy itself.

10   As such, is it well established enough to be

11 used as a surrogate? You're doing your statistics and

12 presenting outcomes based on it as a surrogate. Have we

13 established well enough that higher the proteinuria, the

14 worse the outcome? I think probably much of the discussion

15 that we're having about the statistics right now sort of

16 centers on that question.

17   DR. GOLDMAN: Yes. That's a great question.

18 Bonnie Goldman, Regulatory Affairs.

19   I'd asked that we try to come back because we

20 do have data, if the group would like to see it, especially

21 within this study, about essentially what you're asking

22 about the surrogacy. But it literally would take quite a

23 while to go through during the course of this.

24   The bottom line is, in this study, in fact,

25 there's a very good relationship between the proteinuria

1   and the outcomes. Okay?

2   DR. BORER: At the end of the day, we are not

3   looking at proteinuria as an endpoint, just as an admission

4   point, so that may mitigate against any concern about that.

5   Tom?

6   DR. FLEMING: I think it just might be worth a

7   quick comment, that we've been thinking and talking about

8   proteinuria now in at least three different ways, as a

9   predictor, as an effect modifier, and as a surrogate.

10   Those are in fact completely separate concepts.

11   I am persuaded that proteinuria is a predictor.

12   It is related to the risk of the outcome. Whether it's

13   the triple endpoint, the double endpoint, or the single

14   endpoint, the higher the level of baseline proteinuria the

15   higher the risk of these outcomes we're looking at. So, it

16   is a predictor.

17   Is it an effect a modifier, which might be

18   related to Alan's comment. I'm not sure, but as an effect

19   modifier, the question is, is the treatment effect

20   different in people above 4,000, versus in people 2,000 to

21   4,000, versus less. I don't know the answer to that, but

22   that's an entirely separate question than whether we should

23   adjust for baseline proteinuria if there is an imbalance

24   because it is a potential confounder.

25   The third issue is, is it is a true surrogate?

1 That's the question I ask when I wonder is looking at

2 treatment effect in change in proteinuria levels an

3 adequate measure of whether I'm truly achieving clinical

4 benefit. I would agree that that is entirely

5 unestablished, that proteinuria levels would be an adequate

6 replacement endpoint.

7   DR. BORER: Here we're not doing that,

8 fortunately.

9   Dr. Temple?

10   DR. TEMPLE: Tom's second question would be

11 answered by the display that you initially requested, and

12 that I asked for also, which is to look at what the effect

13 of treatment is in the greater than 4,000 and less than

14 4,000, which is still your poor man's covariate adjustment

15 for people who don't understand covariate adjustments very

16 well. It is very informative. We still hope to see that.

17   DR. BORER: We poor men probably will see that

18 after lunch, and poor women, if there are any of you among

19 us.

20   DR. SHAHINFAR: I think this is where we left

21 off.

22   Next I would like to show you the analysis of

23 primary composite endpoint across predefined baseline

24 subgroups.

25   This slide is intended to convey by visual

1 impact the consistent benefit of losartan across a variety

2 of subgroups. The primary composite endpoint was explored

3 in 18 predefined subgroups, which are shown on this slide.

4   For each subgroup, the point estimates on the graph are

5 all on the left side of the zero line in favor of losartan.

6   Overall, there was no significant interaction between

7 losartan treatment and these predefined subgroups, except

8 for region.

9   When testing as many as 18 subgroups, it's not

10 unexpected that by chance alone one subgroup would have a

11 significant interaction. While it appears that the effect

12 of losartan varies among regions, note than none of the

13 point estimates are to the right of the 0 line.

14   As noted in the FDA review, there is not a

15 significant regional heterogeneity.

16   DR. BORER: Can we just stop you there for one

17 second? I think that one issue that may come up and that I

18 don't understand so well may have to do with definition.

19   Dr. Armstrong, did you want to say something

20 about that?

21   DR. ARMSTRONG: As a non-nephrologist, I would

22 appreciate some discussion about the definition of end-

23 stage renal disease, which is the clinically robust,

24 meaningful component of the double endpoint, which we are

25 relying on. I guess the issue is how systematic is this

1 definition applied across centers and countries, since

2 there were many in your study? To what extent did it

3 relate to some of these other markers such as proteinuria

4 and creatinine?

5   For example, was there heterogeneity across

6 centers or countries as it relates to the application of

7 this to a non-nephrologist's subjective decision about

8 transplantation or dialysis, which is obviously modulated

9 by several factors. So, I would really appreciate some

10 enhanced understanding around this issue.

11   DR. SHAHINFAR: That's a very important

12 question, and the criteria for the definition of end-stage

13 renal disease was a requirement for dialysis or

14 transplantation. As you mentioned, there are some

15 countries where there is less transplantation, and there

16 are more transplantations in other countries.

17   But if the patient required dialysis or

18 transplantation, and the investigator identified that, that

19 this patient needs to be dialyzed, and if the patient

20 refused to be dialyzed, or dialysis was not available,

21 which can happen in some countries, then the Adjudication

22 Committee used the criteria, estimated GFR. The GFR had to

23 be below 10 ml per minute, corrected for body surface area,

24 in order to adjudicate that patient as an end-stage renal

25 disease patient. So, this way we have information on end-

1   stage renal disease in all patient randomized.

2   DR. ARMSTRONG: May I, Mr. Chairman, just

3   pursue this? So, could you then reassure me about the

4   homogeneity versus the heterogeneity as it relates to the

5   application of this across the centers and countries, and

6   the extent to which the definition was aligned with, as I

7   understand it -- we've just had a discussion about

8   proteinuria for example -- could you comment about

9   alignment of that measurement with this endpoint?

10   DR. SHAHINFAR: We used a central lab for

11 measurement for all proteinuria, so it was done uniformly

12 across all countries in the world. With respect to the

13 definition of end-stage renal disease, there are very few

14 patients who either required and did not get dialysis or

15 refused dialysis.

16   DR. HAFFNER: I'm Steve Haffner. I was chair

17 of the Events Committee. It turns out that very few people

18 actually fit into this category. I think there were 16

19 subjects. 10 were in one group and 6 were in the other; 10

20 in placebo and 6 in losartan. I couldn't remember which

21 group it was. It turns out that it was a very small

22 percentage of the people who were identified as end-stage

23 renal disease. We had to go to the Walser formula to

24 characterize them. Of those, I think most were refusals,

25 and not the absence of dialysis as a practical issue.

1   DR. BORER: Looking at it the other way, was

2   there a substantial number of people who were put on

3   dialysis with GFRs that were greater than 10 milligrams per

4   hour or cc per hour, whatever it is, adjusted for body

5   surface area? No.

6   DR. SHAHINFAR: We did not systematically

7   measure estimated GFR. When the physician made a

8   distinction that this patient needed to be dialyzed, based

9   on the condition of the patient and requirement for

10 dialysis, and if that patient was dialyzed, that was

11 captured as dialysis.

12   DR. BORER: So, there might be some non-

13 homogeneity across regions in that regard or no?

14   DR. HAFFNER: We can look at that but we have

15 not looked at that at this point. Once they went on

16 dialysis, we didn't calculate Walser's.

17   There's another issue -- there were some people

18 who got end-stage renal disease who were not classified as

19 doubling. That can happen for two reasons. One is that

20 serum creatinine didn't actually double, or two, in order

21 to be called doubling, they had to get two measures of

22 serum creatinine, and some people were put on dialysis

23 before the second confirmation of it.

24   We actually had long discussions that if there

25 was doubling after dialysis -- you'd figure it would

1 probably double before dialysis -- but we excluded that

2 from the doubling. So, we took what I think is a fairly

3 rigorous point about doubling, and the second measurement

4 also had been done by the central lab. So, there were a

5 few people who didn't make that, but we could do that

6 analysis. But we have not yet by region.

7   DR. BORER: Dr. Nissen?

8   DR. NISSEN: Could you put that slide up on the

9 various subgroups please? I need some clarification

10 because the slide is at variance with the briefing document

11 we received from the FDA.

12   According to our briefing document, the hazard

13 ratio for the Europeans is actually 1.05, so it actually

14 goes in the wrong direction, and you show it in the

15 favoring losartan group.

16   I guess what I want clarification about is that

17 it looks to me, from the FDA briefing document, that

18 virtually the entire benefit for the whole cohort comes

19 from the group from Asia. That is, if you look at the rest

20 of the cohort, there are virtually no effects. The 20

21 percent of patients who were from Asia completely drove the

22 endpoint in the trial. Is that correct or incorrect?

23   DR. SHAHINFAR: You're referring to the region?

24   DR. NISSEN: Yes.

25   DR. KEANE: Again, I'm Bill Keane. Maybe I can

1   take a shot at that at this point in time. I'm in clinical

2   development. I think we were going to get into some of

3   these questions later on, so we can answer it now or we can

4   postpone it to later on.

5   I think one of the important points that Dr.

6   Shahinfar has already mentioned to you is that in fact

7   there was by region a slight interaction that achieved a

8   level of about .047 that was seen in the Asian group. I

9   think as we looked at this with the FDA and in greater

10   detail, actually the FDA -- and I think that's in your

11   briefing document itself -- did not really underscore that

12   this was an important interaction.

13   Now, part of the reason for that is the way we

14   defined regions, first of all. The region was a geographic

15   region that included not only the Pacific Rim but also

16   included the Middle East as well, specifically Israel.

17   There were, from a regional perspective, just inherent

18   reasons in our definitions that maybe this might have been

19   shown as a difference basically, with the point estimates

20   slightly to the left for Asia.

21   DR. NISSEN: No, but your point estimate for

22   Europe favors losartan, and in the FDA briefing document

23   the point estimate favors placebo. So, in Europe this

24   doesn't gibe with the FDA's data that we got.

25   DR. BAIN: Ray Bain, Clinical Biostatistics,

1   Merck Research Labs.

2   If you look at the Merck briefing document,

3   they are all in the right direction. I assume possibly

4   that the FDA was doing a different baseline adjustment. I

5   have to look at their briefing document to figure out

6   exactly what the slight differences were.

7   DR. NISSEN: For the committee, I am looking at

8   page 22 of the FDA's briefing document, and the data don't

9   agree with the data up there. So, I think we really do

10   need to clarify this from the agency as to what are the

11   correct numbers here?

12   DR. BAIN: We also need to look at page 63 of

13   the Merck briefing document because that's what this slide

14   is based on. In the Merck briefing document, we're

15   adjusting for baseline protein as a stratum, but not

16   region, since region is the variable that we're looking at.

17   So, if you look at page 63 in the Merck --

18   DR. NISSEN: I now understand the difference.

19   So, what you did was you took the post hoc adjustment for

20   protein and added it to this.

21   DR. BAIN: No. We took our prespecified

22   adjustment, which is the categories of baseline protein.

23   That was our prespecified analysis. In that analysis those

24   numbers on page 63, although they're in hazard ratios, so

25   you just take 1 minus that times 100, you'll get everything

1 on the left. For example, in Europe it's .943, which is a

2 risk reduction of roughly 5 percent.

3   DR. NISSEN: Tom Fleming, maybe you can help me

4 understand this. I don't understand why the two don't

5 agree here.

6   DR. FLEMING: I think we need to sort this out,

7 as we have a chance maybe over the break, to get a clear --

8 my sense is it has to do with the difference in either --

9 and I don't think it's this exactly -- who's in which

10 region or what covariates are used in these two analyses

11 for adjustments. I would suggest maybe at the break we can

12 get that ironed out.

13   DR. NISSEN: All right. Maybe not now, but I

14 do want to come back to this question later on whether the

15 entire treatment effect for the entire study was driven by

16 the 20 percent of patients that were in Asia.

17   DR. FLEMING: Just on that point, Steve, in

18 either of these two analyses the same general, at least

19 qualitative picture is that Asia carries the greatest part

20 of the signal in either of the analyses.

21   DR. NISSEN: The overwhelming majority of the

22 signal.

23   DR. BORER: Dr. Konstam.

24   DR. KONSTAM: Hi. I'm Marv Konstam from Tufts

25 New England Medical Center. I am here as a paid consultant

1   to Merck.

2   You know, I just wanted to comment from my own

3   experience and perspective about subgroup analyses, and I

4   think the panel is all aware about how treacherous this can

5   be of identifying one subgroup.

6   I just want to point the panel to the FDA

7   medical reviewer analysis of this, because I personally

8   found it enormously instructive. Specifically, in the

9   medical review, page 24, figure 7, it breaks it down by

10   individual countries. What's nice about it is that it

11   shows you the impact of size of the particular subgroups on

12   the relevance of the relative risk that comes out.

13   You can break these down all sorts of different

14   ways, but if you look at this analysis, the individual

15   countries really are all over the map. Actually, it's

16   interesting that the big Asian contribution comes from

17   Israel, by the way, so you can think about that.

18   But, I just want to point that out. I think to

19   me this was a very instructive way of looking at it, and

20   sort of not focusing too much on this Asian business is at

21   least my perspective on it.

22   DR. BORER: Dr. Kopp, you had a comment.

23   Before you do, I just want to point out, Dr. Konstam, I

24   never understood you to be such a humorist. In fact, the

25   countries are all over the map.

1   (Laughter.)

2   DR. KOPP: I wanted to follow-up on a response

3   to Dr. Armstrong's point. I think we had a lot of

4   discussion about how to adjudicate people at the low end of

5   the GFR spectrum who weren't placed on dialysis. I think

6   it is worth thinking a little bit about the patients with

7   presumably GFRs between 10 and 15 or 10 and 16, whatever,

8   who were started on dialysis, and admit that there is

9   undoubtedly both heterogeneity across countries and within

10   countries about whether a particular patient gets started

11   on dialysis on the typical day, and think about what the

12   indications would be. They would certainly, for most

13   nephrologists, include fatigue, anorexia, falling albumin,

14   among the key criteria that would be looked at, that I

15   think would be unrelated that I can think of to the therapy

16   in question.

17   But there are two that at least might play a

18   role that could potentially could be related, and one would

19   be potassium levels, difficulty maintaining potassium,

20   admittedly not too much of a problem with chronic renal

21   failure patients. The other would be difficult to maintain

22   congestive heart failure, a patient for whom diuresis was

23   becoming increasingly difficult. Each of those at least --

24   and here I'm speculating -- run in opposite directions.

25   That is, a losartan patient might be more likely to have

1   hyperkalemia than a placebo treated patient, but less

2   likely to have difficult to manage congestive heart

3   failure.

4   Having said that, there is no way we can really

5   be sure, and I guess the major protection is this idea that

6   it was all placebo-controlled, and so the decision was

7   being made by somebody without advance knowledge about how

8   the treatment was based.

9   But at least maybe you'd comment upon the

10   possibility of how some of those factors that are

11   potentially related to losartan might play into the

12   decision to start dialysis.

13   DR. BORER: You can hold that until you have a

14   chance to think about and come back to it later if you

15   like.

16   Dr. Lindenfeld, did you want to make a comment?

17   DR. LINDENFELD: Just a quick question. When

18   we come back to this issue of region -- and I think we

19   fully understand the problem with subgroups -- I wondered

20   if we could see by these regions the numbers of patients

21   that had a doubling of creatinine versus end-stage renal

22   disease. If we could divide those up by regions and just

23   see if that was different by region.

24   DR. SHAHINFAR: We will show that.

25   DR. BORER: While you're doing that, I think

1 there will be time to respond specifically to Dr. Kopp's

2 question. I know you're going to show us a cardiovascular

3 endpoint analysis, where the heart failure issue will be

4 death with and a safety analysis where the hyperkalemia

5 issue and its relation to sudden death will be dealt with.

6 So, let's bookmark that so you can specifically respond to

7 the question when you get to it.

8   DR. SHAHINFAR: There were two prespecified

9 secondary hypotheses to support the renal protective effect

10 of losartan. The first was that losartan, compared to

11 placebo, would reduce the rate of progression of renal

12 disease as measured by the slope of reciprocal of serum

13 creatinine.

14   This is an important measure that is used by

15 clinical nephrologists to predict the time to dialysis for

16 the patient. Note that the literature on nephropathy

17 indicates that the inverse of serum creatinine value for an

18 individual tends to fall in a linear fashion over time.

19 The slope of this line is an indication of the speed of

20 progression of renal disease. The more negative the slope,

21 the faster the progression. This analysis takes into

22 consideration all patients, not just those patients who

23 have reached a renal endpoint.

24   Another secondary endpoint hypothesis in RENAAL

25 was that losartan would reduce proteinuria during the

1   course of the study, compared to placebo. The next two

2   slides demonstrate the effect of losartan on these

3   secondary hypotheses.

4   For the analysis of the progression of renal

5   disease, we calculated the slope for each patient, and

6   present here in this chart the median slope for two

7   treatment groups. As I referred before, the more negative

8   the slope, the faster is the progression.

9   This slide illustrates the rate of loss of

10   renal function as measured by the slope of reciprocal of

11   serum creatinine. On the y axis is the change in the slope

12   of 1 over sCr. There was a significant reduction in the

13   rate of loss of renal function by 18 percent with losartan

14   with p equals .01.

15   Another secondary hypothesis was the effect of

16   losartan on proteinuria. Reduction of proteinuria has been

17   considered an important therapeutic target for treatment of

18   diabetic nephropathy among clinical nephrologists.

19   On this slide the y axis demonstrates the mean

20   percent change based on geometric mean for urinary protein

21   excretion. The x axis is the duration of follow-up.

22   Losartan was associated with a reduction in

23   urinary protein excretion of 25 percent within 3 months,

24   and this reduction was maintained throughout the study.

25   There was an overall 34 percent reduction in proteinuria

1   compared to placebo, with p less than .001.

2   The significant treatment effect of losartan on

3   proteinuria was unchanged after adjustment for blood

4   pressure at each time point, supporting the conclusion that

5   the antiproteinuric effect of losartan is over and above

6   its blood pressure lowering effect.

7   In summary, in type II diabetic patients with

8   proteinuria, losartan is renal protective by delaying the

9   onset of the primary composite endpoint of doubling of

10 serum creatinine, end-stage renal disease, or death. In

11 the entire cohort losartan reduced the risk of end-stage

12 renal disease by 28.6 percent.

13   Losartan reduces the rate of decline of renal

14 function as measured by the slope of reciprocal of serum

15 creatinine.

16   Losartan reduces proteinuria, and has a

17 beneficial effect on the primary composite endpoint and

18 proteinuria beyond its beneficial effect on blood pressure.

19   I would now like to turn to a discussion of

20 cardiovascular secondary hypotheses. We designed RENAAL as

21 a renal protection study, but recognizing the importance of

22 cardiovascular events in type II diabetic patients, we made

23 a cardiovascular morbidity and mortality a prespecified

24 secondary hypothesis, and adjudicated cardiovascular

25 outcomes.

1   The cardiovascular hypothesis in RENAAL was

2   based on the effect of losartan on cardiovascular morbidity

3   and mortality. We hypothesized that losartan compared to

4   placebo would increase the time to the first event of the

5   cardiovascular morbidity and mortality which was a

6   composite of cardiovascular death, myocardial infarction,

7   stroke, first hospitalization for heart failure, first

8   hospitalization for angina, and revascularization.

9   The next three slides summarize cardiovascular

10   secondary endpoint data in RENAAL.

11   This Kaplan-Meier curve demonstrates the result

12   of the secondary composite endpoint of cardiovascular

13   morbidity and mortality. Although numerically lower on

14   losartan, there was no statistically significant effect of

15   losartan compared to placebo on the composite endpoint of

16   cardiovascular morbidity and mortality.

17   This plot demonstrates the effect of losartan

18   on cardiovascular morbidity and mortality and the

19   individual component of this composite endpoint. The risk

20   reduction and 95 percent confidence interval are presented

21   for the composite endpoint and each of the components of

22   this composite endpoint: cardiovascular death, myocardial

23   infarction, stroke, first hospitalization for heart

24   failure, first hospitalization for angina, and

25   revascularization, both coronary and peripheral

1   revascularization.

2   As you see, the point estimates are all

3   distributed around the 0 line for different components, but

4   overall there is no significant difference in the composite

5   endpoint of cardiovascular morbidity and mortality.

6   During the January 17th advisory committee

7   meeting for irbesartan, this committee expressed interest

8   in the effect of irbesartan treatment on the composite of

9   renal and cardiovascular endpoints in the irbesartan

10   diabetic nephropathy trial. In light of this we performed

11   a post hoc analysis, time-to-event analysis, of the

12   composite of irreversible clinical endpoints of end-stage

13   renal disease, myocardial infarction, stroke, or death in

14   the RENAAL study.

15   As is demonstrated in this Kaplan-Meier curve,

16   losartan significantly reduced this combined endpoint by

17   21.2 percent; p equals .003. This analysis demonstrates

18   that the renal protective benefits of losartan do not come

19   at the expense of increased risk of cardiovascular

20   endpoints, and in fact demonstrates the benefit of losartan

21   in this population.

22   As mentioned earlier, we designed RENAAL as a

23   renal protection study, rather than a cardiovascular study.

24   Therefore, we enriched the population with patients at

25   high risk for progression of renal disease.

1   In summary, in RENAAL there was no statistical

2   significant difference in cardiovascular morbidity and

3   mortality.

4   Post hoc analysis of end-stage renal disease,

5   myocardial infarction, stroke, and death indicate that

6   renal protective benefits of losartan in RENAAL did not

7   come at the expense of increased risk of cardiovascular

8   events, and therefore supports the overall benefits of

9   therapy in these patients.

10   DR. BORER: Excuse me one second.

11   Dr. Kopp, do you want to come back to your

12   issue here. We have just seen the total cardiovascular

13   endpoints. The sponsor hasn't broken out the heart

14   failure, which they did in their briefing document. They

15   did actually have one slide that did. Did you want to

16   restate your question, or are you satisfied with what

17   you've gotten here?

18   DR. KOPP: I don't think it directly addresses

19   the issue. Is it possible that when a clinician is sitting

20   with a patient with a creatinine of 5.5 and trying to

21   decide does this person needs dialysis, would the presence

22   of heart failure or the presence of hyperkalemia have

23   tilted one way or the other that decision. But I think we

24   may get that later from Dr. Haffner's group.

25   DR. HAFFNER: I don't think we're going to get

1 really good data on this. We did not ask people, when they

2 went to end-stage renal disease, to answer a special

3 questionnaire on why they went to end-stage renal disease.

4 Was it dialysis, hyperkalemia, nausea and vomiting?

5   We do have some data on prior events for CHF.

6 We have events on potassiums. But it would be linking data

7 and this isn't all entered. My guess is eventually we

8 could probably figure some of this out, but because they

9 weren't done at the time of dialysis, I'm not sure it's

10 going to be really good data, to tell you the truth.

11   What we clearly could do is we can calculate by

12 regions for instance the Walser to see if creatinine

13 clearance differed by region. We could clearly do that. I

14 am not sure we can do that today. We can clearly do that

15 by whether they were on losartan or in the placebo group,

16 so we can see whether this is systematic bias by area for

17 people who enter end-stage renal disease.

18   But I don't think we're going be able to get a

19 detailed thing about hyperkalemia versus failure. We can

20 look at the events prior to it. We haven't done that

21 because that doesn't enter into the composite. But I am

22 really not so sure, as an epidemiologist who works on

23 clinical trials, how worthwhile that data really is.

24   DR. BORER: Dr. Lorell.

25   DR. LORELL: Yes, I wonder if you can provide

1   us with data, in regard to the all-clause mortality, as to

2   a breakdown of cause of death, including what percent of

3   deaths were cardiovascular deaths? I think it is a

4   potentially important issue for this committee to discuss

5   for a couple of reasons.

6   One is that this trial was, in fact, shaped and

7   stopped early because of ethical safety concerns of the

8   committee regarding the growing evidence of

9   cardioprotective effects of ACE inhibitors on multiple

10 cardiac events. That letter that was sent to the

11 investigators is in our brochure.

12   So, it raises the question, in regard to your

13 last slide, as to the real issue, a real issue that was

14 also addressed by the Safety and Monitoring Board, not

15 whether the renal protective effects of losartan were at

16 the expense of increased risk, but were at the expense of

17 the absence of cardioprotection from a competitive therapy.

18   That was an issue that clearly was a concern for the

19 Safety and Monitoring Board.

20   So, I think it would be of interest for this

21 committee to know the breakdown of all-cause mortality, if

22 you have that data.

23   DR. SHAHINFAR: Can I first clarify one

24 question you raise? You mentioned the Safety and

25 Monitoring Committee. In fact, the study was not stopped

1 by the Safety Committee. It was stopped by the blinded

2 Steering Committee, who didn't have access to unblinded

3 information. So, that decision was clearly unrelated to

4 internal information from RENAAL. That was the decision of

5 the Steering Committee.

6   Now, with respect to the causes of death and

7 all-cause mortality, would you like me to present that now,

8 or do you want me to present the safety and we can present

9 all the information?

10   DR. LORELL: Why don't you include it whenever

11 you think it would be fit. That would be fine.

12   DR. SHAHINFAR: If you agree, I'll finish the

13 presentation of safety. Thank you.

14   Now I would like to present to you the RENAAL

15 safety results. Overall, the safety profile of losartan in

16 this study was consistent with that listed in the U.S.

17 prescribing information for losartan. In this population

18 of patients with type II diabetes and underlying kidney

19 disease, we expected to see many clinical or laboratory

20 adverse experiences. In fact, this is demonstrated in high

21 event rates of clinical adverse experiences in both

22 treatment groups.

23   On this slide, on the y axis we present the

24 percentage of patients with clinical adverse experiences.

25 For clarity the percentage of patients are also shown on

1 the top of each bar. Up to 95 percent of patients in each

2 treatment group had clinical adverse experiences during the

3 study. There was a slightly higher number of drug-related

4 clinical adverse experiences in the losartan group. There

5 were more patients on placebo who had discontinued for

6 clinical adverse experiences. The number of patients who

7 died because of clinical adverse experiences was comparable

8 between losartan and placebo group.

9   With respect to laboratory adverse experiences,

10 we see a similar pattern. It is important to note that the

11 laboratory adverse experiences were those that were

12 reported by the investigators, not based on a predefined

13 laboratory value. The number of patients with drug-related

14 laboratory adverse experiences was higher in the losartan

15 group. This was mostly attributed to a higher number of

16 patients with hyperkalemia. No patient died because of a

17 laboratory adverse experience.

18   Because of the population that we studied in

19 RENAAL, we predefined six adverse experiences of interest,

20 and performed a prespecified analysis. This table provides

21 the results of our analysis on the six predefined adverse

22 experiences that are listed on the left column.

23   The reason for selecting the six adverse

24 experiences was that acute renal failure has been reported

25 by ACE inhibitors and AII receptor antagonists.

1 Hyperkalemia and hypokalemia were adverse experiences of

2 interest since we were studying diabetic patients with

3 underlying kidney disease. Anemia has been reported with

4 ACE inhibitors and angiotensin II antagonists. It is

5 listed in the prescribing information for losartan. It is

6 also common in patients with advanced renal disease. Since

7 we studied diabetic patients, hyperglycemia and

8 hypoglycemia were also adverse experiences of interest.

9   Except for hyperkalemia with losartan, and

10 hypokalemia in the placebo arm, there was no significant

11 difference in any of the predefined adverse experiences

12 between losartan and placebo.   Hyperkalemia is not

13 unexpected in patients with type II diabetes and underlying

14 kidney disease, especially when a drug that blocks the

15 renin-angiotensin-aldosterone system, such as losartan is

16 used.

17   In contrast, the higher incidence of

18 hypokalemia in the placebo arm is probably related to the

19 high use of diuretics. Hypokalemia is important in

20 patients with chronic renal disease. These patients have

21 low bicarbonate, and therefore low serum potassium levels

22 are a true reflection of low intracellular levels of

23 potassium.

24   This slide demonstrates the distribution of

25 serum potassium by percentile in the two treatment groups

1 during the study. The y axis is the level of serum

2 potassium in milliequivalents per liter. The x axis is

3 duration of follow-up. The line in the middle of each box

4 represents the 50th percentile of serum potassium. The

5 bottom of the box is the 25th percentile, and the top of

6 the box is the 75th percentile of serum potassium. The

7 whiskers represent 5th and 95th percentile of serum

8 potassium at each time point.

9   Overall, mean serum potassium was significantly

10 higher in patients who were treated with losartan at each

11 time point. However, the mean differences did not exceed

12 .3 milliequivalent per liter. 95 percent of all patients'

13 serum potassium values were below 6 and above 3.5

14 milliequivalents per liter at each time.

15   This table shows the number of patients who had

16 serum potassium less than or equal to 3.5 and equal or

17 greater than 6.0 milliequivalents in each treatment group

18 at any time during the study. As you can see on this

19 slide, there were more patients in the placebo group with

20 potassium less than 3.5 and more patients in the losartan

21 group with potassium greater than 6.0 milliequivalents per

22 liter.

23   There were more patients with adverse

24 experiences of hyperkalemia in the losartan group. The

25 number of patients with serious adverse experiences of

1 hyperkalemia was small, but higher in the losartan group.

2 Relatively a small number of patients had to be

3 discontinued for hyperkalemia in each treatment group,

4 indicating that hyperkalemia was clinically manageable in

5 these patients. No deaths were attributed to hyperkalemia

6 during therapy.

7   DR. BORER: Dr. Shahinfar, can you just go back

8 to that slide, the last one? That's it. I don't want to

9 overstate the case here. You've shown us total mortality.

10 You're going to show us the breakdown of cause of death,

11 and that's of interest, and overall the difference in

12 deaths was so small that I think that this may not be a

13 major issue.

14   But you say that no death is due to the adverse

15 event or has been attributed -- that was what you said --

16 attributed to the adverse event of hyperkalemia, and I'm

17 sure that's true. I think the only way you could, with

18 certainty, make such an attribution is, the last time you

19 saw the patient alive, the potassium was high.

20   But it's interesting that nominally there is an

21 excess of sudden deaths in the losartan group from your

22 briefing document. Not a tremendous number, but an excess

23 percentage of sudden deaths nominally. It is not

24 statistically significant.

25   I have to wonder whether -- and this may relate

1   more to labeling if the drug is ultimately approved for

2   this indication -- whether this may not have been related

3   somehow to electrolyte imbalance that just wasn't picked up

4   because deaths occur when they occur, not necessarily right

5   after the last lab value was done.

6   Can you just comment on that?

7   DR. SHAHINFAR: What I would like to do,

8   basically in response to all-cause death and cardiovascular

9   death, and for sudden death that you just mentioned, I

10 would like to ask Dr. Jonathan Fox, who is the cardiologist

11 at Merck, to respond to this question.

12   DR. FOX: Thank you, Dr. Shahinfar. My name is

13 Jonathan Fox. I am a cardiologist with cardiovascular

14 clinical research, Merck Research Labs. I will try to

15 address the question. If I could have slide 1228, please.

16   Just to remind members of the committee, you

17 have already seen these data.   These are the data

18 described in the cardiovascular composite endpoint and the

19 components, and I believe you're most interested, as Dr.

20 Lorell already pointed out, the cardiovascular deaths.

21 What I'm going to try to do over the next few slides is to

22 walk you through all of the adjudicated causes of death,

23 and to focus on those that were adjudicated as

24 cardiovascular causes.

25   This table shows you a breakdown of the

1   adjudicated causes of death by the Endpoint Committee on

2   the entire intention to treat population. Those causes

3   were adjudicated into the following categories: fatal

4   myocardial infarction, known non-cardiovascular cause. In

5   other words, that included categories of non-cardiovascular

6   death, for which there were sufficient data or other

7   clinical information to allow the Endpoint Committee to

8   come to that conclusion.

9   There was a category of "not determined".

10 There were other cardiac causes, and those could include

11 arrhythmia, for example; other vascular causes, including

12 hemorrhagic death, progressive heart failure, and the

13 category of sudden cardiac death, which Dr. Borer has

14 already pointed out. There was a numerical imbalance in

15 favor of placebo 45 deaths compared to 30 in the placebo

16 arm, for a total of 158 deaths in the losartan arm and 155

17 deaths in the placebo arm, which contributes to the overall

18 Kaplan-Meier curve you saw earlier, which were almost

19 entirely superimposed.

20   Next, please, 1231. This is a subset from that

21 same table, so the totals are different. These are

22 Endpoint Committee adjudicated causes of cardiovascular

23 death in the entire intention-to-treat population.

24   So, again, the categories are exactly the same

25 as you saw in the previous slide, except that the non-

1 cardiovascular causes have been omitted. The upshot of

2 this slide is in the last category of "sudden cardiac

3 death", where, again, you see 45 deaths in losartan and 30

4 in placebo. But in terms of the percentages, those have

5 now been boosted by the removal of the non-cardiovascular

6 deaths, so that the sudden cardiac deaths comprised 50

7 percent of those adjudicated causes of cardiovascular death

8 in the trial, compared to 38 percent.

9   1232 please. Now, I think it's important at

10 this point to point out what the definition was of sudden

11 cardiac death that was used by the Endpoint Committee to

12 adjudicate these cases of patients who died. If there were

13 insufficient clinical information or other supporting data

14 for the Endpoint Committee to categorize patients' death

15 events as one of the other categories of cardiovascular

16 death, for example, fatal myocardial infarction, those

17 patients were adjudicated as sudden death, regardless of

18 what the actual mechanism might have been. There just was

19 not sufficient information.

20   So, the definition of sudden cardiac death in a

21 way becomes a default category when there is a lack of

22 specific information. So, that included any death

23 occurring without warning, any death occurring within 24

24 hours of new symptoms, and any unwitnessed death at home.

25   Let me just pause there and ask if that

1   satisfies Dr. Lorell and Dr. Borer, if that answers the

2   question.

3   DR. BORER: Dr. Lorell.

4   DR. LORELL: Thank you. That's very helpful.

5   Just to be very clear to me, because I didn't see either of

6   those two tables in our briefing books, could you just

7   restate, of the total deaths in the losartan and placebo

8   groups, what percent of total deaths in each group was

9   cardiovascular?

10   DR. FOX: I believe we can get that information

11   from 1230. There were 90 cardiovascular deaths in the

12   losartan arm out of a total of 158. There were 79

13   cardiovascular deaths out of a total of 155 in placebo.

14   DR. LORELL: Thank you.

15   DR. ARMSTRONG: I found this safety

16   presentation very helpful. Thank you. As an entree to my

17   question, I just want to recap my understanding and focus

18   on hyperkalemia and the relationship between hyperkalemia

19   and the endpoint, i.e., transplantation or dialysis. As I

20   understand it, 1 out of 4 losartan patients and 1 out of 8

21   placebo patients had hyperkalemia, and 1 out of 10 losartan

22   patients had hyperkalemia in excess of 6, and 1 out of 20

23   placebo patients had hyperkalemia in excess of 6.

24   As I understand it, also, this hyperkalemia was

25   perceived to be clinically manageable, and none of this

1   hyperkalemia was perceived to have related to death,

2   notwithstanding the chairman's caveat.

3   My question is, if you look at hyperkalemia,

4   all comers, what proportion of those patients went on to

5   dialysis or to transplantation in the context, as Dr. Kopp

6   pointed out, of that being a meaningful indication for that

7   endpoint, and what proportion of the losartan versus the

8   placebo hyperkalemia led to the development of that

9   endpoint?

10   DR. SHAHINFAR: We can get that information for

11   you. We haven't looked at the relationship between

12   hyperkalemia and initiation of dialysis, if I understand

13   your question correctly. We can look into that and get

14   back to you.

15   DR. KEANE: I think one has to recognize that

16   our values of potassium that were determined were

17   determined on a regular interval, and actually dialysis, as

18   you're rightly pointing out, is a therapeutic intervention

19   that may occur. So, our ability to measure potassium

20   immediately prior to the initiation of dialysis is really

21   not within the design of the trial. So, we really don't

22   have that kind of information those kinds of patients that

23   are actually starting dialysis, to define whether that was

24   truly an indication for initiation of dialysis. I don't

25   think we're really going to be able to adequately define

1 with precision and clinical reliability the exact answer to

2 your question.

3   DR. BORER: Dr. Kopp?

4   DR. KOPP: Just to clarify -- if a nephrologist

5 had a potassium come back of 6, he could call the study and

6 say, tell us if the patient is on losartan or not, and he

7 would have the option of stopping the study drug -- well, I

8 guess at that point they would come off the study in either

9 case. But that would be an alternative to putting the

10 patient on dialysis.

11   DR. SHAHINFAR: They managed patients as they

12 would manage these patients in their clinical practices.

13 Only 6 patients were unblinded throughout the study, so we

14 did not unblind every single hyperkalemia in the study. It

15 was not actually the reason for unblinding. Is that the

16 question you're asking?

17   DR. KOPP: Is that because the physician never

18 contacted the study, or they weren't allowed to ask that

19 question?

20   DR. SHAHINFAR: No, they were allowed to ask

21 any question, but they never asked that question. In fact,

22 the reason for unblinding those 6 patients was not by the

23 investigator; it was by a cardiologist. The patient had

24 heart failure, MI, and they asked for the unblinding so

25 they could make a clinical decision in that patient.

1   Hyperkalemia was overall managed. We had

2   guidelines in the protocol of how to handle hyperkalemia,

3   and people were used to handling these patients with

4   hyperkalemia and underlying kidney disease. So, they used

5   potassium lowering agents in both treatment groups.

6   DR. BORER: Just for clarification, in the FDA

7   briefing document there is a table that presents all the

8   patients who were unblinded, so we have that information.

9   Let me just remind the committee or ask the

10   committee, because there will undoubtedly be some

11   discussion as we move forward through the summary here, if

12   you want to say something and you press the button on your

13   microphone, the light comes on and I catch it immediately.

14   We've taken care of 99 percent of the problem that we've

15   had by shifting the table so you don't have to break your

16   neck to see the slides. But what that does is cause

17   everybody to focus on the slides instead of on the hands

18   being raised. So, if you press the button that will make

19   it easier to recognize whoever wants to talk.

20   DR. FOX: Jonathan Fox, Merck Research Labs.

21   Mr. Chairman, if I could just expand just a

22   little bit on the death issue. I think this will also

23   perhaps anticipate the intersection between the concerns of

24   several of the committee members, in terms of the

25   relationship between hyperkalemia and sudden death, which I

1 believe you raised yourself earlier. If I could have 1236

2 please.

3   This slide is a table of some selected

4 laboratory test results that were associated with patients

5 who died in the trial, specifically patients who were

6 categorized in that adjudicated category of sudden cardiac

7 death that I explained a moment ago.

8   The first column is the last central lab

9 measure that was obtained prior to death, and I'll tell you

10 something about that time interval in a moment. It is

11 broken down between the losartan arm and the placebo arm.

12   We have included some laboratory measures that

13 I think are relevant in this patient population who is

14 quite ill in the trial. It would be the serum potassiums

15 and the serum bicarbs, blood glucose, in this diabetic

16 patient population, the serum creatinine, and the urine

17 protein.

18   The conclusion I would like to leave you with

19 from this slide is that in terms of overall means, for what

20 that's worth, the potassiums were in the normal range at

21 that last central lab visit. The bicarbs were near normal.

22 Blood glucose was reflective of this diabetic population,

23 but not indicative of hypoglycemia. Serum creatinines

24 indicated that these patients were well along the way in

25 their nephropathy, and that's also reflected in the means

1   urine protein.

2   Could I have 1237? This table shows you the

3   results of the deaths of any cause of death in patients,

4   and their potassium results if they had a potassium result

5   less than or equal to 3.5 milliequivalents per liter at any

6   point during the study.

7   So, in the losartan arm there were 70 patients

8   who fell into that category and 90 in the placebo arm.

9   Those are all patients who had that measurement. There

10 were 12 patients in that category who actually died during

11 the trial and 11 in placebo. 10 of the 12 in losartan were

12 categorized as 1 or more causes of cardiovascular death,

13 and 3 of those 10 as sudden cardiac death. 2 of the 11

14 patients who died in the placebo arm were cardiovascular

15 deaths, a 1 of those was a sudden cardiac death.

16   Also on this next slide, these are investigated

17 causes of death in those same patients who had any measure

18 of potassium less than or equal to 3.5 at any point during

19 the study.

20   So, I want to emphasize that, independent of

21 what the adjudication was of the Endpoint Committee, again,

22 they relied on a strict set of criteria that had to be

23 satisfied by a sufficient body of information for them to

24 adjudicate a particular death to one of those categories

25 that I showed you earlier. So, if there is insufficient

1 evidence available to them, many of those patients were

2 categorized as sudden death.

3   So, independent of that adjudication, this

4 table shows you clinical information that was obtained from

5 the CRF narratives entered by the investigator. As you can

6 see, there is quite a broad collection of different

7 diagnoses without any particular pattern that I can discern

8 for you in this table.

9   Now, this takes a look at the same kind of an

10 examination of the information that we have, but looking at

11 patients who had a measurement of potassium greater than or

12 equal to 6 milliequivalents per liter at any time during

13 the study. There were 123 patients in the losartan arm and

14 61 in the placebo. Of those patients, of the 123 in

15 losartan, 23 patients died, 7 of those had a cardiovascular

16 death, and 4 of those were adjudicated as sudden cardiac

17 death. 61 patients in placebo had the results of a

18 potassium greater than 6. 13 of those patients died. 6 of

19 those had a cardiovascular death, and 2 were categorized as

20 sudden cardiac death.

21   This is a similar table to what you saw a few

22 slides ago. The investigator reported causes of death in

23 patients with a potassium result greater than or equal to 6

24 at any time during the study who were adjudicated as

25 cardiac death. Again, it contains quite a broad range of

1   diagnoses without any particular pattern.

2   I promised you that I was going to show you

3   some information that related the measurement of serum

4   potassium to the time interval between when that last

5   laboratory measure was obtained and when the patient

6   actually died.

7   What this plot shows you on the ordinate is the

8   last potassium value that was obtained that went to the

9   central laboratory, and on the abscissa, the time in days

10   to the death event from that last measurement. As you

11   would expect, there is a scatter of those data, both in

12   terms of the values of potassium on the y axis, and a

13   scatter with respect to time on the x axis.

14   The legend is shown underneath the title of the

15   slide: in yellow, losartan; in white, placebo. The

16   circles are patients who were still on study therapy at the

17   time they died. The triangles are those were off therapy

18   at the time they died.   In fact, there was a group of

19   patients you might consider outliers and just in

20   anticipation of the question as to what happened to those 2

21   patients who had values at or near 6 or above at the time

22   they died and close in time to the time they died.

23   This is a listing of some clinical

24   characteristics of those 2 patients. The first patient,

25   allocation number 4141, was a patient who had already

1 achieved end-stage renal disease and was on dialysis. This

2 laboratory result was obtained approximately 6 days prior

3 to death. It was obtained immediately prior to the

4 dialysis session.

5   Concomitant medications the patient was taking

6 are listed there; and concurrent condition, as I mentioned,

7 the patient already had end-stage renal disease.

8   The other patient, allocation 4455, had the

9 laboratory measure taken approximately 4 days prior to

10 death, was on the medications you see listed there. Of

11 note, the patient had chronic acidosis as revealed by the

12 serum bicarb measurement that was obtained at the same

13 time.

14   Is that helpful to the committee?

15   DR. BORER: It is to me. Let me ask you one

16 more question before we get to the summary. You know, I am

17 a cardiologist. I don't know much about endocrinology, but

18 you have a lot of fire power sitting there.

19   It was interesting to me that on losartan and

20 on placebo, although the frequency of hyper- and

21 hypoglycemia was not statistically significantly different

22 in the two groups, there was a different direction in the

23 trend of the events; that is, hypoglycemia up in one, and

24 hyperglycemia up in the other group. Although statistical

25 significance wasn't reached, and in fact, even the nominal

1 criterion for a statistical trend wasn't reached -- the p

2 values were both about .12 and .15, -- still, the fact that

3 they were directionally opposite was interesting to me. Is

4 there any reason why losartan should affect blood glucose

5 differently than placebo?

6 　　　　　DR. HAFFNER: This is interesting. I'm not

7 sure it's going to be resolved, but I'll tell you what I

8 believe. I was one of the PIs in the diabetes prevention

9 program. This is an area we're interested in.

10 　　　　　First of all, the data you've seen is among

11 deaths. So, it's not truly representative of the overall

12 population.

13 　　　　　The hemoglobin A1Cs during the trial did not

14 differ, and that suggests to me there may not have been a

15 major effect.

16 　　　　　On the other hand, there's some very

17 interesting literature with both ACEs and now with ARBs,

18 that maybe these agents could prevent type II diabetes.

19 　　　　　Now, the mechanism is, again, kind of

20 interesting. There is one report of losartan improving

21 insulin sensitivity, but it's a relatively small study, and

22 it clearly needs to replicated.

23 　　　　　So, I think the safe answer would be that the

24 data within this trial does not provide strong evidence for

25 a glycemic effect. There is a related trial we haven't

1   talked about, which did sort of quasi show an effect

2   relative to atenolol, but it could have been the atenolol

3   or it could have been the losartan. And there are certain

4   equivalent data with captopril. I think it's not quite

5   resolved at this point.

6   DR. SHAHINFAR: Just answering, glycemic

7   control was comparable, and glucose levels were comparable

8   between the two treatment groups throughout this study.

9   DR. LINDENFELD: JoAnn Lindenfeld. I'd like to

10 just ask a couple of questions before you finish.

11   Patients were withdrawn from ACE inhibitors,

12 about half the patients in this study as I understand it.

13 There was a 6-week period between withdrawal and

14 randomization. Am I correct there?

15   DR. SHAHINFAR: Yes.

16   DR. LINDENFELD: Can you assure me that those

17 groups were equal in the randomization -- in other words,

18 patients who were withdrawn from ACE inhibitors were equal

19 in both groups?

20   DR. SHAHINFAR: Yes. There was an equal number

21 of patients in each treatment group.

22   DR. LINDENFELD: For my interest, and just a

23 quick answer if you have it -- if not I don't desperately

24 need it -- is there a difference in the results of the

25 study in patients who were previously on ACE inhibitors?

1   DR. SHAHINFAR: There is no interaction between

2   losartan treatment and use of ACE inhibitors on the primary

3   outcome of the study.

4   DR. LINDENFELD: I don't mean the use of ACE

5   inhibitors during the study.

6   DR. SHAHINFAR: At baseline, that's right. And

7   that's in the background that we provided.

8   DR. LINDENFELD: Okay. For clarification, when

9   we come back to discuses cardiovascular endpoints, I know

10   there were a number of exclusions here with recent MI, et

11   cetera. Can you give me a percentage of patients who had

12   had a cardiovascular endpoint at baseline prior to

13   randomization? In other words, what percentage of patients

14   in this trial had had some previous cardiovascular

15   endpoint? I know MI was excluded within 6 months, but how

16   many patients had had a distant cardiovascular endpoint of

17   some type? Again, I'm just trying to get at the risk of

18   this group.

19   DR. SHAHINFAR: This is the history for

20   myocardial infarction, angina, stroke.

21   DR. LINDENFELD: So, less than 1 percent had

22   had a previous cardiovascular event?

23   DR. SHAHINFAR: Yes, that's right.

24   DR. LINDENFELD: Okay. That's 12 percent. I'm

25   sorry. Right.

1   DR. CARABELLO: What was the mean time to

2   difference in endpoint? The time difference. In other

3   words, the losartan delayed the endpoint. What was the

4   difference in time between when patients reached the

5   endpoint?

6   DR. SHAHINFAR: Our analysis was a time-to-

7   event analysis. In the study, during the 3-and-a-half

8   years period of follow-up, we were able to demonstrate that

9   for every 16 patients treated, 1 ESRD was delayed basically

10 or was prevented.

11   DR. BORER: But Blase is asking a different

12 question, which is of interest, although I understand that

13 it's difficult to draw firm inferences since some people

14 didn't ever have an endpoint. Among those who had an

15 endpoint, what was the average time to endpoint in the

16 placebo group versus the average time to endpoint in the

17 losartan group? Do you have that? I think there is

18 something in the FDA briefing document about it. Do you

19 have those numbers?

20   DR. KEANE: That's actually a relatively

21 difficult number to calculate as you would imagine. I

22 think as Dr. Shahinfar has already indicated, what was

23 easier to identify and to calculate is really the number

24 needed to treat, which was 16 patients needed to be treated

25 to prevent 1 case of end-stage renal disease.

1   We were also able to demonstrate that we

2   reduced overall end-stage renal disease days by some 32

3   percent in the losartan group. So, that gives you an

4   estimation of the impact.

5   Considering the fact that the diabetic patient

6   today represents almost 40 percent of end-stage renal

7   disease, and we have already projected by the end of this

8   decade that it's going to up to 50 percent, that's a

9   substantial impact I think from a public health

10   perspective.

11   DR. CARABELLO: I'm still not clear. We have X

12   number of patients that reached an endpoint on losartan,

13   and X number of patients that reached an endpoint on

14   placebo, and each patient reached that endpoint in a

15   certain number of days from when he or she began the study.

16   My question is, what's the difference in days or months

17   between those two endpoints?

18   DR. KEANE: I think we can go ahead and get

19   that analysis for you in a little bit more specific way. I

20   don't have the exact answer right now beyond what I've

21   given you, but we'll provide that in a moment or two.

22   DR. CARABELLO: Thank you.

23   DR. FLEMING: Yes, I think it's in the

24   statistical review and evaluation hand out. I think what

25   you're looking for is on page 8, which is best obtained

1   with a Kaplan-Meier estimate of time-to-event distribution.

2   Is that what you're looking for? The difference in the

3   median times to events by Kaplan-Meier estimates?

4   It is on page 8 of the statistical review and

5   evaluation, and the numbers here are 1,303 days versus

6   1,373 days. It does raise another methodologic issue that

7   I'd like to pursue, but I'd be happy to delay that. I

8   don't need to discuss it yet.

9   DR. BORER: Dr. Kopp?

10   DR. KOPP: I had a question on the same point,

11 and maybe, Tom, this is what you're going to get at. As I

12 understand, that was the primary proposed method of

13 analysis, the time to event. The slide you showed this

14 morning talked about time to event, but then you actually

15 gave risk reduction of 16 percent and p .022.

16   I notice in this table on page 8, that it also

17 gives p .022. So, again, it may be my statistical

18 ignorance, but both are ways to look at time to event? Am

19 I being clear?

20   DR. BAIN: I'm not sure I understand the

21 question.

22   DR. KOPP: I'm confused about when you started

23 out saying this was going to be a time-to-event analysis,

24 and then the slide that kind of captured the key data was

25 actually risk reduction. I had the same question you did:

1   what was the actual data? Now I see it on page 8 of the

2   FDA analysis with the same p value.

3   DR. BORER: I think we may be getting into sort

4   of a semantic issue.

5   DR. FLEMING: This is the slide to show. There

6   really are two separate analyses that are being done. One

7   is where do these two curves cross the 50 percent line,

8   which is basically a difference in median time to event.

9   And another very mainstream analysis -- it's really a

10   separate parameter looking at treatment effect -- is to say

11   suppose there's an underlying failure rate over time on the

12   control arm, and suppose the intervention arm alters that

13   by a multiplicative constant, the hazard ratio.   What

14   is that reduction in relative risk? And that's what the

15   hazard ratio is, and that's a 16.1 percent relative

16   reduction in the failure rate. So, those are related, but

17   those are, nevertheless, separate measures of treatment

18   effect.

19   DR. KOPP: So, is it by chance that they're

20   both .022, or is that inherent in the way these statistical

21   tests are done?

22   DR. FLEMING: The p of .022 I'm sure relates

23   only to this analysis of hazard ratio estimates in the

24   confidence interval. We rarely test that difference in

25   medians as the basis for statistical p values. The p

1   values that you see are going to be based on the

2   proportional hazards model and the estimate of the relative

3   risk, the confidence interval, and the corresponding

4   significance from that.

5   DR. BORER: Dr. Temple.

6   DR. TEMPLE: Tom, help us a little more. It's

7   common in representing the results of a study to give the

8   total number of events, because you can work with that.

9   You know what that means. Whereas, Kaplan-Meier curves are

10 sort of something that doesn't have a number attached to

11 them. You just have to look at them.

12   But you could apply a hazard ratio risk

13 reduction statement either to the total number of events,

14 sort of independent of time -- some studies do that -- or

15 you can do it this way, which as I understand it, is the

16 risk reduction or hazard ratio of the likelihood of getting

17 an event in a given time or over the entire course of the

18 study. The hazard ratio is a time-related function as

19 usually presented in these analyses.

20   DR. FLEMING: There are many different measures

21 that we could use to assess the nature of treatment effect

22 and the strength of evidence that it's been an established

23 effect.

24   The most traditional or most common analysis in

25 a time-to-event setting is to say we're going to make no

1   assumptions on the nature of the failure rate on the

2   control arm. We're only going to make an assumption that

3   if treatment affects that failure rate, it does so in a

4   multiplicative fashion. It reduces the failure rate by

5   some multiplicative constant, that is constant over time.

6   That's what proportional hazards mean. If treatment

7   reduces the failure rate early in time by 16 percent, we're

8   going to assume it's reducing it late in time by 16

9   percent. What is that percent?

10   That is the fundamental common analysis. It's

11 called the log rank test, the Cox regression. Those are

12 all based on that same fundamental principle. Essentially

13 almost all estimates that we would see, which is the

14 relative risk or the reduction, is based on that hazard

15 ratio estimate, with confidence intervals and p values.

16   Now, there are other analyses that we could do.

17   You can look at total numbers of events. I like to look

18 at that as well as just a descriptor. You could look at

19 the differences in rates at a given time, so you might say

20 is what I really care about is, is there a difference in

21 these events at 2 years? In which case, I would look at

22 the difference in Kaplan-Meier estimates standardized by

23 Greenwood variance estimates. That's a different analysis.

24   Another analysis is to look at the medians.

25 It's a good descriptor, although I tend to favor the

1 proportional hazards analysis because the medians is only

2 telling you how the curves separate at one place, whereas

3 the proportional hazards analysis is looking at a weighted

4 average of what the nature of the effect is on the outcome

5 failure risk over the entire duration of the curve.

6   DR. BORER: Still, Blase is raising a point

7 that we really haven't discussed that I think is very

8 important. If I am understanding correctly, the time-to-

9 event analyses that have been done show us that there is a

10 significant effect by this analysis and that the magnitude

11 of the effect -- that is, the failure rate -- is a

12 reduction of 16 percent. Blase is saying, what does that

13 mean to the patient? You know, 73 days more of dialysis?

14 73 less days?

15   DR. CARABELLO: Yes. As sort of the dull

16 normal on the committee --

17   (Laughter.)

18   DR. CARABELLO: -- that was really the intent.

19   If I start a group of patients on this medicine, by how

20 many days will I delay an endpoint? Specifically, that's

21 the question I'm asking.

22   DR. FLEMING: If these curves were exponential,

23 and they are not -- but if they were -- then a 16 percent

24 reduction in the failure rate would translate into a 16

25 percent extension in the average duration of time to when

1   the event occurs.

2   DR. BORER: Good. Well, we've got that one

3   settled for the moment. Ray, did you have anything else

4   you wanted?

5   DR. BAIN: Just as Tom mentioned, the counts

6   are in your background document by the two treatment

7   groups. Our analysis is that 16 percent is based on the

8   Cox regression hazard, with the prespecified adjustment for

9   baseline proteinuria stratum and region.

10   DR. FLEMING: There is one methodologic issue

11   here that I'd like to pursue at least briefly. It doesn't

12   trouble me greatly, and I'll preface my comments by saying

13   that the reason it doesn't trouble me greatly is because --

14   at least as I noted back in January -- I'm much more

15   persuaded by end-stage renal disease/death as a dual

16   endpoint than the primary specified doubling in

17   creatinine/end-stage renal disease/death as a triple

18   endpoint. I am even more persuaded that's the case here

19   because of my understanding of the way follow-up was done,

20   and I'd like to at least clarify to make sure my

21   understanding is correct.

22   I am absolutely delighted to hear, by my

23   understanding, that all patients were followed until the

24   outcomes for end-stage renal disease and death. So, we

25   have complete information on the endpoint that I am

1   referring to as my preferred endpoint, that dual endpoint.

2   But there were a number of people who had a

3   termination of their serum creatinine assessments prior to

4   the time that any of those endpoints, i.e., the triple

5   endpoints, prior to the time that either a doubling of end-

6   stage renal disease or death occurred. So, they hadn't had

7   any of those three components as yet.

8   Those people were in fact, though, followed for

9   subsequent assessments of end-stage renal disease and

10 death. So, the analyses that we get for the endpoint I

11 care most about are fully valid and are perfectly fine, in

12 spite of the concern I am about to raise.

13   My understanding is for the triple endpoint,

14 though, in those cases -- and if I understand there were

15 130 of those people on losartan and 137 on placebo -- 267

16 -- so about 17.6 percent of our cohort were people who did

17 have cessation of assessments of serum creatinine before a

18 triple endpoint occurred and were subsequently followed for

19 the other elements. They are included in your primary

20 analysis.

21   In essence, in those 267 people as you are

22 continuing to follow them, we're really underestimating the

23 subsequent rates at which the triple endpoint occurs,

24 because we're only using the double endpoint assessments in

25 those people. Now, of course that's happening in both

1   treatment arms. So, both treatment arms are being

2   underestimated.

3   But then when questions come up from my

4   colleagues about how do we interpret the extension in time

5   or delay in the triple endpoint, I can't interpret that

6   anymore, because I haven't followed people for the triple

7   endpoint. I followed some for the triple endpoint, but 267

8   people were followed over a substantial duration only for

9   the double endpoint.

10   Of course, I don't care that much about the

11   triple endpoint. I like the double endpoint. So, this is

12   no problem for me on the double endpoint.

13   (Laughter.)

14   DR. FLEMING: But it makes me even more worried

15   about interpreting your data on the triple endpoint. Am I

16   off target here or is my interpretation correct?

17   DR. BAIN: Your interpretation is correct.

18   What we're focusing on right now are those patients who

19   discontinued their therapy, their blinded therapy, prior to

20   one of those triple endpoint events. Once those patients

21   discontinue their primary therapy, their follow-up could be

22   classified into one of three groups.

23   Either they continue their quarterly

24   measurements, which was by protocol, and we continue to get

25   serum creatinines, a potentially documented doubling, which

1 they get counted in the intention to treat analysis.

2 That's one bucket.

3   The other bucket is, as soon as they

4 discontinue their therapy, they go into what we classified

5 as telephone follow-up, where during telephone follow-up

6 we're not collecting serum creatinines.

7   The third bucket is patients discontinue their

8 meds. They go into clinic follow-up for a period of time,

9 and then they go into telephone follow-up.

10   With those three kinds of different classes,

11 it's difficult to really give you a number as to how much

12 is in telephone, et cetera, but we attempted to. What we

13 did was look at the total follow-up time after

14 discontinuation of their study therapy and determined

15 patient years of follow-up from that time of

16 discontinuation of therapy. Then we also calculated what

17 percentage of that time was in clinic follow-up versus what

18 percentage of that time was in telephone follow-up. We

19 estimated that, and 60 percent of the follow-up post

20 discontinuation of the study therapy is 60 percent. 60

21 percent are followed in clinic that time.

22   So, that gives you a general idea of how we are

23 following those patients post discontinuation of the

24 therapy. Obviously we continued to follow them for the

25 hard endpoints.

1   Now, when we go ahead and do that triple

2   endpoint intention to treat analysis, what we are actually

3   doing is what I would consider to be a conservative

4   analysis, because we're not documenting doubling in either

5   group, so we're assuming that any effect that losartan

6   would have would be the same in the losartan and the

7   placebo group after discontinuation. So, our triple

8   endpoint, even though we had 40 percent of the patients in

9   telephone follow-up, actually the analysis is holding up

10 mainly because it's conservative.

11   DR. FLEMING: Just a brief addition to what you

12 were saying. The only conclusion I am confident to make

13 here is, in these 40 percent of the person years of follow-

14 up time after discontinuation, where we no longer continue

15 to follow the triple endpoint -- we're only following the

16 double endpoint -- if you really care about the triple

17 endpoint -- we're underestimating in both arms the time to

18 the occurrence of the triple endpoint.

19   Whether that leads to a conservative or anti-

20 conservative estimate of treatment effect entirely depends

21 on in these people who are discontinued for follow-up of

22 serum creatinine doubling times, in those people who are

23 discontinued, would the doubling time have occurred more

24 rapidly in the placebo versus the losartan arm? I have no

25 clue about that.

1   So, it leaves me uncertain about how to

2   interpret the data, to an extent at least, if I really care

3   about the triple endpoint, because, again, in 40 percent of

4   the person-years of follow-up after discontinuation -- and

5   after treatment discontinuation I do care to continue to

6   follow people -- I might surmise that I would have less

7   treatment effect after treatment discontinuation. I don't

8   know. That's only a guess. But I do care, if I really

9   cared about the triple endpoint, to know what time is to

10   triple endpoint in all patients.

11   My conclusion in this is that there are 267

12   people, balanced by treatment arm, in whom I am

13   underestimating the time to the triple endpoint in both

14   arms. I have no clue if it's more so in one than the

15   other, and it's just another reason that from my

16   perspective the double endpoint, which occurs in this

17   setting not that much later than the triple endpoint, and

18   is clinically a much harder endpoint, and is free of all of

19   these problems, is an endpoint that I particularly would

20   focus on more so than the triple endpoint.

21   DR. BAIN: Correct. Let me make one other

22   point. When we are talking about these patient-years of

23   follow-up and we're talking about the triple endpoint, if

24   you actually calculate the patient-years of follow-up in

25   clinic over the whole time, not just focusing on those

1 patients who discontinued their therapy, the clinic follow-

2 up is over 90 percent. It's only when you get into that

3 subset of patients that it drops to 40 percent.

4   DR. BORER: Dr. Lorell.

5   DR. LORELL: Thank you.

6   In follow-up of Dr. Fleming's comments, there

7 were two queries that I had. One is, in this difficult

8 group of the 40 percent patient-years who have the issues

9 of discontinuing treatment and problems of telephone

10 contact, do you know what percentage of those patients in

11 each of the intention-to-treat groups actually got put on

12 an ACE inhibitor by their clinical nephrologist? Is that

13 known?

14   DR. SHAHINFAR: We know for the entire cohort

15 those patients who were discontinued from the study, and

16 they were placed on ACE inhibitors or AII receptor

17 antagonists. I have to remind you that this collection of

18 the concomitant medication was extremely difficult after a

19 patient was discontinued from the study.

20   DR. LORELL: I understand that.

21   DR. SHAHINFAR: So, it's going to be either

22 underestimation or -- the data that we have -- can I have

23 that?

24   DR. LORELL: Perhaps you can get that to us in

25 a little bit.

1   DR. SHAHINFAR: This is basically those

2   patients who discontinued the study drug, and we have

3   information on them that they went to either ACE inhibitors

4   or angiotensin II receptor antagonist therapy.

5   DR. LORELL: That's very helpful.

6   The second question I had that relates to Dr.

7   Carabello's efforts to understand the clinical impact. In

8   our briefing supplement that we were provided with in table

9   1-A, there is a comment about the median time to reach the

10   triple event, but we're not provided with data, I don't

11   believe, that might address Dr. Carabello's concern and

12   mine too, as to what the median time is in the losartan and

13   placebo group of reaching end-stage renal disease or

14   reaching the double endpoint. Maybe we could be provided

15   with that.

16   DR. BAIN: Ray Bain, Merck Research Labs.

17   Now, Tom kind of caveated around doing this but

18   we did calculate the number. If I understand the question,

19   it's of the patients who reached a primary composite

20   endpoint event, which there are 327 in the losartan group

21   and 359 in the placebo group, if you actually calculate the

22   median number of days to the event, it's 652 days in the

23   placebo group and 724 in the losartan group.

24   So, there is a delay, but that's a subset of

25   the patients. You're just looking at those patients who

1 actually had the event, ignoring all the other patients,

2 which, if you do the median analysis and go across the

3 median and drop it down to your time line, you'll get

4 estimates of differences in time.

5   DR. BORER: That's for the double endpoint?

6   DR. BAIN: That was the triple endpoint.

7   DR. LORELL: That's different from the table.

8   DR. BORER: Yes. Maybe you can pursue this

9 just a little bit.

10   DR. LORELL: In the table 1A that we were

11 provided, the number is actually quite different, but I

12 would also be interested in following up Tom Fleming's

13 comment that I think for many of us the important issue is

14 end-stage renal disease/death -- what the median time was

15 for reaching that double endpoint. Do you have that data?

16   DR. KEANE: Again, are you asking the median

17 time for doubling, or are you asking the median time for

18 end-stage renal disease?

19   DR. LORELL: No. We're provided in table 1A

20 with the median time to reach the triple endpoint. In

21 follow-up of Dr. Fleming's comment and Dr. Carabello's, can

22 we know what the median time is to reach end-stage renal

23 disease and the median time to reach end-stage renal

24 disease or death.

25   DR. KEANE: I think we can go back and

1 calculate that. We just don't have that immediately on our

2 data set here, so we'll find that out and get back to you.

3   DR. LORELL: Thank you, sir.

4   DR. KOPP: Could you explain the discrepancy

5 that your last question just brought up between the median

6 time to event in our table of about 1,300 days for the two

7 groups, and the median time of about, I think you said,

8 about 650 and 704? This is in both cases the median time

9 to the composite endpoint, triple.

10   DR. FLEMING: I think I might be able to, while

11 you're bringing somebody up. The distinction between the

12 two -- the Kaplan-Meier is the 1,300, whereas I think the

13 analysis of the 700 was if you just take the people with

14 the event, what's the median time at which that event

15 occurred. And that's always going to be a lot less. That

16 was 700.

17   DR. BAIN: Yes.

18   DR. FLEMING: And I would caution against ever

19 looking at that because it's very misleading.

20   What I really care about is what's the Kaplan-

21 Meier? What's the percent free of having an event? If I

22 have two treatment arms, and let's say in one treatment arm

23 10 percent of the people have an event at a year, and in

24 the other treatment arm, 10 percent have an event at a

25 year, and another 10 percent have an event at 2 years, the

1   latter is a worse scenario. And yet the median time to

2   event in the latter case is a year and a half, whereas it's

3   a year in the first arm.

4   So, I don't want to look at, given you've had

5   an event, what's the time to event. I want to look at the

6   entire cohort and see what's the percent free of the event

7   and what's the time at which that crosses the median.

8   That's the 1,300 type number

9   DR. SHAHINFAR: In summary, in type II diabetic

10   patients with proteinuria, there were no unusual or

11   unexpected adverse experiences beyond those already noted

12   in the U.S. prescribing information for losartan. Losartan

13   had a higher incidence of hyperkalemia, and lower incidence

14   of hypokalemia compared to placebo. Losartan was generally

15   well tolerated.

16   I would now like to introduce Dr. William

17   Keane, Vice President of Clinical Development, Merck U.S.

18   Human Health. Dr. Keane will provide the review of

19   evidence and conclusions regarding the renal protective

20   effect of losartan in type II diabetes. Thank you.

21   DR. KEANE: Thank you, Dr. Shahinfar.

22   Members of the committee, representatives of

23   the FDA, other invited guests, ladies and gentlemen. My

24   name is Bill Keane, and I'm delighted to have the

25   opportunity to appear before the advisory committee again

1 in my new capacity.

2   As many of you know, I have recently joined

3 Merck as Vice President of Clinical Development in U.S.

4 Human Health after 28 years in an academic practice of

5 nephrology.

6   Most recently I was professor and chairman of

7 the Department of Medicine at Hennepin County Medical

8 Center at the University of Minnesota in Minneapolis. I

9 was intimately involved with the RENAAL study, both as a

10 member of the Steering Committee, as well as a primary

11 investigator, and participated in the design, the conduct,

12 the oversight, the analysis and publication of this

13 important study.

14   In addition, as President of the National

15 Kidney Foundation, which is a patient-focused organization,

16 I can assure you that we have recognized that the treatment

17 of the type II diabetic patient with proteinuria is an

18 unmet medical need.

19   I would like to provide you with my summary

20 that emphasizes the salient features of this study that

21 make it a compelling data set supporting our proposed

22 indication.

23   The strength of the evidence provided by the

24 RENAAL study is sufficient to support our conclusions,

25 based on a number of critical features, including the

1   robust study design, the results that are clinically

2   important, as well as statistically significant, and the

3   presence of internal consistencies across multiple

4   endpoints and multiple subgroups. Moreover, as you've

5   seen, after adjusting for differences in relevant patient

6   characteristics, particularly the chance imbalance that was

7   observed in baseline proteinuria, an even more dramatic

8   impact can be seen.

9   First, let me re-emphasize that this was a

10 large, multinational study conducted in 28 countries at 250

11 clinical sites. It included a diverse study population,

12 with demographics of patients with type II diabetes here in

13 the United States. There were no patients lost to follow-

14 up in terms of ascertaining their clinical status with

15 respect to end-stage renal disease and death. The key

16 renal endpoints and cardiovascular endpoints were

17 independently adjudicated. Furthermore, there were no

18 patients missing from our intention-to-treat analysis for

19 the primary composite endpoints.

20   I would now like to review the main study

21 results in order to emphasize the internal consistencies

22 and reliability across the multiple endpoints and subgroups

23 of the study.

24   RENAAL provides persuasive evidence that

25 losartan delays the progression of kidney disease in type

1   II diabetic patients with proteinuria, as demonstrated by

2   the following results.

3   The primary composite endpoint of the time to

4   the first event of doubling of the serum creatinine, end-

5   stage renal disease or death, which revealed a risk

6   reduction of 16 percent, with a p value of .02.

7   The clinical endpoint of end-stage renal

8   disease, which revealed a very robust risk reduction of

9   nearly 29 percent. Again, I'll emphasize in this

10   particular clinical component, there were 147 events of

11   end-stage renal disease in the losartan group and 194 end-

12   stage renal events that we observed in the placebo group.

13   The clinical endpoint of end-stage renal

14   disease or death, which also showed a significant risk

15   reduction of nearly 20 percent.

16   Our prespecified subgroup analyses, which

17   included those performed for age, gender, and a variety of

18   other categories, demonstrated that losartan provided renal

19   protection across a wide range of patient subgroups.

20   Dr. Shahinfar has already reviewed with you

21   that we stratified patients by baseline proteinuria, either

22   those below 2,000 milligrams of albumin per gram of

23   creatinine, or above 2,000 milligrams of albumin per gram

24   of creatinine.

25   Despite this, we observed an imbalance in the

1   distribution of baseline proteinuria values between the

2   treatment groups, particularly within the higher

3   proteinuria stratum. That is, in those patients that had a

4   urine albumin to creatinine ratio of greater than 2,000

5   milligrams per gram of creatinine.

6   Given that baseline proteinuria was a strong

7   predictor of the risk of subsequent renal events for

8   patients in both treatment groups, and the risk

9   dramatically rises for patients with high levels of

10 baseline proteinuria, it seemed particularly appropriate to

11 adjust for this observed imbalance.

12   As you can see in the right-hand column, when

13 we adjusted for baseline proteinuria as a continuous

14 covariate, these post hoc analyses showed that the risk

15 reduction for the primary composite endpoint of doubling of

16 serum creatinine, end-stage renal disease or death improved

17 now to some 22 percent, with a p value of .001.

18   The risk reduction for end-stage renal disease

19 improved to nearly 37 percent, and the risk reduction for

20 end-stage renal disease or death improved to greater than

21 25 percent.

22   Thus, these analyses reinforce the conclusions

23 of our primary analyses.

24   It is critical to emphasize the importance of

25 effective blood pressure control in patients with type II

1   diabetes and proteinuria. It is well recognized that

2   patients with type II diabetes and nephropathy either have

3   hypertension at the time they begin to develop nephropathy

4   or become hypertensive by the time they reach one of the

5   clinical endpoints defined in our RENAAL study.

6   In the RENAAL study aggressive treatment of

7   blood pressure was specified in the protocol, and as Dr.

8   Shahinfar has shared with you today, the majority of

9   patients were well controlled in both groups. The

10 differences in blood pressure between the treatment arms

11 were small, and our prespecified analysis for the small 2

12 millimeter differences in mean arterial pressure did not

13 substantially alter the treatment effect on the various

14 renal endpoints. This supports the overall conclusion that

15 the benefits of losartan treatment in this population are

16 not attributable to blood pressure control alone.

17   There were additional secondary renal endpoints

18 in the study. These also provide consistent and persuasive

19 evidence of the treatment benefit of losartan in this

20 patient population. Compared to placebo, losartan showed a

21 significant 18 percent reduction in the rate of progressive

22 loss of kidney function, as estimated by the reciprocal of

23 the serum creatinine. In addition, we found that, compared

24 to placebo, losartan also had a significant 34 percent

25 reduction in proteinuria.

1   Although RENAAL was designed specifically as a

2   renal protection study, because of the recognized increased

3   risk of cardiovascular events in the RENAAL patient

4   population, we prespecified the composite endpoint of

5   cardiovascular morbidity and mortality as an important

6   endpoint. This composite endpoint included all-cause

7   cardiovascular death, myocardial infarction, strokes, time

8   to first hospitalization for heart failure, and time to

9   first hospitalization for angina, and all revascularization

10   procedures, both within the coronary vasculature as well as

11   in the peripheral vasculature.

12   There was no treatment effect demonstrated for

13   the cardiovascular composite endpoint overall. An

14   examination of the individual components revealed the

15   expected fluctuations -- some positive, some negative --

16   that led to the nonsignificant p value for the

17   cardiovascular composite endpoint.

18   While Dr. Shahinfar has already reviewed these

19   findings in detail and we have discussed them also in

20   detail, I simply really wish to emphasize that the benefits

21   of losartan treatment on our renal endpoints did not come

22   at the expense of an increased risk of cardiovascular

23   events in the losartan arm. This is probably best

24   illustrated by our post hoc analysis on the bottom portion

25   of this slide which demonstrated the combined endpoint of

1 end-stage renal disease, myocardial infarction, stroke, or

2 death, and this showed a 21 percent risk reduction with

3 losartan.

4   In conclusion, for patients with type II

5 diabetes and proteinuria, the specter of inexorable

6 progression to end-stage renal disease requiring renal

7 replacement therapy is a frightening prospect. Those of us

8 that have cared for these patients recognize the enormity

9 of disease burden that is borne by these individuals. In

10 my view, the sum evidence of our analysis for the RENAAL

11 data that we have shown you today demonstrate robust,

12 reliable, and clinically relevant evidence that is

13 applicable to a broad population of type II diabetic

14 patients.

15   In addition, our data confirm that the safety

16 profile of losartan in this population is consistent with

17 the U.S. prescribing information for losartan.

18   Finally, in patients with type II diabetes and

19 proteinuria, the treatment effects of losartan across

20 multiple endpoints in the RENAAL study provide persuasive

21 evidence for the renal protective effects of losartan.

22 Indeed, we estimated that over a 3-and-a-half year time

23 period for every 16 patients treated, 1 case of end-stage

24 renal disease will be prevented. RENAAL provides new data

25 that support the role of the renin-angiotensin system

1   blockade for renal protection in diabetes and kidney

2   disease.

3   Thank you very much for your time and

4   attention.

5   Mr. Chairman, I was going to just take the

6   liberty, because there were a number of questions that had

7   come up during the presentation that we thought we could

8   provide some answers to.

9   DR. BORER: That would be helpful, but I think

10   on your behalf really we have some more questions from the

11   committee that may require that you gather some more data,

12   and it might be nice for you to have the break to do that.

13   So, let me take the last few minutes before the lunch

14   break to go to some of these questions. You may be able to

15   answer them now, you may not. If you can't, then you'll

16   have a few minutes to get the information together and

17   we'll go back over all the questions after lunch.

18   Dr. Nissen, you had some concerns?

19   DR. NISSEN: Obviously, we're all very cautious

20   about subgroup analyses, but there were, I think, a lot of

21   questions that I had about the subgroups in the study. I

22   would hope maybe somebody could put of table 14 from the

23   Merck briefing document. That's on page 63 for those of

24   you on the panel that want to look at it. I assume you

25   have a slide with that because I think there are some

1 issues that it brings up about who in fact benefits from

2 this therapy. Is that possible?

3   DR. KEANE: I don't have a slide of that

4 directly, but we'll get maybe an overhead.

5   DR. NISSEN: All right. Well, let me just

6 prime you then with the questions. When I look at this,

7 what I see is, just in terms of counting events -- I

8 understand what we're looking at is time to event, but just

9 counting events -- there were 78 in the losartan group and

10 80 in the placebo group, virtually an identical number, in

11 Latin America. For Europe, there were 58 in the losartan

12 group and 51 in the placebo group. There were more events

13 in the losartan group in Europe. In North America, there

14 were 142 in losartan and 150 in placebo. So, if you look

15 at the Asia group, the 250 patients in Asia provided

16 virtually all of the endpoint differences in the trial. I

17 mean, it is very, very striking.

18   And I recognize the hazards of subgroup

19 analysis, but it's so striking that I went and I looked at

20 the racial background, which is also in table 14, and you

21 see exactly the same thing: 40 percent event rate among

22 African American or black; Hispanic, 55 and 54; white, 40.5

23 and 43; and then a huge difference in the 250 Asians. So,

24 it does speak to the heterogeneity of the response and the

25 robustness of the findings.

1   It looks to me, when I look at these subgroups,

2   that it's all driven by those 250 Asian patients, and I

3   need to understand that better to understand whether this

4   is, in fact, an effect of this drug that's applicable in

5   the patients that come in my clinic and that we see with

6   the disorder.

7   Similarly, if you look at the creatinine data,

8   there's also this very striking disparity where, in fact,

9   there's a higher event rate in the losartan group for those

10   with a creatinine of less than 2, which is by the way the

11   vast majority of patients, and for the somewhat smaller

12   subgroup, about a third of patients where the creatinine is

13   elevated, there's a very striking difference.

14   So, again, not necessarily now, but I really

15   need to understand this very striking heterogeneity, which

16   I recognize does not rise to the level of statistical

17   significance with the exception of region, which does reach

18   statistical significance. But in terms of the point

19   estimates, it's really a striking difference, and I really

20   need to understand that better.

21   DR. LINDENFELD: Just to emphasize that, I

22   wonder if maybe you could show us the creatinine and

23   proteinuria in the Asian region group compared to the

24   others.

25   DR. KEANE: If you have time now, I can sort of

1   begin to address some of these issues because they are

2   obviously important and we obviously recognize that region,

3   and the equivalence of region and race I think we need to

4   recognize is different because region is a geographic area

5   that is quite larger than what actually the ethnicity or

6   racial backgrounds would be.

7   DR. NISSEN: But it appears in both columns.

8   DR. KEANE: Let me then, for purposes of what I

9   think is really sort of more consistent, look at race at

10 this point in time. We can always go back to region per

11 se, but I think the racial differences are important for us

12 to understand because I believe that's applicable then

13 regionally when we start looking at that.

14   So, let me first reiterate your point, that

15 this was a subgroup analysis, and we in fact had 18

16 subgroups, and that in and of itself creates a set of

17 problems.

18   The second thing that I would like to actually

19 address is the fact that there are differences between

20 races and between regions. Specifically there are

21 differences between our regions or races. Let me have

22 slide 624.

23   As you recall, when we looked at proteinuria

24 and showed you the risk that proteinuria has in terms of

25 predicting subsequent events, as you increase your degree

1   of proteinuria, the amount of hazard or the risk for a

2   primary event and also the primary events that occur in the

3   highest group of proteinuria patients dramatically

4   increase. It's in many ways like the old adage that we

5   have in clinical medicine, that is, 10 percent of the

6   people have 80 percent of the events. So, this appears to

7   be in the area of proteinuria as well.

8   And this was an important analysis going into

9   the trial that we recognized. In terms of recognizing, the

10   risk was part of a larger component of things in terms of

11   risk that we actually prespecified. It's called the risk

12   score, and I'd be more than happy to get into that in a

13   moment or two. But we had prespecified our analyses based

14   upon risks that we thought were important in the patients

15   with type II diabetes.

16   We also recognized that proteinuria was one of

17   the most important drivers of the overall risk, so that we

18   focused on proteinuria because it's a clinically relevant

19   measure. It's simple to do.

20   And already, as you see within this particular

21   slide, there are ethnic/racial differences within this

22   important risk factor -- this progression promoter, as it's

23   called -- between Asians, the black patients, the

24   Hispanics, and the whites. In fact, the Asian population

25   had one of the highest rates or highest levels of urine

1   protein excretion rate, so pushing them, if you will, up

2   the slope of risk for a renal event.

3   Now, within the different groups, as Dr.

4   Shahinfar has already alluded to, there were imbalances in

5   terms of stratification to losartan versus placebo that

6   also occurred within the trial. So, this is one big issue.

7   The second big issue that I think is important

8   for us to recognize --

9   DR. FLEMING: Before we leave this big issue --

10   DR. KEANE: Yes.

11   DR. FLEMING: Slide 624. Just to interpret,

12   this is at a certain level relevant. What we're seeing is

13   that the Hispanic population, the Asian population had

14   higher baseline proteinuria. That would lead me to think

15   that they should have had a higher rate of events.

16   So, if we go back to page 63, table 14, that

17   explains the relationship of the events within the placebo

18   arm by country. It explains why the Hispanics and the

19   Asians in the placebo arm had the higher rate. That

20   explains that region would be a predictor of rate of

21   outcome.

22   It tells us nothing, though, about why region

23   should be an effect modifier, so it doesn't answer Steve's

24   question unless you want to go one step further, unless you

25   want to make the statement that not only is proteinuria a

1 predictor, but it's also an effect modifier so that we

2 would expect higher rates in Asia and Hispanics and we

3 expect a bigger effect. But those don't logically follow to

4 me because they are different concepts.

5   DR. BORER: Not only that, we didn't see it.

6   DR. TEMPLE: Yes, you did. If you look at the

7 results by various underlying factors, almost the entire

8 effect is in the people with proteinuria over 2 grams. You

9 did see that before. It would be equally true for 4 grams

10 I'm sure.

11   DR. NISSEN: Yes, but Bob, the 277 patients in

12 the Hispanic group who have the highest proteinuria,

13 there's no treatment effect. So, this doesn't make any

14 sense to me. One of the high groups, the Asians, has all

15 the benefit and a group that's even higher with proteinuria

16 has actually a hazard ratio that's worse in the losartan

17 group. So, this doesn't explain anything.

18   DR. TEMPLE: Well, you have to see how these

19 break down by region as well. This is not broken down by

20 region because some people in each region are both. But

21 you did actually see -- I thought it was fairly striking --

22 that if you look at the hazard ratios, essentially all of

23 the effect was in the people who were above 2 grams, which

24 could have something to do with that.

25   DR. KEANE: Can I go on? Because I think

1   that's an important set of issues here. But I do have,

2   beyond this, some specific, I think, explanations that we

3   need to see to interpret actually what we're talking about

4   right now.

5   May I have the next slide? This really then

6   underscores the second feature that is present that is

7   different amongst Asians or different, I should say,

8   amongst ethnic groups, racial groups, as well different

9   amongst the different regions.

10   But here displayed are really the racial

11   events. As you can see, there are different levels of

12   discontinuation that are occurring prior to the first

13   event, so prior to our primary event. Within the Asian

14   group, there are highly compliant groups of individuals

15   while we have in caucasian and Hispanics somewhat less

16   compliance or utilization of the drug. Now, this has an

17   impact, and let me show you the next slide please, and that

18   should be 627.

19   If one takes our primary endpoint and just does

20   the evaluation -- this is the primary composite endpoint

21   indicated in the dark lines here, the solid lines with the

22   circle point estimates -- as you look at those point

23   estimates and confidence intervals, and then you adjust for

24   those patients who are on treatment who actually took the

25   drug, and then you adjust for those patients who were on

1   treatment that had a change in urine protein excretion

2   rate, as you can see, the point estimates for the Asians,

3   the blacks, Hispanics, and whites gradually evolve to the

4   left-hand side of the line of 0, supporting at least the

5   importance of both proteinuria, as well as being on therapy

6   as modifying this primary composite endpoint across all

7   races.

8   This is, again, supported by our overall look

9   at there was no interaction between races and treatment

10   arms. So, I think this is supportive and consistent data

11   that shows that we can actually benefit these renal

12   outcomes in all of our patients of these different ethnic

13   and racial backgrounds.

14   DR. BORER: Rather than go on to any other

15   issues -- I think these were important slides, and you may

16   have some more that you will want to show us after the

17   break. Having been stung by the criticism of lack of break

18   last week and since it is now exactly 12 o'clock and it

19   says on the schedule that you can go to lunch at 12

20   o'clock, including the FDA people, 12 o'clock it is and

21   lunchtime it is, and we'll get back together at 1:00.

22   (Whereupon, at 12:00 p.m., the committee was

23   recessed, to reconvene at 1:00 p.m., this same day.)

24

25

1   AFTERNOON SESSION

2   (1:00 p.m.)

3   DR. BORER: Okay. It's 1 o'clock and 30

4   seconds, so we're a little late starting here.

5   At this point there are several unanswered

6   questions and, as yet, unasked questions from the committee

7   that we'd like to raise, and I want to say for all of us to

8   the sponsor that, especially since we're going to move into

9   a period where the questions may become more intense and

10   the discussion may become more intense, all of us

11   appreciate the efficiency and completeness with which the

12   sponsor has presented the data. I know you'll have

13   additional information for us, and we appreciate the superb

14   consultants you brought along to help answer the questions.

15   So, with that having been said, let's move right along

16   here.

17   Dr. Nissen, you were in the middle of your

18   questions and then we have several more that I marked down

19   to go back to from other committee members, and there may

20   be some additional ones as well. Steve, why don't you

21   start?

22   DR. NISSEN: Thanks very much, Jeff.

23   I want to continue with this regional and

24   ethnic imbalance and see if I can explore this a little bit

25   more. But actually before I do, we really do have a

1 problem here with the FDA data and the company data not

2 agreeing. Tom, I particularly think I need your help with

3 this.

4   If you look at the table on region, you see

5 that there are 58 events in your table in the losartan

6 group and 51 in the placebo group, and the hazard ratio is

7 .943. Now, I assume that that's the case because, even

8 though there are more events, the time to events would

9 presumably have been much shorter in the placebo group.

10   But the same number of events in the FDA

11 analysis on page 22 of the briefing document gives a

12 completely different hazard ratio. It's 1.05. That's a

13 pretty big difference, and I don't get it, Tom. Or to the

14 company, I don't understand why they don't agree.

15   DR. BAIN: Yes. This was one of the

16 housecleaning activities that I was going to come back to.

17   We went back and looked at the FDA background

18 document versus the Merck background document. Let me

19 point out that in the Merck background document, as

20 prespecified in our protocol and data analysis plan,

21 whenever we do a subgroup analysis, we also adjust for the

22 baseline proteinuria category or stratum. And when we do

23 that in our analysis, which is the prespecified analysis,

24 we get our results.

25   We went back and confirmed that if you

1   eliminate that baseline proteinuria as a covariate in the

2   analysis, you get the FDA results. So, theirs is

3   completely unadjusted. Ours is adjusted for what we

4   randomized on, which was a prestratification factor, which

5   was baseline proteinuria less than 2/greater than 2.

6   DR. NISSEN: That helps me a lot.

7   Again, we can argue about how robust the effect

8   is, but clearly those 250 patients that were in Asia, that

9   are either defined racially as Asians or geographically as

10 Asians, provided almost all the treatment effect in the

11 study. That's obviously an extremely striking finding.

12 So, in exploring your data, I was looking for an

13 explanation for that.

14   I'd like to ask you if you could show by region

15 the rate of discontinuation of medication. I have it from

16 the FDA briefing document on page 16 for the panel members.

17   What is very interesting here is that there is a huge

18 imbalance between placebo and losartan in drug

19 discontinuation in the Asian group but not in the other

20 groups. So, I think potentially this is a smoking gun that

21 explains why there's such a big difference here.

22   If you look at this, fully 45 percent of the

23 placebo discontinued and 26 percent of the losartan group

24 discontinued; whereas, in the other regions, there's very

25 little difference in discontinuation rate. I'd sure like

1   an explanation for that because, again, it's a very

2   striking finding. I think it could explain all of this

3   because if a patient discontinues, they obviously get less

4   intense follow-up, and I'm worried that those discontinued

5   patients had their blood pressures going out of control and

6   that's why we see this. So, many more of the patients in

7   the placebo arm were discontinued in Asia than in the

8   treatment arm.

9   Can you help me with this?

10   DR. KEANE: Maybe I can. Let me just jump back

11 a little bit to sort of set the stage. Again, these are

12 all a result of our subgroup analyses that were done. I

13 want to emphasize two points.

14   One is the fact that these patients did have

15 differences in proteinuria, and I did want to emphasize the

16 point that we have differences in discontinuations, as

17 you've already alluded to.

18   Now, probably the most important point, in

19 terms of us now looking at this, will be to look at what,

20 in fact, happened to end-stage renal disease and death

21 because that's where we have captured 100 percent of all of

22 the events in all of the patients. So, this is very, very,

23 I think, powerful data for us to look at.

24   I can show you I think both by region, as well

25 as by race -- and recognizing we have these differences in

1   terms of the geography, as well as compared to ethnicity.

2   So, let me just show slide 629, if I may.

3   I think as you can see here, this is for end-

4   stage renal disease or death, which I think we have been

5   discussing this morning as, in fact, being the hard outcome

6   that is of particular relevance in any kind of renal

7   protection trial. I think across the board, as you can see

8   in the solid line, which is our primary analysis, and then

9   as we look at on-treatment, that is the patients who

10   sustained therapy throughout the trial, as well as then

11   those patients who were on treatment who had an adjustment

12   for proteinuria, again this being an important risk for

13   progression of kidney disease, our point estimates for the

14   different ethnic groups, again, move slightly to the left

15   of the 0 line, again favoring losartan. Now, this is by

16   race.

17   Let me just show you then by region, and I

18   think that's slide 850.

19   DR. NISSEN: You already showed this to us I

20   think before lunch, didn't you? This is the same slide?

21   DR. KEANE: No, no.

22   This is ESRD. This is 829. This is ESRD or

23   death. Again, I think the same events are evident in here,

24   with these adjustments that I've just gone through, on-

25   treatment, on-treatment, and adjusted.

1   Now, if we go by region, again by Asia, Europe,

2   Latin America, and North America, again we believe that

3   there is a shift of the point estimate more or less to the

4   left, again favoring losartan in all the different regions.

5   So, I think that at least gives us confidence

6   in these exploratory analyses that in fact the direction

7   that we're going is correct. It's applicable across

8   multiple groups, multiple ethnic groups, and in fact across

9   this region that we prespecified as one of our prespecified

10 subanalyses.

11   DR. BORER: Dr. Brem?

12   DR. FLEMING: Can we comment on this before we

13 take off?

14   DR. BORER: We can, sure. Is this about this

15 particular issue?

16   DR. FLEMING: Yes.

17   DR. KEANE: Yes. I was just turning to my

18 colleague now because I think part of Dr. Nissen's question

19 had been related to what happens if you do the analysis

20 with or without different countries or different regions,

21 and I was going to ask Dr. Bain to actually address that

22 specifically because we have done that.

23   DR. NISSEN: I do want to see it for the

24 unadjusted because I really want to see the raw data. I

25 want to see the data without all that proteinuria

1 adjustment and all that. I just want to understand it with

2 the raw data.

3   DR. BAIN: In that primary analysis up there,

4 the only adjustment was for what we prespecified in the

5 data analysis plan as being our primary. It's just the

6 adjustment for baseline proteinuria strata, two strata, and

7 the region.

8   Now, what Dr. Keane alluded to was the issue

9 that Dr. Nissen brought up about, gee, all the effect seems

10 to be going away if, for example, you looked in the regions

11 other than Asia. We were, obviously, interested in

12 exploring that issue also. Unfortunately, I'm going to

13 have to put an overhead slide up here, which is going to be

14 pretty difficult to read, but let me do that.

15   What we're doing here is we're looking for

16 influential either regions or countries within a region,

17 and I'll explain this. I actually have hard copies for the

18 committee.

19   Now, what I'm focusing on there is the

20 composite endpoint of ESRD or death by the intention-to-

21 treat analysis. And if you remember from the main

22 presentation, the risk reduction for this particular

23 outcome, ESRD or death by intention-to-treat, was 20

24 percent overall.

25   Now, if you look within a region -- and those

1   regions are highlighted with brackets around them -- Asia,

2   Europe, Latin America, North America -- what this table

3   shows you is when you eliminate that country or region

4   that's on the left-hand column, if you go across to the

5   third column, it has a risk reduction. That tells you what

6   the resulting risk reduction is. So, for example, if you

7   were to eliminate the region Asia from the analysis, the

8   risk reduction goes from 20 percent down to 13 percent. If

9   you eliminate Europe, 21.9; Latin America, 21.6; North

10   America, 23.3. Now, that's by region.

11   Now, what has been alluded to earlier is we

12   prespecified region and the countries that went into that

13   region, but that's just geographic. But now, look at the

14   countries within Asia. The countries are Hong Kong,

15   Israel, Japan, Malaysia, Singapore. What this shows is if

16   you eliminate them one at a time -- for example, if you

17   eliminate Hong Kong, the risk reduction goes from 20

18   percent to 16.5. If you eliminate Israel, it goes to 16.8.

19   So, you see within Asia, it ranges from 16 to 21.

20   As a matter of fact, if you do that one-country

21   elimination at a time -- without eliminating any countries

22   it was a 20 percent reduction. And now if you eliminate

23   one country at a time, it ranges anywhere from 16.5 to 23

24   is the number I'm picking out, which is roughly around that

25   20 percent. So, what we're doing here is an analysis to try

1 to figure out if there are influential countries.

2   DR. NISSEN: This is for the double endpoint.

3   DR. BAIN: This is ESRD or death.

4   DR. NISSEN: Do you have it for the triple

5 endpoint? Because that was your primary efficacy

6 parameter.

7   DR. BAIN: Now, this one, the overall result

8 was 16 percent when we did the triple endpoint, 16 percent

9 reduction. Again, when you eliminate a whole region, it

10 has a major impact: 7.1 percent in Asia, which is a pretty

11 big impact. But if you actually go in and eliminate one

12 country at a time, now we're talking about a range from 13

13 to 23 in a risk reduction.

14   DR. NISSEN: Right, but what happens when those

15 257 patients from Asia are eliminated out of the 1,500, the

16 statistical significance is lost completely. Now the

17 confidence intervals overlap no benefit.

18   DR. BAIN: I would agree that eliminating a

19 whole region is going to have an impact here, but what

20 we're interested in looking at, we're looking at the

21 countries within a region. So, when you look at

22 eliminating one country at a time, within Asia it's 13 to

23 16.

24   DR. TEMPLE: But to be fair, it's not

25 eliminating a whole region that's the problem. It's

1 eliminating Asia. If you eliminate the other regions,

2 nothing happens at all. In fact, the whole thing gets

3 better. If you eliminate North America, and all of a

4 sudden you're up to 22.4 percent, so that's a big

5 improvement. So, it's that Asia drives the triple

6 endpoint.

7 　　　　　DR. ZEGER: My name is Scott Zeger.

8 　　　　　DR. TEMPLE: What that means is hard to say,

9 but it's true.

10 　　　　　DR. NISSEN: I'm not passing judgment on what

11 we do with that information, but I guess what I wanted to

12 drill down on is the fact that if you take the 257 patients

13 out of the 1,500 in Asia, the study loses any statistical

14 significance for the triple endpoint.

15 　　　　　DR. FLEMING: Could I maybe add a little bit to

16 this? There have at least maybe three issues put on the

17 table as we've been trying to explore and understand this

18 better.

19 　　　　　One is that these analyses are being done by

20 the stratification factor for baseline proteinuria, and I

21 would strongly agree that's the right thing to do. As your

22 primary analysis, you ought to be at analysis accounting

23 for structure you imposed at randomization. So, what the

24 sponsor is doing here in this stratification seems

25 appropriate.

1   The explanation, given a couple slides back on

2   what happens when you look at the on-study or per-protocol

3   treatment, I'm less persuaded by because that's not

4   preserving the randomization. And to defend the sponsor,

5   they weren't putting that forward as their primary analysis

6   either, but I don't see that as being particularly

7   persuasive.

8   The third issue, though, is they are looking at

9   this issue as it relates not only to the triple endpoint

10   but also the double endpoint. Again, it may be my

11   perspective coming through again that I believe that double

12   endpoint is, A, the most clinically relevant and, B, the

13   most interpretable because I'm not exactly sure what impact

14   it has when we stop following some 267 people in the course

15   of the study for changes in doubling in creatinine times.

16   As a result, if either you look at this slide

17   or you go back to the previous slide that shows these

18   results of the impact of taking out region, looking at this

19   -- actually in fact maybe what I'm really looking at --

20   well, this is fine. I wanted to actually look at the

21   overhead slide as well, but this is fine.

22   Essentially what we're seeing, when we take out

23   Asia, is a reduction in the estimate here that would have

24   been 19.9 percent down to 13 percent, and for the triple

25   endpoint, it was a reduction from 16.1 down to 7. So,

1   taking out Asia has a bigger relative effect here in the

2   robustness of the triple endpoint, taking it from 16 down

3   to 7; whereas for the double endpoint, it takes it down

4   from 19.9 to 13.1, and it's almost significant.

5   And in fact, to be fair to the data, if we eye

6   the data and we find the worst region or the region that

7   accounts for most of the effect, and we pull that out and

8   say, gee, does the remainder still achieve statistical

9   significance, there are two problems with that. One is

10 there's less data, so you weren't necessarily powered to

11 show significance, and secondly, it's data dredging in the

12 reverse direction where you're taking out the best results

13 and hoping that it stands.

14   So, Steve, your issues are relevant. I think

15 it's very important to do the probing that you're doing so

16 that we can get a sense because we're going to be asked

17 later on, does a single study stand, and we're going to be

18 asked to address this particular kind of issue. Is there

19 robustness when you look at issues such as subgroups?

20   My own sense about this, though, is I find it

21 reinforcing that when I look at the double endpoint, the

22 amount of the effect that's being accounted for by Asia to

23 me seems to be less. I'm more confident that these data

24 seem robust through this issue on the double endpoint than

25 on the triple endpoint.

1   DR. NISSEN: Although you would have to agree,

2   Tom, that the primary prespecified efficacy parameter was

3   the triple endpoint. So, I would tend to focus on what was

4   prespecified up front, and what happens, when you take out

5   the Asian population, is it's no longer significant.

6   DR. BORER: But to be entirely fair, the

7   prespecified endpoint didn't include a subanalysis by

8   region.

9   Did you have a --

10   DR. ZEGER: I could never have made the point

11   as eloquently as Dr. Fleming.

12   (Laughter.)

13   DR. KEANE: I wonder if we could just continue

14   along this vein because I think there have been some other

15   issues that came up, Mr. Chairman, that I think are

16   important for us to answer to help further clarify some of

17   the relationships between proteinuria and some of the

18   endpoints that we looked at.

19   Specifically, I think the question this morning

20   of end-stage renal disease and whether or not proteinuria

21   was a useful parameter or risk to actually predict end-

22   stage renal disease in this whole setting, and I think that

23   would be an important component to our discussion, if I

24   may.

25   DR. BORER: Before you do, Dr. Brem had a

1   question earlier. Go ahead.

2   DR. BREM: I wanted to ask whether two issues

3   might have impacted your information that you've presented.

4   One is in the stratification, you had patients

5   who received 50 milligrams and another group of people who

6   got 100 milligrams. And is there a dose dependency in

7   this, and did one group perhaps in Asia get 50 milligrams

8   or 100 milligrams and others get 50? Was there a

9   difference by dose?

10   And then the other question I had -- and

11   perhaps you may not be able to answer this -- is these

12   patients were older and could certainly have acquired other

13   forms of preexistent renal disease on top of their

14   diabetes. And since we do know that IgA nephropathy tends

15   to occur in significant amounts in Asian populations, could

16   these patients have two processes that would perhaps both

17   benefit from treatment with an ACE inhibitor or an ARB?

18   DR. KEANE: Let me respond to the initial

19   question first in terms of actually the amount of drug that

20   was used. Over 70 percent of our patients actually were

21   utilizing 100 milligrams of losartan per day. In fact, the

22   way we utilized losartan was to titrate it up based upon

23   blood pressure. Really, that's the fairest way to look at

24   this. If we were going to do something, did we see a dose

25   dependency, in terms of any effect, I think we would have

1 had to look at a totally different design for our clinical

2 trial. So, we haven't really addressed that within the

3 RENAAL trial as a specific endpoint.

4   The second issue is that the diagnoses that

5 were made here in terms of the clinical diagnosis of type

6 II diabetes and nephropathy, one would have to recognize

7 that this was a clinical diagnosis. It was made in clinic.

8 In fact, it was made by experienced clinical

9 investigators, mind you, and experienced nephrologists and

10 endocrinologists used to dealing with this patient

11 population. So, while we did not, and were not able to by

12 the design of the study, ascertain whether or not there was

13 something else going on, all of these patients had clinical

14 characteristics, as you already saw today, that were

15 consistent with the diagnosis of type II diabetes, as best

16 we're able to do in a clinical trial of this nature.

17   So, if that helps to answer your questions.

18   DR. BREM: Yes.

19   The second point I just raise out of curiosity,

20 not that you'd have the answer.

21   The first point, however, the dose dependence.

22 Is there any information that you've been able to put

23 together that looked, at least, at whether 50 milligrams in

24 that 30 percent of patients had an effect? Was there any

25 effect at all?

1   DR. KEANE: I think the fairest answer in that

2   was that we have not looked and we didn't plan to look in

3   terms of whether or not there was any dose dependency in

4   terms of the effect. We were again titrating towards blood

5   pressure and achieving the blood pressure that we have

6   already talked about this afternoon.

7   DR. ARMSTRONG: I was going to wait, but since

8   the issue of dose has been raised, Mr. Chairman, first a

9   comment and then a question.

10   I'm persuaded that in the Asian subgroup that

11   it wasn't so much the discontinuation of placebo, which is

12   comparable, but as has been said by the sponsor,

13   compliance. In fact, they complied with losartan far

14   better than any other subgroup. So, if there is a

15   plausibility associated with this, I think it probably is

16   driven by that.

17   But do I understand correctly that the sponsor

18   is not in a position to address the issue of dose response

19   and efficacy? If that's correct, fine. Are they in a

20   position to address the issue of safety? Because it took

21   about 6 months to get the 70 percent of the population up

22   to 100 milligrams and although we've seen the Kaplan-Meier

23   curves on efficacy, we've seen the safety data not

24   presented according to its time dependency. And it would

25   be of interest and I think relevance to the label and to

1   advice to practitioners for me to understand, in

2   relationship to the final ascertainment, about the issues

3   of safety and dose and time course.

4   DR. KEANE: Again, I don't think we have a

5   specifically evaluated dose and time and safety related

6   issues. What I can say clearly is that overall throughout

7   the entire conduct of the study, the adverse events that we

8   saw, both clinical and laboratory, were relatively small.

9   Dr. Shahinfar has already presented that information to you

10 today.

11   Again, I'll go back to my answer previously.

12 We really didn't look at any kind of dose dependency with

13 regards to any of the responses that we saw in these

14 patients.

15   Finally, I'll make the point that you have to

16 remember that all of these patients, in large part, have

17 progressive loss of kidney function, and at any time

18 interval throughout their course, they're going to have

19 different clinical manifestations of their disease. Their

20 blood pressure may be more difficult to control. They may

21 have differences in levels of proteinuria when you look at

22 the disease itself. So, I think that should answer, I

23 believe, your questions in terms of differences in the drug

24 utilization.

25   DR. ARMSTRONG: With respect, Mr. Chairman, the

1   notion of safety and issues that were relatively small, as

2   I understood it, 1 out of 4 patients with losartan had an

3   adverse event characterized by hyperkalemia and 1 out of 10

4   had hyperkalemia in excess of 6. So, as a non-

5   nephrologist, I wouldn't characterize that as a small

6   frequency of adverse events. I think it's a genuine issue

7   and I was simply asking whether there was a time course

8   relevant to the appearance of hyperkalemia, which is a

9   clinically relevant event.

10   DR. BAIN: I'll let Dr. Keane respond to that

11 clinical question, but let me first go back to your desire

12 to want to look at dose effect. This particular study

13 design was not a forced titration. Patients were titrated

14 based on their response to blood pressure. So, it's very

15 difficult to do any type of a "randomized comparison"

16 between dosages when they're being up-dosed based on how

17 they're responding to therapy.

18   DR. BREM: So, you essentially, in asking for

19 approval, would recommend what dose? The 100 milligrams or

20 the 50 milligrams?

21   DR. KEANE: As the trial was designed, it was

22 an up-titration to blood pressure. So, we're starting at

23 50 and then moving up to 100 to satisfactorily control

24 blood pressure at 140 over 75, which is what was achieved

25 in this clinical trial.

1   Let me go back to address some of the other

2   issues regarding the clinical aspects of this. All of

3   these patients are sick patients, as you know. This is a

4   group of individuals with advanced renal dysfunction that

5   frequently have problems with hyperkalemia, and so the fact

6   that we only saw 1 in 10, for me as somebody who has been

7   in the practice of nephrology, is almost routine. We know

8   these kinds of abnormalities are happening. We actually

9   aggressively treat for them and manage these patients such

10 that hyperkalemia or related potassium issues are not seen

11 very frequently in this patient population. So, I think

12 that is part the management of patients with more advanced

13 renal dysfunction and the problems of hyperkalemia are not

14 uncommon.

15   DR. BORER: Dr. Hirsch?

16   DR. HIRSCH: Dr. Keane, I want to go back,

17 nevertheless, and beat on the dose-response question one

18 more time because I'm still intrigued by moving from

19 preclinical pathophysiology to human disease. Although

20 there wasn't a real effort to be able to evaluate the

21 actual drug dose and response, nevertheless there is a

22 blood pressure effect.

23   So, you must have had the opportunity to look

24 at the change in blood pressure in cohorts or in tertiles

25 of blood pressure lowering to outcome because they aren't

1   identical between the losartan and the placebo groups. So,

2   one might get some information. In other words -- you know

3   where I'm going with this.

4   DR. KEANE: Yes. I think the issue with us is

5   that you have to recognize that, again, blood pressure was

6   difficult to treat in these patients. We required about

7   three-and-a-half additional medicines on average to

8   actually control blood pressure. So, to actually interpret

9   any dose titration that might be occurring -- are any of

10 these drugs going down, are they being upped -- is

11 virtually impossible for us I think to get at this point in

12 time any reasonable explanation or reasonable data

13 regarding dose titration because there are so many things

14 consistently going on within an individual patient because

15 our goal was to lower the blood pressure and we were using

16 three-and-a-half plus drugs to achieve that.

17   DR. HIRSCH: I know it's difficult but perhaps

18 that can explain some of the regional heterogeneity.

19 Obviously, blood pressure lowering is a key determinant of

20 the renal outcome. So, I'm still curious.

21   DR. KEANE: We can probably look into that, Dr.

22 Hirsch, and see if there's any data that we can pull out to

23 satisfy your inquiry.

24   But I will emphasize again that we were trying

25 to control blood pressure, not looking at dose-response

1 curves, and if we wished to do that, we would have done a

2 different trial. That's something maybe in the future that

3 we can do. I think that's something that's interesting.

4   DR. TEMPLE: Are you asking about the

5 relationship of outcome to success in controlling blood

6 pressure or to dose?

7   DR. HIRSCH: The former, the success in

8 controlling blood pressure as being a means to determine

9 and achieving that clinical outcome regardless of how

10 difficult it was to get there.

11   And that gets back in a sense to the earlier

12 discussion of how we make adjustments, adjusting over a

13 group mean -- I want to do a regression and say, well, on

14 balance, the whole population had a benefit that's

15 independent of the blood pressure. But it may really well

16 be that those patients treated with whatever combination

17 drugs, losartan achieved the greater blood pressure

18 lowering in those that had a clinical benefit.

19   And it has impact on how I translate this in my

20 patients if this drug were to achieve approval. Overall,

21 if I can achieve the blood pressure lowering, one way or

22 the other, with compliance in any region, I may achieve a

23 comparable benefit. Blood pressure is important here.

24   DR. TEMPLE: So, you might do this by -- that

25 is, compare people who got below systolic of 140 with

1   people who didn't, things like that?

2   DR. HIRSCH: You can look at those who achieved

3   target. You could do it by tertiles. You could do an

4   actual regression within each of the treatment groups. A

5   change in the relationship between the two treatment groups

6   in a regression would satisfy me. A different outcome in

7   the two treatment groups for comparable blood pressure,

8   getting rid of that delta, would satisfy me. That would

9   tell me it's the drug not the pressure.

10   DR. KEANE: We do have some data in terms of

11   actually trying to address the issue, Alan. It is

12   confounded by the fact that all these things are going on.

13   DR. HIRSCH: I know how difficult it is. I

14   really realize that there are many things going on here.

15   But nevertheless, if I had to look at one factor, other

16   than region, compliance, et cetera, it would be blood

17   pressure in a hypertensive diabetic population.

18   DR. KEANE: Yes, and I think clearly this gives

19   you the ranges of blood pressure that actually we achieved

20   in the overall trial. So, it's hard actually. It doesn't

21   answer precisely your question in terms of how we got

22   there, but I think, as you can see, in amongst the

23   different regions, blood pressure was reasonably -- and

24   this is the mean arterial pressure -- controlled.

25   Do we have a stratification by achieved blood

1   pressure?

2   DR. BORER: While you're finding that, just to

3   get back to Paul's issue, I wonder if you have some

4   information about the distribution of adverse events in the

5   treated group over time. Forget about the relation to when

6   they were titrated up or titrated down. If you saw that

7   the rate of adverse event occurrence was approximately

8   similar across the duration of the trial, then that would

9   give you some confidence that you're not seeing something

10   happen because more drug is being given over time. So,

11   while you're looking for the data to answer Alan's

12   question, maybe you can see if you have that as well.

13   DR. KEANE: Fine.

14   DR. BAIN: Dr. Borer, related to that issue of

15   adverse events, we prespecified in the protocol -- I think

16   there were -- six prespecified adverse events, which we

17   looked at specifically, and what we did in that analysis

18   was a time to the first event of that prespecified adverse

19   event. Do we have that slide?

20   Now, just to confuse you, we have hazard rates

21   here rather than risk reductions, but essentially to get

22   the risk reduction, you just take 1 minus that hazard rate

23   and multiply by 100. So, for each one of these, we looked

24   at was there a difference between the two treatment groups

25   in the time to the first occurrence of the adverse event

1 that we prespecified. And as you go down the list, which

2 was already introduced in the main core presentation, we

3 did find a difference in hyperkalemia and also hypokalemia.

4   DR. BORER: Thank you, Ray.

5   And with regard to Alan's question?

6   DR. KEANE: We'll have to look at the database

7 in greater detail to see if we can ferret or tease out some

8 of that information.

9   DR. BORER: Okay.

10   DR. KEANE: Would you like me to actually try

11 to clean up some of the issues that we addressed while we

12 get this answer for you?

13   DR. BORER: That would be fine. Before we

14 leave this regional issue, though, which we've had a lot of

15 discussion about, the FDA reviewed this data. We have a

16 medical reviewer. We have two statistical reviewers, Dr.

17 Hung and Dr. Chi, and they saw all these things and didn't

18 flag these as being show stoppers. I'd like to just hear

19 from the FDA about the FDA reviewers' conclusions about the

20 issue of differences among regions and differences among

21 races. Dr. Hung, are you back there?

22   DR. HUNG: Basically I did some analyses and

23 tried to explain potential differences between the Asian

24 region and the other regions. I seem to feel that for some

25 reason the Asian people have higher baseline proteinuria

1   levels. So, I kind of got the impression that that

2   probably at least partially explains the differences among

3   this potential heterogeneity. Other than that, I really

4   cannot conclude anything else. That's my best explanation.

5   DR. BORER: But you didn't find that the

6   outcome, skewed as it might have been in terms of

7   subanalysis by region, precluded the ultimate conclusion

8   that the drug worked and that it was reasonable to infer

9   that the drug worked. Is that correct?

10   DR. HUNG: Yes.

11   DR. BORER: You just didn't think the regional

12   issue was a show stopper.

13   DR. HUNG: Right. I don't think the regional

14   issue is sort of a killer for the evidence. But I feel

15   that all the evidence is not strong, although I realize

16   that because the triple endpoint has -- remember, this is a

17   loss of information about creatinine in some patients. So,

18   the current analysis, which is an intent-to-treat analysis,

19   may dilute some of the potential signal. That's my

20   feeling. I cannot say one way or the other.

21   DR. BORER: Bob?

22   DR. TEMPLE: Well, I don't have to tell you or

23   anybody on this committee that this is one of the big

24   conundrums in analyzing trials, and we've had some of those

25   before this committee. There's a strong bias supported by

1 strongly worded papers that instruct you that if you do

2 subset analyses, you're some kind of idiot. Yet, the

3 plausibility and the interestingness of them is

4 overwhelming in the other direction. They seem very hard

5 to ignore. It's perfectly obvious that if you take the

6 triple endpoint and remove Asia, you've got very little

7 left. Well, as I think Paul Meyer wrote in a paper, if you

8 take the strongest anything out of a trial, it always looks

9 weaker. Of course, from the other end, people like to drop

10 the worst clinic because it was obviously a bunch of shoddy

11 practitioners and you shouldn't leave them in. And then

12 the study always gets stronger.

13   So, we're tormented by this constantly. I

14 don't know how much attention people have paid to it, but

15 the MERIT study of metoprolol in heart failure had a strong

16 finding overall on the combined endpoint of hospitalization

17 and death and a very strong finding everywhere in the world

18 but in the U.S. on death alone, a nearly 50 percent

19 reduction in mortality in the rest of the world and a 0

20 percent effect essentially in the United States.

21   So, we said in the label very carefully, this

22 may be true, may be not true, and have been abused all up

23 and down the world since then for relying on a subset

24 analysis, which everybody knows is stupid because Richard

25 Peto shows that you can use adiacal signs and make

1   convincing arguments and stuff like that.

2   In some sense, there's no really perfect answer

3   to this, which is why you're looking at all these other

4   subsets. You're looking at the double endpoint. It's not

5   as strong there. That makes some sense. But there is no

6   perfect answer to these questions. You make the

7   observation. If there's an obvious explanation, then

8   everybody is happy, but there never is.

9   I think our overall impression is that you

10   should make major decisions based on subgroups like that

11   very cautiously. I won't say never. I think sometimes

12   they're so overwhelming you can't sensibly ignore them, but

13   you do it with the greatest possible care and you try to

14   think of everything that might explain it and look in other

15   places and do your best. But nobody can give you a yes or

16   no answer. Therefore, we never do.

17   DR. NISSEN: If I can just comment very

18   briefly, I think that was obviously wise advice. I try to

19   restrain myself from looking at those too. When a study is

20   very powerful, a strong p value, robust findings, I tend to

21   look a little harder if something is marginal. I suspect

22   that this committee in the past -- I have only been on here

23   a year or two -- I think probably has done that. So, where

24   we begin to take more credence in those groups is when we

25   have an effect that's kind of marginal and now we're trying

1   to understand why is it marginal. That is why I probed

2   this area. I would never have probed this area if the

3   treatment effect had been substantially larger and the p

4   value a lot stronger.

5   DR. TEMPLE: Before you leave that, it's also

6   true that if they're really, really strong, you can almost

7   never make them go away by looking at a set. Well, so

8   there's a certain tautology in that. It's true. When the

9   p value is .02, all kinds of things can make it go away.

10   It's not that hard. There we sit stuck on this pin.

11   DR. BORER: Before we go on to this next issue,

12   Tom, you wanted to make a point?

13   DR. FLEMING: I'd just add a little more

14   philosophy to this. As both Steve and Bob have

15   acknowledged, this is an issue that is extremely difficult.

16   It's an art.

17   We all recognize that in all likelihood the

18   efficacy and safety of treatments probably do differ by

19   various patient characteristics, and yet our trials are

20   barely powered to be able to reliably determine treatment

21   effect in the aggregate. So, when you start breaking down

22   into subgroups, you're inevitably going to be underpowered

23   to be able to really reliably detect the signal when there

24   really is a difference, so you have false negatives. But

25   you also have a great risk of false positives, because

1   you're testing inherently so many different hypotheses by

2   looking in all these subgroups, that you may see something

3   that looks like it's an effect modifier and it's spurious.

4   My own sense is that doesn't mean we shouldn't

5   look at subgroups and have some general sense of whether or

6   not this is giving us greater confidence or lesser

7   confidence about the reliability of the results. But most

8   would argue in most settings, if we see something that is

9   in fact evidence of effect modification, it's generally an

10 hypothesis generation that needs some kind of external

11 validation.

12   In fact, I've always argued when I look at

13 subgroups there are three fundamental things I look for.

14 One is what is the overall strength of evidence here that

15 we have. How strong is the statistical evidence. And one

16 of the many ways of looking at this are tests for

17 interaction. The tests for interaction on a region is a

18 .04.

19   I suspect when you take into context all of the

20 subgroups that were looked at here, the probability that

21 you're going to see something of this order of magnitude by

22 chance alone is not negligible.

23   At the same time, the reason it concerns me a

24 little bit is I care the most about the U.S. at this point

25 because we're an advisory committee for a regulatory

1 authority looking at U.S. applications, and the U.S.

2 population does certainly show less effect than the

3 average. But basically from a strength of evidence here,

4 this isn't a show stopper as I see it.

5   The second criterion is biological

6 plausibility. How plausible is it that there really is

7 effect modification? The example I always use is

8 herceptin. Herceptin is an intervention that was developed

9 based on the concept of Her-2/neu overexpression. So, if I

10 see effect modification by level of Her-2/neu

11 overexpression in an advanced breast cancer patient, I'm

12 not surprised. That's highly biologically plausible.

13   So, a lot of the probing you've been doing,

14 Steve, I think is very appropriate here. Is there some

15 rationale here that explains this just beyond statistical

16 association? Right now, from what I've seen, I don't see a

17 smoking a gun. That doesn't mean that it's not true, but I

18 don't see anything that's truly substantially establishing

19 plausibility.

20   The third criterion is independent

21 confirmation. There needs to be some independent

22 confirmation. My own sense about this is looking at

23 region, it's in most trials likely that what Peto would say

24 or Salim Yusef or many others who've written on this, their

25 advice is wise. Most of these signals are, in fact,

1   spurious. We need confirmation.

2   My only twinge of reservation here is it seems

3   like we've seen quite a few studies coming before us where

4   the North American or the U.S. population shows less

5   effect, and that just may be a spurious observation on my

6   part. But it would be interesting to go back and look more

7   globally. I don't generally trust the results in a single

8   trial that there's a region effect modification, but might

9   there be more here that if we looked more widely, as the

10 FDA can do with its benefits of seeing so much of what's

11 happening in research -- and of course, this is an answer

12 that I don't want to see be proven because we really do

13 want to be able to rely on international results, and yet

14 we do need to also know what the truth is.

15   So, my own sense, in terms of confirmation, is

16 we have this single study, and one of the limitations is it

17 doesn't give us an ability to confirm whether there's a

18 region effect modification for losartan in this indication.

19   But it would be of interest to see whether, in a broader

20 sense, other studies that are at least in related classes

21 might show any evidence of region effect modification.

22   DR. NISSEN: Tom, I'm sorry. One quick follow-

23 on. I really wasn't probing the concept necessarily that

24 this group had some modification of effect, but I was

25 terribly struck by the fact that so many more patients in

1   the placebo arm in Asia discontinued than in the treatment

2   arm. And I wondered if the behavior of the practice

3   patterns, the clinicians, how patients got in and out of

4   the trial, was somehow different in this region and that

5   that's driving some of this.

6   DR. FLEMING: Well, I think what we're seeing,

7   as you astutely pointed out, for the differences I think is

8   that so many on losartan in Asia didn't discontinue. What

9   was really distinguishing was the Asian population on

10 losartan had a very low rate of discontinuation. Now, that

11 might, in fact, influence enhanced efficacy if higher

12 levels of adherence implies higher levels of efficacy.

13   Also though, as you pointed out, a valid

14 concern is if, therefore, there is particular adherence in

15 the Asian population to losartan and more so than in the

16 placebo Asian patients, does that in any way reflect on or

17 influence the level of follow-up for outcome. I haven't

18 heard anything on end-stage renal disease/death outcomes,

19 but it might for the triple endpoint. But for me, I'm not

20 so worried about that because I'm going to look at the

21 double endpoint.

22   DR. NISSEN: Right, and the reason I was

23 probing that, Tom, is why should they be so much more

24 compliant with losartan in Asia than they were with

25 placebo? It's a very, very striking difference.

1   DR. BORER: Everybody was more compliant with

2   losartan than placebo, according to the data. The

3   magnitude varied but everybody was, I think.

4   There was one, to me, striking point that came

5   out of your regional blood pressure data that will lead

6   into Alan Hirsch's question that I'll let him present

7   himself. In the Asian group, the blood pressure effect of

8   treatment was, to me, importantly less than in the other

9   regions; that is, in fact, although we get into the mean

10   arterial versus systolic versus whatever issue that we

11   raised earlier, the mean arterial pressure for the last few

12   years in the Asian group was actually higher on losartan

13   than on placebo. So, the fact that the effect was seen in

14   that group as strongly as it was, despite the fact that the

15   blood pressure was higher on the putatively active agent,

16   is an interesting piece of confirmatory evidence to me

17   about the blood pressure.

18   But Alan raised another question about the

19   relation of change in blood pressure to outcome, and

20   perhaps you want to ask that directly.

21   DR. HIRSCH: It's not easy to sit between these

22   two sides of the table and get a point out.

23   Just to make one more philosophical point

24   before leading into the data, we're obviously looking for

25   biologic reality not for differences only in practice

1 standards or in how we defined end-stage renal disease. I

2 hope. Because biologic reality is if the molecule works,

3 hopefully, more or less genomically similar, that it will

4 work everywhere in the world. At least I am going to make

5 that assumption for the moment.

6   So, to link the two arguments here for a

7 minute, my worry is that something is happening. There's

8 something we're seeing in this signal in whichever

9 countries comprise Asia whereby this is a group that has --

10 and here's my hypothesis -- a higher baseline protein

11 excretion, perhaps again a higher placebo discontinuation

12 rate, hitherto unexplained, and perhaps -- because we

13 really were not sure -- a lesser blood pressure lowering

14 effect, and therefore the losartan group looks better

15 there. I don't know if that's true or not, but I was

16 trying to make a chain of biologic causality.

17   So, what I was trying to come up with -- I

18 think angiotensin II is potentially a toxic agent, but this

19 is a drug approved for blood pressure lowering in a trial

20 that was designed to lower blood pressure. I came up with

21 two analyses that I thought might work again.

22   One again is since you're titrating the target

23 blood pressure, could we see data that simply segregates

24 all the patients in the trial into those that achieved

25 their target and those that did not achieve their target

1 and then look at the effect on ESRD or any event rate by

2 achievement of target blood pressure. If all those

3 patients that achieve target blood pressure have the same

4 outcome, regardless of treatment allocation, then it's not

5 the molecule. It's the blood pressure. Everybody with me?

6   Or another way of looking at it is to create,

7 again, a regression or a slope. The y axis, for example,

8 might be a risk or a hazard ratio, and the x axis, for

9 example, might be again a change in blood pressure because

10 you do have sequential clinic visits every 3 or 4 months,

11 and again a change in the slope there would also indicate

12 an effect of the drug versus placebo.

13   DR. BAIN: We have not done the analysis which

14 looks at only those people who achieved their blood

15 pressure and then what the outcomes are because essentially

16 we're getting into this area of two outcomes and adjusting

17 one outcome for the other and not really doing a randomized

18 comparison. So, it's very difficult and complex. We can

19 do the analysis. It's the interpretation that becomes

20 extremely difficult.

21   DR. HIRSCH: I realize I may be asking for

22 something more than can occur, but nevertheless, I'm making

23 an effort and I'll look to my other colleagues for support

24 or not.

25   DR. TEMPLE: In his discussion of this, Salim

1 distinguishes between sort of good things to adjust for and

2 look at and bad things to adjust for. The good things are

3 all baseline characteristics because those are at least

4 randomly assigned or at least you're pretty sure they are.

5 Adjusting for outcome variables is very treacherous

6 business because one factor can have different effects on

7 both. So, as was just explained, they tend not to do those

8 kinds of things. It doesn't mean you can't do them, but

9 you've got to be careful and think hard about it.

10   DR. BORER: With that having been said, we have

11 several more questions still unanswered, and I think, Dr.

12 Keane, you were going to move on to clean up some of those

13 and we'll see if you go down the whole list here.

14   DR. KEANE: Let me just bring back up Dr. Bain.

15 I think this is a very important issue related to the

16 outcomes in relationship with proteinuria and looking at

17 end-stage renal disease as the endpoint. I think Ray has

18 provided us with that information now so that you can take

19 a look at it. It really is, I think, a very important

20 relationship.

21   DR. BAIN: A little housecleaning first. Table

22 1 on page 8, where we were discussing earlier looking at

23 the median time, and it looked like losartan was 13.3,

24 1303, and placebo was 1373. Essentially what was done in

25 this table was they went to the median on the y axis, drew

1 a line across until they hit the two curves, and then

2 dropped the line down to estimate the median time. It

3 turns out that these numbers are flipped. We confirmed

4 that losartan is actually 1373 and placebo was 1303, and

5 you can confirm that yourself by going to that figure of

6 our triple endpoint and drawing a line for yourself and

7 dropping it down. You'll see that you hit the placebo

8 cumulative incidence curve first and you drop down to 1303.

9   DR. THROCKMORTON: What page?

10   DR. BAIN: Page 8 in the FDA, table 1,

11 statistical review.

12   DR. BORER: Yes. Where it shows a 70-day

13 difference, the 70-day difference is in favor of losartan.

14   DR. BAIN: So, that's number one.

15   Going back to -- it seems a very long time ago

16 -- a conversation, where Tom nicely laid out the different

17 types of adjustments that are typically done. We talked

18 about a baseline predictor, and then we talked about an

19 effect modifier. I want to take the first one first, and

20 we're back to the overhead.

21   This is a request where, remember, in the main

22 presentation we showed the baseline prediction of the

23 triple endpoint, and then there were a lot of requests for

24 the prediction of ESRD, the prediction of ESRD/death, and

25 Dr. Temple wanted a prediction of doubling ESRD.

1   That's what we showed in the main presentation.

2   Remember when we got out to about 16, we drew a line over,

3   it was like 12, 15. Here, this one is the doubling ESRD,

4   so there's a steeper curve so that baseline proteinuria is

5   actually very predictive of ESRD doubling, and it's most

6   predictive of end-stage renal disease. Again, remember,

7   that's baseline proteinuria. So, that's the answer to that

8   question.

9   DR. KOPP: Just one other point. That's

10   proteinuria defined as milligrams of albumin per gram of

11   creatinine.

12   DR. BAIN: Yes. Urinary albumin to creatinine.

13   So, that was our baseline predictor analysis.

14   The next one that you requested was the effect modifier

15   analysis to see whether or not the risk reduction varied

16   across the categories of baseline proteinuria. Slide 605.

17   So, what we're doing here is we have five

18   categories of baseline proteinuria. We have the total

19   sample size of individuals within each one of those

20   categories. And the last column is the risk reduction.

21   Now, remember, this is the risk reduction for the primary

22   composite. Remember, overall the primary outcome was 16

23   percent. So, you can see that when you're less than 1,000,

24   it's a risk reduction of 4.6. It goes up to 15 when you're

25   in 1,000, and then 2,000, it's up to 17, all the way up,

1   and when you're greater than 4,000, with 163 patients

2   distributed between the two groups, you're at about 20

3   percent. So, that's the risk reduction as a function of

4   baseline proteinuria category. So, that's housecleaning

5   number two.

6   Now, one last thing that I'd like to do is

7   something that we talked about much earlier today, which

8   was the prespecified analysis for what we called the

9   baseline risk score. Could I see slide 1339?

10   This is just a little paragraph from our data

11   analysis plan that indicates what this analysis is. So, we

12   were looking at the treatment effect comparing losartan to

13   placebo, adjusted by various baseline covariates, and this

14   analysis was done in two steps. The first thing we did was

15   we developed a risk score. What we did was we took pooled

16   data. We pooled the placebo and losartan data, and

17   formulated a baseline risk score for our primary composite

18   endpoint. Then after we did that, we took that risk score

19   and estimated the treatment effect when we controlled for

20   this baseline risk score.

21   1340, please. We prespecified in the DAP a

22   total of 15 baseline risk factors that we would be

23   interested in evaluating in this manner, and they are

24   listed there.

25   1341. Essentially what we did for our primary

1 composite outcome, the baseline risk score was defined as a

2 linear combination of those covariates that were

3 significantly selected among the covariates. The way we

4 did that was we just did a stepwise selection procedure

5 using the Cox regression model without treatment effect in

6 the model, meaning we were pooling the placebo and

7 treatment groups. Then the treatment effect was determined

8 by performing this model with terms, including the

9 treatment effect and the baseline score. So, that was the

10 second part. And then we reported the results with a p

11 value and 95 percent confidence interval.

12   Now, we're on to 1135.

13   DR. FLEMING: If you go back a slide for a

14 second.

15   DR. BAIN: Okay. So, urine albumin to urine

16 creatinine ratio. That was our prespecified stratum. So,

17 those are the 15 characteristics, some of them continuous,

18 some of them categorical.

19   DR. FLEMING: So, certainly key ones would be

20 systolic blood pressure based on what we've seen. You're

21 going to be identifying those that are predictive of

22 outcome and independently predictive, and that's a very

23 rational thing to do. At the same time, what guides some

24 of our interest as well is whether factors are imbalanced,

25 and one that's not as strongly predictive, if it's

1   imbalanced, really is key. So, hematuria and systolic

2   blood pressure would be two that we would think that

3   there's interest in.

4   DR. BAIN: Okay. So, we'll take a look at

5   those.

6   So, now we're on to slide 1135. So, in

7   summary, we used the multivariate Cox regression model,

8   pooled the treatment groups, and looked at the primary

9   composite endpoint as a dependent variable, and selected

10 significant predictors by a stepwise procedure. Then we

11 calculated the risk score as a sum of the products of the

12 significant predictors based on their regression

13 coefficients from those that remained in the Cox regression

14 model after the stepwise procedure.

15   Next slide. Now, this is two slides, but what

16 I'm going to show you here is these are the two groups.

17 Although we did the analysis pooled, I'm going right back

18 to our baseline slide where, remember, we had a slight

19 imbalance in the mean proteinuria between the two groups,

20 and that's still there. And you can see serum albumin,

21 serum creatinine, hemoglobin, sitting systolic blood

22 pressure. So, on this slide you have five of the ones that

23 remain in the risk factor model.

24   What I put on the right-hand side is kind of an

25 indicator of the strength of an individual variable and its

1 relationship with the risk score. It turns out that the

2 strongest of our baseline risk score factors was urine

3 albumin to creatinine ratio.

4   The next slide will give you the rest of the

5 covariates that were in this model. It turns out that

6 Latin American, yes/no, insulin use, and at the bottom here

7 you see what I was alluding to earlier, the linear score of

8 significant factors. The more negative that value is, the

9 higher your risk. So, you can see that, when you do a

10 linear combination of these risk factors, you tend to see

11 that the placebo group is -- I'm sorry. The other way

12 around. The more negative, the less at risk you are.

13 Therefore, what's shown up here is the losartan group has a

14 higher risk when you look across not just one factor, but

15 all seven of those factors.

16   Next slide. So, then what we did was we took

17 it to step two which was take that risk factor score, which

18 is a single score for each individual and enter that into

19 our original model, which was our primary results model,

20 which was where we showed that 16 percent reduction. And

21 if we now adjust for their baseline risk score, the risk

22 reduction goes from 16.1 to 23.9.

23   Graphically it's shown on the next slide.

24 There's our primary outcome above, and when we adjust it, a

25 stronger treatment effect, less than .001.

1   Although we developed the risk factor score

2 based on the triple endpoint, we actually used that risk

3 factor score to see what effect it had on our other

4 clinical endpoints, and that's on the next slide. You can

5 see that you see that same effect. For ESRD, the treatment

6 effect got stronger, and for end-stage renal disease or

7 death, the adjustment made it slightly stronger.

8   DR. BORER: Ray, can I just ask about the

9 factors you used? It seems that all of them are reasonable

10 except perhaps for region. That sort of begs the issue.

11 Did you sort of look at this? Latin America, yes/no,

12 probably was down on the list.

13   DR. BAIN: Well, no, the original list had all

14 regions. It just turns out that that particular region of

15 the four --

16   DR. BORER: No. I understand. But you

17 ultimately used Latin America, yes/no, in the model that

18 you used for adjustment. Wrong?

19   DR. BAIN: No. Latin America went into the

20 risk factor score. It was one of the things that you

21 multiplied by in order to come out with a single number for

22 a patient.

23   DR. BORER: Right. That's what I mean. So, it

24 was used to adjust for risk.

25   DR. BAIN: Correct.

1   DR. BORER: And all I wanted here is that if

2   you took Latin America out of there, you've still got a

3   directionally similar movement --

4   DR. BAIN: We would have to run that analysis.

5   We just did? The same.

6   DR. FLEMING: It should be.

7   It's certainly relevant to know that we didn't

8   just look at proteinuria, but what's apparent from this is

9   that when you look at those covariates that are going to

10 fall out of a variable selection model, the one that's

11 dominating here is proteinuria. It's very predictive of

12 outcome, and it's the one that is influencing outcome

13 effect because there's also this imbalance in the tail.

14 So, this is certainly a reassuring analysis to say it's not

15 just that we're looking at proteinuria because we could see

16 that it had this imbalance.

17   It would be relevant, though -- at least for

18 me. I'd like to see the analysis that simply adjusts

19 simultaneously for baseline systolic blood pressure because

20 the differences that we see over time were largely already

21 apparent at baseline. And Bob Temple is right. One has to

22 be really careful when you're using post-baseline values of

23 covariates and how you interpret the results. But some of

24 the blood pressure difference was already apparent at

25 baseline. So, even if it doesn't show up in your variable

1   selection model, it could be an influential factor as a

2   confounder because of that imbalance.

3   My suspicion is that the most significant

4   confounder here is proteinuria. It's increasing the

5   estimate of effect from 16 to 23 percent or 22 percent, and

6   systolic blood pressure at baseline I'm guessing will

7   correct that back 1 or 2 points, and in the end you'll

8   still have a net increase but not quite as much when you

9   just look at proteinuria, which is more or less what's

10 showing up out of that analysis.

11   DR. BAIN: So, we'll do that.

12   DR. BORER: While you're doing that, JoAnn, you

13 had several questions related to looking at the double

14 endpoint, and perhaps you want to restate them if they

15 haven't been answered already.

16   DR. LINDENFELD: No. I think I've gotten an

17 answer to those in this data.

18   DR. BORER: Blase, I think you had asked about

19 the time to event when you looked at the double endpoint as

20 an outcome, the average time to event rather than the

21 triple endpoint. I'd like to hear that too, if you happen

22 to have that, understanding, as we all do, that it's a poor

23 man's way of looking at anything; that is, the average time

24 to event among those people who had events when the event

25 was the real hard endpoint.

1   DR. BAIN: You wanted it for ESRD only, Jeff?

2   DR. BORER: ESRD or death.

3   DR. BAIN: Okay. So, why don't you put up the

4   ESRD slide from the core presentation, or whatever one.

5   Now, of course, in this particular outcome, we

6   don't get to 50 percent of events on the y axis, so we

7   can't talk about the median time. But we can talk about,

8   for example, the time to 20 percent of the patients

9   reaching their endpoint. Therefore, you just draw a line

10   over from 20 and drop it down. So, it's about 2-and-a-half

11   years for placebo and 3 years for -- so, about a 6-month

12   difference.

13   DR. BORER: How about if you do the same thing

14   since that's obviously a reasonable way to get a gestalt of

15   the number we asked for. If you look at the post hoc

16   analysis curves where you accounted for MI, stroke,

17   cardiovascular endpoints, so we're seeing a net effect.

18   DR. TEMPLE: What are you asking, Jeffrey?

19   They saw no difference in those.

20   DR. BORER: No, no. What they did was to

21   combine ESRD, death, myocardial infarction, and stroke in

22   one analysis.

23   DR. BAIN: So, Jeffrey, let me make sure I

24   understand. Which endpoint?

25   DR. BORER: There it is.

1   DR. BAIN: Now, here you could probably maybe

2   go up to 40 percent, although it's getting pretty thin up

3   there. But again, you would do the same thing. You could

4   draw a line from either 40 or 30 around, and you're going

5   to see that there's a difference in the time to the events.

6   DR. BORER: Yes. We're still talking about 6

7   months.

8   DR. BAIN: 6 months.

9   DR. BORER: Beverly?

10   DR. LORELL: I think the other way, Tom

11   Fleming's comments notwithstanding, that both Blase and I

12   were interested in getting a feel for is among those

13   patients who had a major heart event, what was the average

14   time to that event.

15   DR. BORER: These are the people who had

16   endpoints. So, that's about the best we're going to do,

17   but it looks like it's about 6 months.

18   DR. FLEMING: Before we leave this, could I

19   comment on these two slides, 379 and 73, maybe going to 397

20   first?

21   From a renal perspective, this is what one

22   might expect to be the component of a composite endpoint

23   when you look at the clinical endpoints, the component that

24   would be presumably most specifically being targeted,

25   prevention of end-stage renal disease. It's interesting,

1   when one is doing studies such as these that there's a lot

2   of wisdom for not doing a study that would have 2 years of

3   median follow-up. And this study, in essence, has

4   information predominantly through 3 years, a limited amount

5   of information out to 4 years.

6   Just to follow up on some previous discussion,

7   this estimate is a 28.6 percent relative reduction in the

8   rate of failure. That's based on a weighted average of

9   what the true reduction is at all points over time. The

10 true reduction in the first 18 months is 0. The curves are

11 overlapping through the first 18 months, which means that

12 the true reduction between 18 months and about 42, when you

13 have most of your data, is probably about 40 to 45 percent,

14 meaning that if you do a study like this and you use the

15 log rank and the Cox regression methods and get relative

16 risk reductions, those estimates are a weighted average

17 over time of what truly isn't a truly constant reduction

18 over time. The reduction in the first 18 months is 0; in

19 the last 18 months is 40.

20   So, if you had done this study with one less

21 year of follow-up, you would be weighting much more

22 proportionally on the 0 rather than the 40, and your

23 estimate would have been 20 percent. If they had done

24 another year of this trial, and these curves represent

25 truth, the estimate would have been even greater than 28.6.

1   So, it's interesting to look at these curves

2   and understand what these relative risk estimates mean, in

3   particular when there's evidence such as this that the

4   reduction isn't constant over time.

5   The second point on the next slide, if you look

6   at slide 73, you see the same basic phenomenon. One of my

7   questions here is this is in fact an endpoint that some of

8   us in January had really wanted to focus on if we wanted to

9   focus on clinical measures that were combining both the

10   renal as well as cardiovascular elements. In the renal, we

11   were saying end-stage renal disease/death; in the

12   cardiovascular, were cardiovascular death, MI, and stroke.

13   So, I'm delighted the sponsor presented this.

14   Essentially what we're looking at is this is

15   made up of 47 fewer end-stage renal disease events, 18

16   fewer MIs, 3 fewer strokes, and 3 excess deaths, which are

17   made up of 11 excess cardiovascular deaths, but 8 fewer of

18   the non-cardiovascular deaths. That's a net difference of

19   65 events, although I can't tell how many people that is.

20   I'm assuming it's probably about 40 to 55 fewer people have

21   at least one of these events because this is a time to the

22   first of those types of events analysis. Can the sponsor

23   clarify what that is?

24   DR. KEANE: We're just looking, Dr. Fleming.

25   DR. FLEMING: You can tell me later after you

1 have a chance to look.

2   DR. KEANE: It is.

3   DR. FLEMING: What's the answer?

4   DR. KEANE: Time to event.

5   DR. FLEMING: I can add up and see there are 65

6 fewer events, but I can't tell how many fewer people had at

7 least one event. That's what this analysis is looking at.

8 It's time to the first of those types of events. I'm

9 guessing it's 40 to 55.

10   DR. KEANE: We're in the process, as I said, to

11 get the number of patients that were involved with this.

12   DR. BAIN: One more housecleaning chore. Tom

13 asked when you go and do the Cox proportional hazards

14 regression on the triple endpoint, remember it was a 16

15 percent reduction. When you adjust for baseline systolic

16 blood pressure, it goes to 21.6 in addition to baseline

17 proteinuria stratum.

18   DR. BORER: My list of questions is exhausted

19 but yours may not be. Did you have some other

20 clarifications you wanted to give us?

21   DR. KEANE: Yes. If you will just give us a

22 couple of more seconds, we'll give the response to Dr.

23 Fleming's question in terms of the number of patients that

24 the event curves actually encompassed.

25   DR. BORER: While you're doing that, what we'll

1   move on to next, as soon as you have that answer, is the

2   questions, and we'll structure the rest of the discussion

3   around those.

4   DR. KOPP: One additional question.

5   DR. BORER: Two. I think JoAnn has one there

6   also.

7   DR. KOPP: To return to the issue of how you

8   define end-stage renal disease, it was suggested during the

9   break that one additional analysis would be to ask what was

10 the final creatinine before somebody went on dialysis and

11 did it differ between the two groups.

12   DR. BAIN: Now, I believe the question was that

13 and by region for serum creatinine. At least, that's what

14 I have here.

15   Let me tell you by region these are median

16 serum creatinines. I'm going to give you losartan then

17 placebo. In Asia, it's 7.0 and 6.2. In Europe, it's 4.9

18 and 5.3. In Latin America, it's 5.2 and 6.6. In North

19 America, it's 4.4 and 4.9.

20   Now, the interesting thing about those numbers

21 is you'll probably notice that they tend to be lower in

22 Europe and North America. Well, it turns out that the time

23 from the serum creatinine to end-stage renal disease is

24 actually higher in those two groups, probably driven by

25 study drug discontinuation and then some of those patients

1   going into telephone follow-up. So, therefore, you're not

2   getting serum creatinines very close to their ESRD events.

3   DR. BORER: It seems clear, if I heard the

4   presentation correctly that you just made, that the

5   creatinines at endpoint were systematically higher in

6   people on placebo than on losartan. Is that correct? Did

7   I hear that right?

8   DR. BAIN: No. They go back and forth. It's

9   true in Asia. It's not true in EU. It's not true in Latin

10 America, and it's not true in North America.   So, in Asia

11 it tends to be a little higher.

12   But now, remember, we're talking about in Asia

13 a total of 60 events; in EU, a total of 40; 60 in Latin

14 America; and North America -- you know. So, the numbers

15 are pretty small here. Remember, these are only people who

16 actually had the event of end-stage renal disease.

17   DR. BORER: Right. Is there any reason that

18 there should be a discrepancy as large as 1 milligram

19 percent of creatinine between those groups? Does that have

20 to do with timing of checking --

21   DR. BAIN: I'll put out a possibility there.

22 These are people who are going to end-stage renal disease.

23   So, it really is probably a function of exactly where

24 you're picking them up relative to their end-stage renal

25 disease. That's a guess.

1   DR. BORER: It's probably an unanswerable

2   question.

3   JoAnn?

4   DR. LINDENFELD: I have two questions about

5   secondary endpoints. The first is we've seen that there's

6   a nice reduction in proteinuria. Could you tell me if the

7   reduction in proteinuria correlates with the doubling of

8   serum creatinine or end-stage renal disease? Just in terms

9   of how we use these drugs, I'm interested in knowing if the

10   change in proteinuria correlates with the other endpoints.

11   DR. KEANE: It does.

12   DR. LINDENFELD: Strongly?

13   DR. KEANE: Strongly.

14   DR. LINDENFELD: Good.

15   Then in terms of cardiovascular endpoints, I

16   know this is a difficult issue, but I'd like to hear your

17   discussion. The study was stopped prematurely because of

18   data with ACE inhibitors and cardiovascular mortality.

19   Here we see very little signal for cardiovascular

20   mortality. I understand there's a little bit shorter

21   follow-up here and fewer numbers, but we see very little

22   signal there. I wondered if you could just tell me your

23   thoughts about why there doesn't appear to be much effect

24   on cardiovascular mortality.

25   DR. KEANE: There are a number of things that I

1   think are clinically relevant. First of all is the RENAAL

2   trial is a renal protection study. It wasn't a study of

3   cardioprotection. So, we had a smaller group of patients,

4   1,500. Usually when you look at a cardioprotective study,

5   it's substantively larger. So, that was one set of issues.

6   And number two is actually the duration of the

7   trial was relatively shorter as compared to most

8   cardioprotection studies.

9   When we look at the type of patient we had in

10   our study, we made a very concerted effort to not have

11   patients that had a lot of cardiovascular disease

12   antecedent to our randomization process for the RENAAL

13   trial, so that we had lower cardiovascular disease

14   manifestations or disease history. We had a smaller group

15   of patients. We were looking at specifically enriching our

16   population for renal events. So, I think when you look at

17   all of that, I think that explains, at least in part, the

18   reason why we didn't see a major difference in

19   cardiovascular endpoints.

20   Again, our composite, I'll just underscore, was

21   almost a 10 percent risk reduction for the composite. So,

22   it was in the right direction, and as I showed in my

23   concluding slide, there was some noise around the 0 line in

24   terms of the point estimates for each of the components of

25   the overall. So, I think that's most likely, as best I'm

1 able to look at, the explanation for why there wasn't more

2 robust changes in cardiovascular disease endpoints.

3   DR. BORER: We'll go on to the -- I'm sorry.

4 Blase?

5   DR. CARABELLO: But from a functional

6 standpoint, the fact of the matter is, the Data and Safety

7 Monitoring Board said these patients should not be

8 precluded from being on an ACE inhibitor, or maybe you

9 could even take that as a recommendation that they should

10 be on an ACE inhibitor. I've got a sea of folks in my

11 hospital who are diabetics and already on an ACE inhibitor.

12 We don't have any data about that interaction. What are

13 we supposed to do?

14   DR. KEANE: I'm not sure I completely

15 understand what question you're asking me.

16   DR. LORELL: May I help?

17   DR. KEANE: Yes.

18   DR. LORELL: I think I know what Dr. Carabello

19 is getting at. I think it's a very difficult issue here.

20   The issue of use of an ACE inhibitor was raised

21 in two ways in this trial. It was raised in study design

22 by prohibition of use of an ACE inhibitor during the trial

23 and a washout period. Secondly, it was raised, as Dr.

24 Carabello pointed out, by the Steering Committee

25 prematurely stopping this trial because of the issue of

1   cardioprotection in multiple arenas of the use of an ACE

2   inhibitor.

3   We've seen data presented here, very elegantly,

4   of really an extraordinary tight link in this patient

5   population of renal events and cardiovascular events. If

6   my numbers are correct, 1 out of 5 of the patients in this

7   study died, and in the losartan group, 57 percent of those

8   were cardiovascular events. So, this is a major clinical

9   issue for Dr. Carabello's patients and most of us around

10 the table.

11   So, I think one of the real dilemmas here that

12 was part of design and part of trial stoppage is the issue

13 of how you think about this drug for renal protection in

14 the absence of demonstration of a cardioprotective effect,

15 which is what kills many of these patients. And it's very

16 problematic. We don't have any data here in this

17 population about combined use of ACE inhibitor and ARB.

18   So, I think what Dr. Carabello and I might like

19 to hear is your thoughts in industry, were this drug to be

20 approved, as to how you would recommend the use of this

21 drug relative to the absence of a demonstrated

22 cardioprotective effect as your secondary endpoint and the

23 ethical issue that was raised by the Steering Committee in

24 stopping this trial of potential ethical need to use an ACE

25 inhibitor.

1   DR. BORER: While you're answering that, just

2   clarify for me. I believe you had 100 patients who

3   actually were on ACE inhibitor because the ACE inhibitor

4   prohibition was by amendment after the trial had started,

5   if I'm not mistaken. So, you may actually have some data

6   that are relevant.

7   DR. KEANE: Actually that is not correct. All

8   the patients prior to randomization had their ACE inhibitor

9   or ARB stopped. Let me just make some points and then we

10   can have some additional discussion.

11   We did look at interactions, as you saw,

12   between prior ACE use, prior ARB use, and either the renal

13   or cardiovascular endpoints, and there was no interaction,

14   as best we could see, in that data set. So, it didn't look

15   like prior utilization of ACEs or ARB impacted any of the

16   results that we had.

17   Number three is that in terms of the Steering

18   Committee's decision to stop the trial, obviously we didn't

19   know what the recommendations were at that point in time.

20   Dr. Brenner is here, if you'd like to have this discussion

21   in greater detail. What our concern was, in a more global

22   perspective, is that we had a placebo group of patients

23   that were not on any AII blockade. With the Mann data that

24   came out in the Annals last year, that raised at least a

25   concern for us in terms of continuing the trial. And that

1 was really what I think our issue was. It wasn't that we

2 weren't seeing any other benefits for ARB, but the issue

3 was that we had half of the trial that was not on any AII

4 blockade.

5   Then finally, let me just make the point that

6 you have to take our data in the context of what the study

7 was. This was a study that was done in patients with

8 advanced renal functional declines, type II diabetics with

9 proteinuria, and all had fairly advanced disease. All of

10 the other ACE data that is out there is not in this

11 population. So, it does present us with a bit of a

12 difficulty in terms of what should be done on an individual

13 patient basis, but our focus really was in the patients

14 with advanced renal disease, with proteinuria, and looking

15 at renal outcome. So, we didn't have that data at that

16 point in time when we stopped our trials.

17   DR. BORER: Steve and then Bob.

18   DR. NISSEN: Yes. I think we're all saying

19 about the same thing. Let me see if I can be very precise

20 here.

21   Our diabetic hypertensive patients with renal

22 insufficiency are, by and large, all on ACE inhibitors, and

23 they're on them for two reasons I think. One is that

24 there's some pretty good evidence of cardiovascular

25 protection that I think most people would generally accept,

1 and many individuals have extrapolated from the type I data

2 and said, well, if it works in type I nephropathy, it

3 probably works in type II even though the agency never

4 approved it. So, now we're confronted with if the agency

5 approves losartan for this indication, clinicians are faced

6 with a really big dilemma. Do you take the patient off the

7 ACE inhibitor and switch them over to losartan? Do you add

8 losartan to an ACE inhibitor?

9   I think what people are getting at and I would

10 like to be very specific about is our fear that for

11 patients that are stable and doing well on ACE inhibitors,

12 because of a label change, someone is going to say to the

13 physicians, here's the only labeled drug for renal

14 protection in type II diabetes. Let's have you take your

15 patient off of your ACE inhibitor and put them on losartan.

16   Then we don't know whether the cardioprotective benefits

17 of ARBs are comparable to ACEs or not. We don't know that.

18   So, this creates a huge dilemma and that

19 dilemma was manifest by the Steering Committee of this

20 trial feeling like they couldn't go on with the trial

21 because they couldn't withhold ACE inhibitors from these

22 patients. So, we're really on the horns of a terrible

23 dilemma as a consequence of that.

24   DR. KEANE: Let me just call on Peter for a

25 second here.

1   DR. BORER: Just before you do, Bob, did you

2   have a comment to make first? Then, Peter, maybe you can

3   comment.

4   DR. TEMPLE: I just thought it would be very

5   helpful to pin down exactly which treatments are because

6   we're analogizing and doing our best and which treatments

7   are really well documented. The only data comes from HOPE.

8   Right? Not the same population. No renal disease, but

9   they did have macroalbuminuria. Right. So, it's those

10   people you'd be worried about, people who are being put on

11   some ACE inhibitor or other on the basis of HOPE or

12   ramipril itself, which is the only one that was actually

13   studied. So, that's the group that you're worried about.

14   What do you do with those people now? If they turn out to

15   have a little elevation of creatinine, do you now ignore

16   those results and switch or things like that? Good

17   questions.

18   DR. BORER: Peter?

19   DR. KOWEY: Let me just address this. Peter

20   Kowey, paid consultant for Merck.

21   Blase, let me put this in some perspective

22   because it's a question that's come up repeatedly in

23   looking at this information. A lot of people have already

24   asked this question. And the answer is that from my

25   perspective as a cardiologist, we frequently have patients

1   that have competing risks and have competing diseases for

2   whom there are some therapies that actually overlap. There

3   are situations where we have to make a value judgment as to

4   how important the cardiovascular end of things are going to

5   be in this scenario versus how important is the renal end

6   of this disease in this scenario. Because you're right.

7   We do not have data on combined use of these two drugs.

8   So, we can't advocate that.

9   As a cardiologist, my answer is that the more

10 I'm concerned about these patients being disposed to a

11 renal endpoint from the point of view of how they look,

12 vis-a-vis the patients that were enrolled in the trial, the

13 more likely I am to use an ARB, and the more likely they

14 are to look to me like a cardiovascular patient, the more

15 likely I am to use an ACE inhibitor. But it's a judgment

16 that needs to be made on a patient-to-patient basis.

17   I think it's a little tiny bit unreasonable to

18 expect a trial like this to answer every question that can

19 be asked about cardiovascular disease. It can't. There

20 are data on both sides of the question for ARBs and ACE

21 inhibitors even within this realm.

22   So, I understand your question but I don't

23 think that approving this drug for this indication

24 necessarily places patients at risk. It places doctors in

25 a position where they have to make a clinical judgment, but

1   you do that all the time anyway. So, that's where I think

2   this sits.

3   DR. BORER: I'd like to weigh in here just for

4   a minute because this is a drug approvability panel,

5   advisory panel. I think that we have to consider what the

6   FDA does and what it doesn't do, and as Bob pointed out,

7   what the data that we're weighing in against are.

8   My understanding of the HOPE trial is it

9   involved individuals who were greater than 55 years of age

10   with known coronary disease and at least one other risk

11   factor and that risk factor could have been diabetes. It

12   could have been hypercholesterolemia. It could have been

13   hypertension. And one drug was used. Actually two, if you

14   include vitamin E, but that didn't work. So, that's the

15   database. That's it.

16   Having said that, the FDA doesn't establish

17   medical practice. Sorry, Bob. I know that bothers you.

18   (Laughter.)

19   DR. BORER: No, the FDA doesn't mandate medical

20   practice. It may indirectly, but that's not what it does.

21   So, in a sense this issue is not a primary FDA concern.

22   The medical practice is determined by consensus, by

23   advisory panels, which I'm not too happy with, and by the

24   courts based on what evidence you can bring to bear if

25   something goes wrong and somebody says it's your fault that

1   it did.

2   Ultimately there aren't the data to draw the

3   firm conclusions that people might draw about should you be

4   on an ARB, should you be on an ACE inhibitor, just as Peter

5   said. The data aren't there. You have to make your best

6   judgment based on the data that exist.

7   I would like to suggest, therefore, just so we

8   can take this issue off the table and not make it an

9   approvability issue, when I don't think it really primarily

10 ought to be, but it's worth a great deal of thought because

11 it's a very important issue because people do act on the

12 basis of just what Steve said and Beverly said -- that is,

13 if the indication is there, then it may be malpractice not

14 to do this -- that perhaps the FDA should consider, if

15 everybody on the panel agrees to this, something in

16 labeling that says what we know and what we don't know and

17 that anything that's said about this drug shouldn't be

18 construed to suggest that the approval, if it happens to be

19 approved for this indication, should be construed as a

20 mandate that it must be used, that indeed competing risks,

21 individual patient, et cetera. This is a drug that can do

22 certain things or maybe can't. If we find that it can,

23 then it can.

24   I think that this is something that we've never

25 considered before in a formal way, and I think considering

1 the possibility of putting something into the label about

2 it might help. But I think that fundamentally we shouldn't

3 make approvability decisions based on this because the data

4 aren't there to allow us to do it. So, I throw that out

5 for discussion so we can get rid of it before we go on.

6   Bob?

7   DR. TEMPLE: It's an interesting thought. We

8 occasionally do say what is now known about something

9 although we don't we do it very often. It gets very, very

10 difficult. For example, I'm sure most people think that

11 ACE inhibitors should be used in the population that was

12 studied in HOPE. The fact is only one drug of that class

13 has been studied. There isn't a second study. The result

14 was dramatic and, incidentally, not so impressive in the

15 United States.

16   (Laughter.)

17   DR. TEMPLE: For what you will choose to make

18 of that.

19   Well, if you really wanted to set the whole

20 stage, you'd have to write a little essay describing all

21 those things and say what you should when one member of a

22 class does something. How much should you believe about

23 all the others? And then by the time you're done talking

24 about people with other risks -- for example, if you have a

25 little heart failure, well, there's a lot more data on ACE

1   inhibitors than there is about AII blockers. So, that

2   might influence you.

3   This is not an easy thing to write. I think

4   you should write a chapter. But we would certainly

5   consider trying to provide some perspective as best we can.

6   But our trouble is we're not supposed to infer things too

7   much. We're supposed to be even more data-dependent than

8   you guys are, and that really means you can't speculate at

9   all in labeling. So, it's a problem.

10   DR. BORER: Steve?

11   DR. NISSEN: The reason we have this dilemma,

12 of course, is that a therapy, ACE inhibitors, in this

13 population became virtually the gold standard without ever

14 coming before the FDA for approval. That is to say, ACE

15 inhibitors for renal protection. If you talk to

16 diabetologists and to nephrologists -- you guys correct me

17 if I'm wrong -- but for many a year everybody has put these

18 patients on ACE inhibitors for their renal protective

19 effects. That's reality and we have not changed that. So,

20 you see the reason it's a little bit different than some

21 other circumstances is not so much a question of competing

22 risks, it's also a question of are ARBs as good, even

23 though ACE inhibitors were never approved, so that what

24 will the public policy implications be of approving under

25 those circumstances.

1   DR. TEMPLE: It's not not approved. They

2   weren't studied.

3   DR. NISSEN: I understand.

4   DR. TEMPLE: It's not the same thing.

5   DR. NISSEN: Okay, I understand.

6   But I'm saying a therapy that was neither

7   studied nor approved has become the gold standard. So, now

8   you've got this gold standard that's actually made of

9   bronze, and now what we're looking at is what evidence do

10   we require in order to set the conditions in motion for

11   people changing that practice.

12   DR. TEMPLE: I will say something about that.

13   This comes up when we try to think about how something

14   compares to "available therapy." Well, what does available

15   therapy mean? What people do or what we've actually

16   written up? We actually have just put out a final guidance

17   on this. This is important because it determines whether

18   you're a priority drug or not and other things that you

19   probably don't care that much about.

20   What we have is a strong bias toward available

21   therapy, meaning something that has been through our

22   review. You might think we would think that and you

23   wouldn't be surprised. But it means someone has bothered

24   to pull the data together and put it forth, and you get

25   extra credit for having done that. Our inclination is to

1   think that approvals and things like that should take into

2   account what has been well documented, but probably

3   shouldn't worry too much -- you may choose to worry about

4   it; that's your privilege -- about what might be true but

5   nobody has ever bothered to study or been able to study.

6   It would be hard to study those things now. That's

7   probably the reason nobody does it.

8   In labeling and other places, we do tend to

9   focus most on what's actually known and studied and been

10   before us and been reviewed by expert committees and less

11   on things that might be true but haven't been studied.

12   DR. BORER: Dr. Haffner, did you have a comment

13   before Paul and Beverly?

14   DR. HAFFNER: Yes. First of all, I understand

15   I have been active in the ADA in professional practice, and

16   this is a very difficult issue. In fact, the ADA came out

17   with new recommendations on their professional practice

18   recommendations in January and they disagree in different

19   position papers. The hypertension paper said that ARBs and

20   ACEs were both first line partially because we hedged our

21   bets for the cardiovascular issue. The nephropathy

22   guidelines said that ARBs were first line and ACEs were a

23   second choice. And this is actually the same professional

24   organization.

25   I should mention that the entire thing is

1   driven by HOPE data, and the HOPE study, as you know,

2   didn't actually examine this issue. There is no ACE data

3   in people with advanced renal failure. And if you go back

4   to the two years before HOPE came out, in fact many people

5   thought that ACE inhibitors might not be so great on the

6   basis of the UK PDS data. So, HOPE isn't the only study in

7   diabetics. The UK PDS data compared this relative to

8   atenolol and actually atenolol did a little bit better than

9   an ACE inhibitor in spite of the fact the ACE inhibitor is

10 better tolerated.

11   So, I agree. I think ACEs are a good therapy.

12   I don't think they have been well established in

13 progression of renal disease, but I don't frankly know in

14 these sorts of patients whether ACEs are better than ARBs.

15   We don't actually have that sort of comparison, and my

16 guess is we'll never actually have that comparison. So, I

17 think there is some general uncertainty and you have to

18 look beyond the most recent study. There is a long history

19 there with some real questions involved in it.

20   DR. BORER: Thank you. I should point out too

21 that the issue of approval of ramipril for the

22 renoprotective effect that was putatively seen in HOPE was

23 voted against by this panel when it came up a couple of

24 years ago.

25   Paul and then Beverly.

1   DR. ARMSTRONG: In responding to your

2   challenge, Mr. Chairman, which I think is were this drug to

3   be approved, what would the label look like, my own view

4   would be that it does work in a very specific population

5   that we've heard about today and does not cause harm

6   relative to some other issues that we would be concerned

7   about that coexist in these patients and indeed in the

8   broader population that we all see. So, I think crafting a

9   label, to the extent that we know what it does or we think

10 we know what it does in a fairly select population where a

11 number of issues that patients receive ACE inhibitors for

12 are not present, would be prudent. We obviously wish to

13 avoid the issue that Dr. Carabello has raised which would

14 be that a broad number of patients at risk to

15 cardiovascular disease who are receiving ACE therapy now

16 for good indications and evidence-based medicine would not

17 be switched off them because they have co-existent renal

18 disease.

19   DR. BORER: Beverly?

20   DR. LORELL: Thank you. Well, that really

21 underscores a concern that I had along this issue. I think

22 that if cardiovascular events were defined not as a

23 retrospective, ad hoc look but as a clear secondary

24 endpoint in this trial -- and I think one of the concerns

25 in my mind, just as was pointed out in the presentation

1   earlier today, is the data on cardiovascular events were

2   inconsistent in this trial. They didn't all go the right

3   way. The cardiovascular death event -- and cardiovascular

4   death was 57 percent of all deaths in the losartan arm --

5   in fact, went the wrong way. So, I think it's an added

6   source of some unease in this discussion that the

7   cardiovascular death, in fact, looked to go the wrong way.

8   The data were not internally consistent in sitting on the

9   left of the line, and this committee really wrestled with

10 that issue as a component of our decision regarding a

11 different ARB for the same indication not too long ago.

12 So, it is problematic.

13   DR. BORER: Yes. It's a problem. Clearly,

14 again, the cardioprotective studies didn't involve people

15 with near end-stage renal disease and whatever. So, it's

16 hard to get to. But that's why I think, at the end of the

17 day, we may have to suggest to the FDA that it do some

18 label crafting.

19   Bob?

20   DR. TEMPLE: Remind me. But except for HOPE,

21 most of the cardioprotective effects of ACE inhibitors have

22 been shown in people with ventricular dysfunction.

23 Somebody needs to correct me if this is wrong, and that's

24 not true of HOPE. So, these people didn't have that. The

25 only figure that related to heart failure actually was

1   going the appropriate way. So, I'm not so sure, except for

2   HOPE, which I do find inspiring -- it's not quite clear

3   what the effects of ACE inhibitors are in all those other

4   settings in the absence of ventricular dysfunction. I

5   think that's true.

6   DR. BORER: Yes, that's true, and I think you

7   would have said HOPE is hopeful, had you the facility with

8   words that Dr. Konstam does.

9   (Laughter.)

10   DR. TEMPLE: Of course, as someone who lives in

11 the United States, I'm not sure I know about that

12 statement.

13   DR. BORER: Why don't we move ahead to the

14 questions.

15   But before we do that, I'm going to have to ask

16 a point of information. It says on here that there is to

17 be a break at 3 o'clock. Now, it's a quarter of 3:00. I'm

18 wondering if we're mandated to take that break? We're not?

19   We're not. Okay.

20   Oh, excuse me. One thing I've forgotten to do

21 that I should have done is I didn't ask if there was any

22 public comment. The meeting should have been open at 1

23 o'clock for public hearing. We didn't have any formal

24 requests, but was there anyone who came here to make a

25 public statement?

1   (No response.)

2   DR. BORER: No. The record should show that

3   there was no request for public comment.

4   Now let's go on to the questions here. The

5   Cardio-Renal Advisory Committee is asked to opine on the

6   benefits and risks of losartan, an angiotensin II receptor

7   antagonist, for the treatment of nephropathy in type II

8   diabetes. Reviews of chemistry, pharmacology, toxicology,

9   biopharmaceutics, biometrics, and clinical safety present

10   no apparent barriers to its approval.

11   The committee is asked if it believes the

12   strength of evidence for a treatment benefit supports

13   approval.

14   The direct evidence is derived from one study.

15   RENAAL enrolled 1,513 subjects with type II diabetes,

16   hypertension, proteinuria, albumin to creatinine ratio

17   greater than or equal to 300 milligrams per gram, and serum

18   creatinine between 1.5 and 3 milligrams per deciliter.

19   Subjects were randomized to placebo or losartan, titrated

20   as tolerated from 50 milligrams to 100 milligrams, and

21   followed for a mean of 2.4 years. The primary endpoint was

22   a time-to-first-event comparison of losartan and placebo

23   for death, end-stage renal disease, or doubling of serum

24   creatinine. The result was an estimated risk reduction of

25   16 percent, p equals .022, with treatment groups diverging

1 after about 6 months.

2   So, our first question. There were 686 total

3 endpoint events in the placebo and losartan groups, 32

4 fewer in the losartan group than on placebo. One of the

5 characteristics of a none-too-small p value is that the

6 result is sensitive to the handling of subjects with

7 incomplete data. And Tom actually got into that in some

8 detail earlier. In RENAAL, there were no subjects

9 randomized but not treated, no subjects with questioned

10 event adjudication, and no subjects lost to follow-up for

11 end-stage renal disease or mortality.

12   So, 463 subjects discontinued the drug. How

13 were they handled? How should they have been handled? And

14 what effect did the sponsor's rules for handling dropouts

15 have on the credibility of the principal findings?

16   We can deal, I think, with all of those

17 together. Tom, do you want to start off?

18   DR. FLEMING: How were the patients who

19 discontinued drug handled? My understanding is they were

20 all followed from that point forward. All of them were

21 followed for the end-stage renal disease/death endpoints.

22 As I understand, 40 percent of the person-years of follow-

23 up subsequent to that time, though, patients were not

24 followed for the change in doubling in creatinine time. As

25 a result, the procedure used by the sponsor to handling

1 those patients who discontinued was fully appropriate,

2 giving us complete follow-up information about end-stage

3 renal disease and death.

4   There is, however, a problematic issue arising

5 with the 267 patients who did, in fact, have

6 discontinuation of their follow-up of doubling in serum

7 creatinine time prior to having any of the elements of the

8 triple endpoint. While those people did, in fact, have

9 subsequent follow-up for end-stage renal disease/death, it

10 makes the triple endpoint analysis a bit more difficult to

11 interpret, but the double endpoint, end-stage renal

12 disease/death, analysis is fully free of any of that

13 concern.

14   DR. BORER: JoAnn, you were the committee

15 reviewer. Do you have any other issues?

16   DR. LINDENFELD: No. I have nothing to add to

17 that. I agree.

18   DR. BORER: Does anybody around the table

19 disagree with those conclusions?

20   (No response.)

21   DR. BORER: No? Great.

22   We will move on to number 2. Of the 686

23 primary endpoint events on placebo or losartan, 52 percent

24 were creatinine elevation and 48 percent were death or need

25 for dialysis. All of the treatment difference was the

1 effect on creatinine. Was this a statistical anomaly? Was

2 this because there were just so few clinical outcome

3 events? Was this because the effect on clinical outcome

4 would not be expected over 54 months? Was this because an

5 effect on serum creatinine is a poor predictor of clinical

6 outcome?

7   Why don't we stop there, and JoAnn, why don't

8 you take those four together? Then we'll go on to number

9 5.

10   DR. LINDENFELD: Let me start off with was this

11 a statistical anomaly. I don't believe so, and I don't

12 believe that this was just that there were so few outcome

13 events. I believe that the serum creatinine is a predictor

14 of clinical outcome. I think when we look at the

15 combination of end-stage renal disease and death, that's

16 positive. So, I would say that, to just phrase this a

17 little bit differently, we did see the double endpoint of

18 end-stage renal disease and death was positive, and I think

19 the creatinine is predictive of that. So, let me answer

20 that that way rather than these specific questions.

21   DR. BORER: Okay. With that having been said,

22 what we saw I think was that when you looked at time to

23 first event, in fact, all the action was here, but when you

24 looked beyond that to death or end-stage renal disease, bad

25 things happen maybe because the disease progressed, which I

1   think is what you're saying.

2   DR. LINDENFELD: Exactly.

3   DR. BORER: Bob?

4   DR. TEMPLE: It still seems strange and not

5   fully explained although, for the reasons you just gave,

6   not worrisome. When the first thing that happens is end-

7   stage renal disease, somehow that's not influenced. When

8   end-stage renal disease follows creatinine doubling, which

9   in some sense it always must, then it turns out to be okay.

10   There must be something in the analysis that led to that

11   conclusion because it all doesn't make sense, but maybe it

12   doesn't matter for the reasons you just gave. There's

13   something odd about it.

14   DR. BORER: Statistical anomaly.

15   Before we go on to 2.5, does anybody on the

16   committee have a different view of 1 through 4? Steve?

17   DR. NISSEN: I just would say if it's a

18   statistical anomaly, if I'm not mistaken, the same thing

19   was seen in the previous trial, the IDNT trial. So,

20   there's obviously something biologically going on here, and

21   I worry about these people who didn't have creatinine

22   measured, whether somehow that's influencing it. How do

23   you get to have end-stage renal disease before doubling

24   your creatinine? Well, one of the ways to get there is

25   nobody has your creatinine in hand, and so they don't know.

1   Maybe that's what's going on here, Bob. That would be one

2   of my guesses.

3   DR. TEMPLE: But you'd still expect it to be

4   influenced. If there's an overall delay, there ought to be

5   an overall delay on end-stage renal disease where you

6   didn't get a creatinine just as much as where you did.

7   DR. NISSEN: I hear you.

8   DR. TEMPLE: There's something wrong with the

9   analysis here that we haven't been smart enough to figure

10   out. That's what I think.

11   DR. BORER: Tom, are you smart enough to figure

12   it out?

13   DR. FLEMING: Well, I just want to take the

14   burden off the statisticians and put it back on the

15   clinicians here.

16   (Laughter.)

17   DR. FLEMING: I can figure it out

18   statistically, but I don't know what the true clinical

19   answer is.

20   Look at figure 379. You can't but just

21   remember when you did look at figure 379, which is the

22   figure that showed what was the time to end-stage renal

23   disease distribution. Remember we were saying those curves

24   overlapped in the first 18 months and then separated

25   thereafter. So, statistically part of the reason that we

1   are seeing the numbers of people who have end-stage renal

2   disease as their first event not being different between

3   arms isn't surprising when I look at this curve.

4   Now, I'm going to ask my clinical colleagues

5   the harder question. Why is it, if there's an effect, that

6   it doesn't show up at all for the first 18 months and then

7   emerges thereafter?

8   DR. BORER: Yes. I will try to answer that

9   even though I'm not a nephrologist.

10   DR. FLEMING: Before you answer it, because I

11 really do want you to, one other aspect of this that does a

12 bit to complicate things when we look at the triple

13 endpoint is when you look at doubling first and then you're

14 not necessarily following time to doubling in all people,

15 quite frankly I have a lot of trouble understanding the

16 triple endpoint when we have 267 people who aren't followed

17 for one element for a significant period of time. So, I

18 prefer to look at the double endpoint or the single

19 endpoint here, ESRD, and in this endpoint the question I

20 would ask you clinically is, is there an explanation that

21 you have for why you don't prevent events in the first 18

22 months and then you do thereafter?

23   DR. BORER: The entry criteria for this study,

24 as I understand them, was a creatinine of 1.5 to 3. Renal

25 failure nominally is a creatinine of 6. So, nobody entered

1 even close to renal failure and they had to at least double

2 their creatinine to make it, and it takes some time to do

3 that. So, I'm not at all bothered by the fact that there

4 was a period of no effect when you look at the ESRD as the

5 endpoint.

6   Bob?

7   DR. TEMPLE: I guess one explanation is let's

8 hypothesize that there's a delay before you accomplish much

9 with this therapy. That means the end-stage renal disease

10 endpoints that turned up as initial endpoints were people

11 who turned up with that problem very early. The die had

12 been cast, if you like, and wasn't as influenceable as

13 later end-stage renal disease. That makes some sense.

14 Maybe we can model that or something.

15   DR. NISSEN: But the data was to the contrary,

16 though, because the higher your creatinine at the

17 beginning, the more likely you were to see a benefit. If

18 you look at the subgroups of creatinine less than 2 and

19 greater than 2, almost all the benefit was in the people

20 who started out greater than 2.

21   DR. BORER: Ray, would you like to weigh in

22 here?

23   DR. BAIN: Yes. We did look at those 64 and 65

24 end-stage renal disease events that occurred without a

25 doubling, and we looked at a number of factors to try to

1 understand why this occurs. One of the things that was

2 curious was you remember that the average baseline serum

3 creatinine across all groups was 1.9. If you look at those

4 64 and 65 patients who went to dialysis without doubling,

5 they had a higher serum creatinine. So, they were worse

6 off coming into the trial and maybe had a different

7 trajectory.

8   DR. BORER: Let's go on to 2.5. Is everybody

9 else satisfied with this discussion so far?

10   Let's go on to 2.5. Subjects who experienced

11 doubling of serum creatinine could later have end-stage

12 renal disease or die. When these events are counted, the

13 relative risk of death on losartan was 1.02 and the risk of

14 needing dialysis .71. Are these data supportive of an

15 effect on clinical outcome?

16   I think we just answered that one.

17   3. In RENAAL, the mean blood pressure was

18 significantly lower in the losartan group than in the

19 placebo group. How does one know that blood pressure alone

20 was not responsible for losartan's treatment effects? And

21 3.2, is the mechanism of the treatment effect relevant to

22 the description of trial outcomes?

23   JoAnn?

24   DR. LINDENFELD: I'm not sure we absolutely

25 know that this wasn't a blood pressure effect, but we saw

1   the data corrected for differences in systolic blood

2   pressure, pulse pressure, which made more of a difference

3   than the mean blood pressure. Although the effect was

4   somewhat less, the effect was still present. I feel

5   relatively assured, based on this and other data comparing

6   amlodipine that we've reviewed previously, that this wasn't

7   all a blood pressure effect.

8   DR. BORER: JoAnn has added a new wrinkle to

9   the discussion that we'll come back to later. Are there

10 any other comments about that? Steve?

11   DR. NISSEN: Yes. I basically agree.

12   The difficulty I have is estimating the

13 magnitude. Again, the reason it becomes relevant here is

14 this issue of a relatively marginal statistical

15 significance for the overall trial. When you've got a

16 marginal result, then this analysis becomes very important.

17   So, I think it's very difficult to estimate the effect of

18 blood pressure here. They made their best guess at it. It

19 was very reasonable and so on. But if it were a larger

20 effect due to blood pressure, then that marginal p value

21 becomes even more marginal. So, it becomes relevant in the

22 context of a very subtle drug effect.

23   DR. BORER: Dr. Brem?

24   DR. BREM: Well, I'd like to come back to the

25 dose issue again. The design of the study was to titrate

1   the medication up to dose effect and then there seems to be

2   a paradox that, once you've done that, there's no effect of

3   blood pressure on renal preservation. I'm still having

4   trouble grappling with the separation.

5   If the blood pressure isn't important, why

6   didn't everybody get 100 milligrams and then you titrate

7   the blood pressure so that you know 100 milligrams works or

8   it doesn't work. Now, we have a third of the patients who

9   had 50 milligrams. Again, in reference to a prior study

10 that we reviewed in January, there was a dose dependence.

11 So, I still come back to separating the direct effects on

12 the kidney from those that are directly related to blood

13 pressure.

14   DR. BORER: Yes, that's a toughy. For myself,

15 I'd come back to the Asian data that we saw. The effect on

16 outcome events was biggest and the effect on blood pressure

17 was negligible, if any, which would be consistent.

18   Blase, was that your light on or Alan?

19   DR. CARABELLO: The blood pressure in the

20 Asians was a little higher.

21   DR. BORER: But the treatment effect was less.

22   The effect of losartan relative to placebo was the least

23 on blood pressure.

24   Alan, were you going to say something?

25   DR. HIRSCH: I was just going to repeat my same

1 point. I feel like I've gained some support here. Just

2 that I think it's hard to know the blood pressure effect

3 simply using adjustments within the study regressions.

4 This committee has often looked at this issue and

5 determined that in different populations one can predict

6 different effects of a net blood pressure difference. I

7 would simply say for the record I don't think we know.

8   DR. KEANE: And if I may just underscore the

9 fact that we actually titrated or up-dosed the losartan to

10 achieve a blood pressure effect. We weren't looking at the

11 reverse of that. There were at least three-and-a-half

12 additional agents that these patients were on at any given

13 time interval. So, it makes it very difficult to tease out

14 what actually is going on with the effect of the drug as

15 you change the dose.

16   DR. BORER: Tom?

17   DR. FLEMING: Just maybe to draw another

18 distinction here and follow up on what Alan is saying.

19 There are at least two ways to look at adjustments for the

20 blood pressure. As I see it, the particular differences

21 are in the systolic blood pressure. Those are apparent at

22 baseline as well as over time. The imbalances at baseline

23 we can handle through a traditional covariate adjustment,

24 and both that factor and proteinuria are imbalanced at

25 baseline. As the analyses that have been presented to us

1   show, the particular influential covariate there is

2   proteinuria, much more so than the imbalance in baseline of

3   systolic blood pressure.

4   But they started off, I think, at 153 versus

5   150, and over time they ended up at 142 or 143 against 140.

6   So, the separation was maintained.

7   So, the other question to ask, beyond whether

8   there was confounding because of baseline imbalance, is to

9   what extent is the effect of treatment mediated through the

10 changes or differences that are seen over time in blood

11 pressure. Bob was talking earlier about the caution one

12 has to have when you're using time varying covariates to

13 essentially try to address the question, is the effect of a

14 treatment on outcome entirely mediated through a marker, in

15 this case blood pressure over time.

16   One classical approach statistically to do that

17 is to use what's called a time varying covariate, not just

18 to adjust for differences in that covariate at baseline,

19 but differences in that covariate over time, so that at the

20 time of any event, you take into account what the person's

21 blood pressure was at that particular time.

22   The caution one has to have is that the way you

23 interpret that, if there's no difference after adjusting

24 for that covariate, isn't that treatment is not influencing

25 the outcome, but the entire effect of treatment seems to be

1   accounted for by the effect of treatment on that covariate,

2   on that marker.

3   When this is done here, some of the effect is

4   accounted for by the differences in blood pressure,

5   although it looks like, from what I've seen, the majority

6   of this effect is still there even when you adjust for the

7   time varying covariate of blood pressure over time.

8   I agree with Alan's point about, however, as

9   sophisticated as these analyses are, you've got to

10   interpret them with great caution. For example, that

11   analysis is basically assuming that if the time varying

12   blood pressure is, in fact, influencing risk of outcome,

13   it's specifically mediated through what that exact last

14   measured value was. Maybe it isn't. Maybe it has more to

15   do with what the value was over a period of 6 months before

16   that time or a combination of that blood pressure and any

17   other things, such as diastolic blood pressure or other

18   factors.

19   So, it's statistically the best approach I can

20   think of doing. It's what the sponsor did. It gives you a

21   clue about whether or not the effect of treatment is at

22   least partially mediated through these differences in blood

23   pressure, but it's only a clue and one has to interpret it

24   very cautiously.

25   DR. BORER: We've said a lot of things here and

1   I'm going to try to summarize them just to make sure

2   everybody agrees so that the FDA has a clear statement.

3   With regard to 3.1, how does one know that

4   blood pressure alone was not responsible for losartan's

5   treatment effects? I think the general consensus is we

6   don't know, but we think it probably didn't because of all

7   the things that people have said here.

8   And is the mechanism of the treatment effect

9   relevant to the description of trial outcomes? Well, we

10   don't really know that either, but we think that the

11   outcome is not solely based on the effect on blood

12   pressure, but we can't say that rigorously.

13   Does everybody accept that? Okay. FDA you've

14   just heard it.

15   Comment on other secondary endpoint in RENAAL.

16   There was a prespecified analysis of time to first

17   cardiovascular death, nonfatal MI, hospitalization for CHF

18   or unstable angina, stroke, or coronary or peripheral

19   revascularization. There were 515 such events with no

20   significant difference in the distribution between groups.

21   Is this evidence of a lack of clinical benefit? Is it

22   comforting that there was a lack of apparent harm? Were

23   there simply too few events to show a meaningful effect?

24   JoAnn, why don't you go ahead on 4.1?

25   DR. LINDENFELD: I think that there are too few

1   events here, too short a period of time, and a population

2   that does not have as high a cardiovascular risk as we

3   might expect. So, I would say that this is not necessarily

4   lack of clinical benefit, it also makes it difficult to say

5   that there's lack of harm. We see very little difference.

6   I'm comforted that there's no trend here toward harm. I

7   think we'd have to follow these patients longer to see

8   evidence of clinical benefit. I'm not disturbed, from what

9   I've heard, by the lack of clinical benefit. I think that

10 we just would have to follow more patients for a more

11 prolonged period of time.

12   DR. BORER: Is everybody in agreement with

13 that? Are there any other comments? Tom?

14   DR. FLEMING: Just to maybe refine, I agree

15 with JoAnn, just to add a bit to it in the spirit of what

16 we also said three months ago in January.

17   It's very relevant to assess these

18 cardiovascular events. Clearly, a major portion of what's

19 happening to these patients clinically that's very

20 important goes beyond the specific renal events into the

21 cardiovascular arena.

22   If one looks at the aggregation of these six

23 components, one sees an estimate of about a 9 percent

24 decrease. If one had expected to have had sensitivity, I

25 guess I would have to say to you clinically how big does

1 the study have to be, and the answer to that depends on

2 whether you would require a 30 percent relative reduction

3 or a 10 percent relative reduction or a 5. If you actually

4 required a 10 percent relative reduction to be clinically

5 meaningful, which is consistent with what the point

6 estimate is here, we would have needed to do a study of

7 about 10,000 to 15,000 people. With 10,000 to 15,000

8 people, instead of 1,500 people, we would have been

9 adequately powered to discern the difference between a 10

10 percent reduction and no reduction.

11   So, I would disagree with the sponsor who, at

12 one point, said these data show no effect on these

13 endpoints. I think these data suggest a 10 percent

14 reduction, and it's not possible to discern whether or not

15 that's reliable evidence of a reduction or consistent with

16 random variability with no true reduction at all.

17   I also, though, break this down a little bit

18 further to say, as we said three months ago, not all of

19 these are equally important, and we wanted in particular

20 three months ago to focus on cardiovascular events, MI, and

21 stroke. When I look at those sub-elements, it's about a 5

22 percent relative reduction if we wanted high sensitivity.

23 If you view a 5 percent relative reduction to be clinically

24 relevant, you want to distinguish that from no reduction,

25 it would take 50,000 people.

1   So, my overall sense here is these data are

2   suggestive a reduction of 10 percent. That's consistent

3   with none. At least we can rule out that there's not a 30

4   percent reduction. So, if you say that's what we need,

5   then this study is conclusively ruling out the kind of

6   benefit you would expect or you would want to see. I

7   suspect that we wouldn't say there has to be a 30 percent

8   reduction. On the other hand, we could rule out that

9   there's harm by 10 percent.

10   Now, one of the comments that came up is look

11   at cardiovascular death though. That's going in the wrong

12   direction. That's 90 versus 79, 10 percent in the wrong

13   direction. That is something to think about. That is, in

14   fact -- and I will maybe discuss this more -- a signal that

15   there might be an increase, but in that small subgroup,

16   that's entirely consistent with worse than a 10 percent,

17   maybe a 30 percent, reduction or entirely consistent with

18   no reduction at all to a 10 percent benefit.

19   So, in the same sense that I would caution

20   against looking at 50 against 68 nonfatal MIs, saying, ah,

21   we've clearly prevented nonfatal MIs, I would caution

22   against looking at cardiovascular deaths of 90 versus 79,

23   saying we've done something bad there. When we start

24   subdividing these into these sub-elements of the six, we

25   really push the data beyond the limits of what they can

1   reliably be telling us.

2   So, my overall view of this is an extension of

3   what JoAnn has said. This study clearly should have, as it

4   did, look at cardiovascular events. It's suggesting a 10

5   percent reduction, but it would have had to be 5- to 10-

6   fold larger to be able to reliably discern whether that's

7   truth or whether that's in fact random variability off of

8   no difference at all.

9   DR. BORER: Is everybody in agreement with Tom?

10   Are there any concerns? Paul?

11   DR. ARMSTRONG: Are we going to have a chance

12   to talk about the potential for harm at some other point in

13   the questioning sequence? I don't see it, and if you want

14   to reserve it to the end, that's fine.

15   DR. BORER: We will in the very next question.

16   DR. ARMSTRONG: I'll keep my powder dry.

17   (Laughter.)

18   DR. BORER: Actually the one after 4.2. Once

19   we get to 5, we get into the meat of the issue here. I'm

20   sorry about that. We're talking about proteinuria, and I

21   said the "meat" of the issue. Sorry.

22   (Laughter.)

23   DR. BORER: 4.2. Proteinuria, assessed as

24   milligram per gram of creatinine was lower on losartan at

25   all times after baseline. Additionally, the rate of loss

1   of renal function, assessed by the slope of reciprocal of

2   the serum creatinine over time, was significantly lower by

3   about 13 percent in the losartan group. What did these

4   results contribute to the confidence one has in the

5   clinical benefits of losartan in RENAAL?

6   DR. LINDENFELD: These add confidence to the

7   benefits we've seen. I think these are all consistent

8   based on what we think the pathophysiology of this disease

9   is, to see a reduction in proteinuria and a decrease in the

10   slope of creatinine, and the fact that also that the

11   decrease in proteinuria correlates with the outcome. So, I

12   think these are all consistent and add somewhat to the

13   confidence of the results.

14   DR. BORER: Are we all okay with that? Okay.

15   Number 5. I'm sorry, Paul, I misspoke. We'll

16   get to the issue that you raised somewhere in here, but not

17   quite with this one because the focus of number 5 is a

18   little different.

19   Are the results of RENAAL alone an adequate

20   basis for approval of losartan for the treatment of type II

21   diabetic nephropathy?

22   A drug with a related mechanism of action,

23   captopril -- oh, sorry. I'm moving on here.

24   Are the results alone an adequate basis for

25   approval?

1   DR. FLEMING: Just for clarification, you were

2   right when you told Paul that it's question 5. I assume in

3   question 5 we now bring everything together, including

4   safety.

5   DR. BORER: Yes, okay. Paul, did you want to

6   say something about that?

7   DR. ARMSTRONG: Well, I wanted to reflect on

8   the fact that in the safety presentation -- first of all,

9   I'm convinced this drug is effective. I'm also convinced

10   that it has the potential for harm and that in

11   understanding that, a better appreciation of some of the

12   issues around hyperkalemia in particular seems to me to be

13   germane.

14   So, where I'm going with this, Mr. Chairman, is

15   that the sponsor in the safety presentation suggested that

16   there were no deaths attributable to adverse events. Yet,

17   we saw data on two or three patients who died suddenly who

18   had potassiums of 7 and 6 as the last measured biochemical

19   indicators, which to me, while not establishing cause and

20   effect, nonetheless we're not able to dismiss that the

21   sudden deaths in those patients were not attributable to

22   those potassiums.

23   Although we've heard from elegant and

24   sophisticated consultants about the fact that hyperkalemia

25   is common with these patients and therefore we can expect

1   that 1 out of 4 or 1 out of 10 might have either

2   hyperkalemia or potassiums greater than 6, many physicians

3   treating these patients will not be as sophisticated as

4   those in this room. So, the issue around how to balance

5   that and to weigh it into a label and a caution is the

6   issue I wanted to bring forward because I was uncomfortable

7   that we have had adequate discussion around that. And I

8   say that still with the notion that this is an effective

9   drug.

10   DR. BORER: We ought to have a little bit of

11   discussion about that. I think that we have to remember,

12   in the context of that discussion, that in talking about

13   risk, we have to consider risk in the context of its

14   acceptability for the intended use, and the sponsor did

15   give us an all-cause mortality, all-cause horror show, risk

16   versus benefit relationship analysis. So, ultimately we're

17   really talking about the relation of benefit to risk.

18   Having said that, this is an issue that we

19   didn't really get into in any major way. Perhaps we ought

20   to talk about that a little bit.

21   Bob, did you want to say something?

22   DR. TEMPLE: Yes. It may not be obvious from

23   the question, but recall in January in a similar situation

24   the issue was whether a single study with a p value in the

25   neighborhood of .02 was sufficient evidence. So, this is

1   intended to introduce that --

2   DR. BORER: Yes. We'll get to that.

3   DR. TEMPLE: I just wanted to be sure.

4   DR. BORER: It hit me over the head like a

5   sledgehammer that that's where we were going here, but

6   let's get the safety issue off the table first. Beverly?

7   DR. LORELL: Well, the discussion today has

8   raised an issue that I hadn't thought about previously, and

9   that deals with the time course of apparent benefit that

10   Tom Fleming brought up where one must wait for about 18

11   months to see the curves begin to diverge.

12   We've also seen some evidence which is

13   suggestive. Although the trial was not designed to look at

14   this, there are some very elegant data suggesting that the

15   likelihood of benefit is greatest in those patients who

16   have a more severe degree of renal dysfunction, whether as

17   estimated as a marker using serum creatinine or magnitude

18   of proteinuria.

19   So, I think the risk of hyperkalemia for the

20   general public is a weighty one in that the issue comes up,

21   do we know whether or not we are exposing a population that

22   is going to have much less relative benefit in terms of

23   renal protection to a risk of hyperkalemia. I guess that

24   here what I think we didn't quite ever see that I think Dr.

25   Hirsch brought up is it would have been nice to see sort of

1   the time course of time to hyperkalemia to understand

2   whether or not the time course of exposure to risk of an

3   event that is at minimum a huge hassle for the clinician

4   and the patient and at worst life-threatening, follows a

5   similar time course of benefit or whether there's a

6   discrepancy there. I'm not sure if said that clearly.

7   DR. BORER: No, you did. It sounds as if we

8   don't, at first glance, have the data to answer the

9   question rigorously.

10   But before Dr. Kopp weighs in here, Paul

11   specifically raised this issue in the context of a labeling

12   discussion, and I would ask you whether you think that your

13   concern here is one that rises to the level of

14   approvability or is this something that really requires a

15   big bold caution in the label because we just don't know

16   and we're not sure exactly what subgroup really benefits?

17   And obviously hyperkalemia kills. So, is this a labeling

18   issue? Is this an approvability issue? What do you think?

19   DR. LORELL: I'm not sure about it. I think in

20   looking at the numbers that I've written down during the

21   day, there was a sizeable number of patients who had

22   hyperkalemia of a magnitude that would, at minimum, warrant

23   getting the patient to the emergency room to give an anti-

24   hyperkalemic therapy. It looks like the development of

25   even a single hyperkalemic 6.0 or higher event was somewhat

1   predictive of death. So, I guess I would welcome

2   discussion among others on the panel on this.

3   DR. BORER: Dr. Kopp?

4   DR. KOPP: My comment was actually not so much

5   about hyperkalemia. I don't know if it's going to be off

6   target, but it relates to this issue of clinical benefit

7   and who benefits the most. It's true if the outcome is not

8   seeing dialysis, not going on dialysis during the course of

9   the study, the greatest benefit was in those who had the

10   highest levels of creatinine. But if we understand this

11   drug as slowing the rate of decline of renal function, then

12   you can argue that the person who starts it earlier with a

13   lower creatinine will enjoy more days of not having

14   dialysis because their rate has slowed. So, they might

15   enjoy 1 or 2 years of being dialysis-free, whereas the

16   patient who begins it late with a creatinine of 3 or 4 has

17   fewer months or years of benefit.

18   DR. BORER: Bob?

19   DR. TEMPLE: Is it a fair presumption that the

20   people most likely -- maybe it's known from the data -- to

21   become hyperkalemic are the people who were more impaired?

22   I ask that because these drugs are already approved for

23   the treatment of hypertension, irrespective of whether they

24   prevent renal dysfunction, and they, ACE inhibitors, and

25   beta blockers all increase the rate of hyperkalemia. We

1   know that. It's in the label and there are warnings about

2   it.

3   So, are we looking at something that's worse

4   than usual, and if it is worse than usual, is it in the

5   people who you think get the most benefit or is it in

6   everybody, including the people who don't seem to benefit

7   very much; that is, the people who aren't as impaired?

8   The company may have data on this.

9   DR. BORER: Yes. Do we have an answer to that

10   question, Dr. Keane?

11   DR. KEANE: Yes. I was just going to show,

12   first of all, one of the slides to show the overall

13   magnitude of the potassium levels throughout the entire

14   trial to reemphasize the fact that potassium is in the

15   range, throughout most of the trial, in the upper 4

16   milliequivalents so that we're really not seeing a huge

17   degree of hyperkalemia in this patient population overall.

18   DR. ARMSTRONG: Mr. Chairman, 1 out of 4

19   patients were hyperkalemic with losartan. So, when you say

20   you were not seeing a lot of patients, for me 1 out of 4 is

21   a substantial number. I'm sorry.

22   DR. NISSEN: This slide is not relevant here.

23   DR. BORER: Yes. The average values may not

24   speak to the point.

25   DR. NISSEN: They don't speak at all to it.

1   DR. KEANE: This is the percent of patients

2   with an event described as hyperkalemia in the losartan

3   group over time compared to the placebo group.

4   DR. HIRSCH: So that is a fourth. I think our

5   concern is not the mean but obviously those patients who

6   lie near the limits would be at risk.

7   DR. TEMPLE: Is that a percent or a fraction?

8   What is on the y axis?

9   DR. KEANE: That's percent of patients with an

10 event.

11   DR. BORER: So, it's .2 percent.

12   DR. TEMPLE: Is it 3 percent, not 30 percent?

13   DR. KEANE: 25 percent.

14   DR. TEMPLE: So, it isn't the percent. It's

15 the fraction.

16   DR. BORER: Beverly?

17   DR. LORELL: I'm not sure I know what to do

18 with this. But I think it's of interest in thinking about

19 this because the time course of accumulating severe

20 hyperkalemic events starts early and progresses. So, we

21 have, in terms of thinking about risk benefit, a period

22 that goes for many months where there's no difference

23 between placebo and intervention up against a period of

24 enhanced risk. I think all would agree, relative to your

25 question, Bob, that this is a different level of risk of

1 hyperkalemia than is seen in the hypertension trials. In

2 fact, the hypertension trials would have excluded many of

3 the patients, not all but many of the patients, in this

4 study.

5   DR. BORER: In all fairness, though, and

6 without wanting to advocate one position or another, when

7 you look at the mortality curves, they're spot on too

8 during that period. So, it's a risk, but people weren't

9 dropping like flies because they incurred that risk.

10 Obviously, whoever was managing them saw the problem and

11 dealt with it adequately. Again, I think we have to

12 consider -- maybe we just have to keep it in mind for

13 subsequent points on this list of questions -- that this is

14 an open issue. Should this be an approvability issue or

15 should it be a labeling issue?

16   Let's get to the intent of question number 5.

17 This is a single study.

18   DR. KEANE: Can I just add so that we're clear

19 about what the potassium values were? I think as you look

20 at the distribution of K levels between 5.5 and up to 7,

21 the distribution that is occurring within the vast majority

22 of these is weighted at the lower levels, i.e., 5.5 to 6

23 and 6 to 6.4, towards losartan. But as you get into the

24 higher potassium levels that we were able to determine,

25 they're fairly comparable both in the losartan group and in

1 the placebo group. So, I think that should be taken into

2 consideration when one talks about what the potassium

3 values are in these patients that are going to have

4 hyperkalemia.

5   DR. BORER: Okay, thank you.

6   Well, the intent of number 5 really is whether

7 a single trial is adequate as a basis for approval. We

8 have this study alone. We saw a study in a related

9 compound or a pair of studies in a related compound with at

10 least some similar pharmacologic effects three months ago.

11 We've heard about data, and this committee when it was

12 differently constructed, considered other data that might

13 be related having to do with a compound that has some

14 effects on the same system, the renin-angiotensin system.

15   So, the question is do we have enough

16 information from this one trial alone, and if we don't, is

17 there sufficient information available from other sources

18 that we have enough information in aggregate to draw a

19 conclusion about approvability.

20   With that in mind, we were all sent --

21   DR. THROCKMORTON: Jeff, I think I'd like to

22 break those up just a bit. Let's stay focused on are the

23 results from RENAAL alone an adequate basis without taking

24 into account any other data that you might want to. You'll

25 have chances in later questions to do that.

1   DR. BORER: Okay. Well, then let's just do

2   that since that's what the FDA wishes us to do.

3   Are the results of RENAAL alone an adequate

4   basis for approval of losartan for the treatment of type II

5   diabetic nephropathy? JoAnn?

6   DR. LINDENFELD: RENAAL, taken in isolation, I

7   don't think would make this an approvable drug. I think

8   the p value was not what we would usually consider for one

9   multicenter trial. We saw that as the primary time to

10   first endpoint, this was primarily a doubling of

11   creatinine. My answer to this would be no.

12   DR. BORER: Does anybody else have any comment

13   about that? Does anyone disagree with it? Steve?

14   DR. NISSEN: I don't disagree, but I want to

15   make sure I say why I don't think it's adequate.

16   First of all, it is a single trial. That alone

17   is not a bar if the single trial is very robust, but it's a

18   single trial with a fairly marginal p value.

19   Tom, in all deference to your comments, I have

20   to use the triple endpoint here. That was the prespecified

21   endpoint. So, I focus a lot of my thinking on you get one

22   chance up front to choose your endpoint and this is what

23   they chose. Right or wrong, it's pretty marginal.

24   Then I've got all these confounders to deal

25   with. I've got the problem that if you take out the 250

1 patients from Asia from either the triple or the double

2 endpoint, it no longer is statistically significant. Now,

3 that does not meet my standard for a robust effect when it

4 seems so clear that it's being driven by a very small

5 population. Similarly, there are other confounders here,

6 like the blood pressure difference.

7   So, when you take a marginal p value for the

8 principal endpoint of the trial and then you erode it with

9 these other factors, then it doesn't rise to that level of

10 evidence that we've typically required for approval. So,

11 alone RENAAL doesn't meet the standard from my perspective.

12   DR. BORER: Does anybody else want to state an

13 opinion about this? Beverly?

14   DR. LORELL: I would like to. I spent some

15 time actually reviewing the criteria that the FDA itself

16 has put out for a single trial because we wrestled with

17 this issue very recently.

18   I think that there was very compelling data

19 presented both from this study and in aggregate for many

20 studies supporting a role of the renin-angiotensin system

21 in accelerating progression of diabetic renal disease. And

22 I doubt any around the table would disagree with that

23 biology.

24   But if one looks at the guidelines from the FDA

25 itself to both industry and those of us as reviewers for

1 evidence of effectiveness from a single study, there are

2 several concerns, and I agree with JoAnn.

3   First, with regard to the endpoints that were

4 presented to us in trial design, there is not evidence of a

5 highly statistically persuasive outcome. The statistical

6 outcome for the predefined primary endpoint was marginal.

7   Secondly, we're advised to look at consistency

8 across subgroups. Here I think the issue of the gnarly

9 problem of the data from Asia is very problematic and

10 really counts as a point of concern about consistency.

11   Third, very explicitly, we are advised to look

12 in a single trial as to whether or not there is evidence of

13 efficacy in multiple endpoints involving different events.

14   The example that's given in the publication from the FDA

15 is quite helpful here. In this trial, the different events

16 that we are given to look at are end-stage renal disease

17 and all-cause mortality. I think one could argue very

18 strongly that doubling of creatinine and end-stage renal

19 disease are highly coupled, and we know that because the

20 median time from going on to end-stage renal disease after

21 doubling of creatinine is only 30 days. So, if we look at

22 the criteria of different endpoints regarding clearly

23 different events, this trial does not quite make that

24 criteria. There was not an effect on all-cause mortality,

25 nor was there an effect on a very important predefined

1   secondary endpoint of major cardiovascular events.

2   Finally, I am influenced by the concerns that

3   the Steering Committee of this trial itself had regarding

4   the use of this drug in the context of albeit insufficient

5   data regarding ACE inhibitors in cardioprotection.

6   So, I think with the criteria that the FDA

7   itself provides to its advisors for thinking about efficacy

8   in a single study, it doesn't quite reach the burden.

9   DR. BORER: I'm going to ask in a minute

10 whether everybody agrees with this, which I think we do.

11 But I want to just ask for a little clarification about the

12 last statement. What I heard -- and we have the person

13 here who can tell us about it -- was not that the Steering

14 Committee was concerned about people not taking ACE

15 inhibitors, but they were concerned about half the patients

16 not taking any drug that impacted on the renin-angiotensin

17 system. I think we don't want to over-interpret what they

18 did based on something they didn't mean. So, can we just

19 have a clarification about that?

20   DR. BRENNER: My name is Barry Brenner. I had

21 the pleasure as serving as the PI and the chairman of the

22 Steering Committee.

23   You're correct. The late January '01 meeting

24 of the DSMB issued a directive based on their review not

25 only of HOPE but of another publication that was soon to be

1   printed, the Mann paper, which was a substudy of HOPE

2   dealing with patients who had renal disease. In that study

3   there was cardiovascular protection with ramipril. That

4   was the first time that a population akin to the RENAAL

5   trial showed a benefit in a clinical trial with

6   interruption of the renin-angiotensin system. That was

7   late January.

8   Our committee convened on 10 February, very

9   soon after learning of the concern of the DSMB. And we

10 were blinded, although they were not of course. And we

11 voted unanimously to terminate the trial a year before it

12 was scheduled to be terminated because our concern was that

13 in the placebo group there was no renin-angiotensin system

14 blockade.

15   The decision was based on increasing evidence

16 from HOPE to some extent but much more compellingly from

17 the Mann paper, not yet published, but which we had in

18 manuscript form, that in patients with renal disease ACE

19 inhibitors may be effective in reducing cardiovascular

20 events, as I say, in patients who had cardiovascular risk

21 factors. So, it was because the placebo group had not

22 received and could not in the trial receive blockade of the

23 renin-angiotensin system.

24   Recall that when the trial began, there was

25 virtually no evidence about protective effect on the heart,

1 cardiovascular system, with ACE inhibitors. And the first

2 paper that was compelling in this regard in diabetics was

3 the substudy of HOPE, and that was in the year 2000, five

4 years after we began. So, once we had now additional

5 evidence, obviously only coming from HOPE -- but that's all

6 there was -- dealing with renal disease and showing a

7 cardiovascular protective effect, that drove us as an

8 independent body to terminate the trial.

9   DR. BORER: Thank you. I've just learned that

10 the FDA would like a formal vote on this question.

11   DR. FLEMING: Could we have further comment

12 first?

13   DR. BORER: We sure can.

14   DR. FLEMING: I'd like to just add a little bit

15 to this. This certainly to me is the most critical

16 question on the agenda.

17   As my colleagues have pointed out, great

18 emphasis should be given to the primary endpoint of the

19 trial. There certainly is evidence of benefit here. The p

20 value was .02 on that primary endpoint. When we saw a

21 similar phenomenon or a similar strength of evidence in

22 January, some of us judged that as consistent with one

23 positive trial but not two positive trials.

24   Going beyond that, as has been pointed out,

25 there are some safety issues here, most discernably or

1 notably the hyperkalemia. There are some concerns about

2 subgroups. As the FDA has asked us to look at consistency

3 across subgroups, we see within the Asian population an

4 apparent dominance in terms of where much of the positive

5 signal is. And as has been pointed out, there are some

6 issues to address relating to the ACE inhibitors and their

7 efficacy and how does that complicate this. These are all

8 areas of concern.

9   Having acknowledged those areas of concern,

10 though, I think there are a number of really critical

11 issues to consider. I'd like to turn in particular to the

12 specific criteria the FDA has asked us to consider about

13 whether a single study is adequate.

14   We, in fact, have a large multicenter trial.

15 That's the easy part.

16   Going beyond that, though, of real critical

17 importance are the criteria, are there multiple endpoints

18 that essentially reinforce our sense of strength of

19 evidence, and are these results statistically very

20 persuasive findings. My own sense about that, even though

21 it's subjective, is something I've always attributed to Ray

22 Lipicky although he denies it's his, but I always think of

23 .025 squared times 2 as a two-sided significance level that

24 might be viewed as what you need to see in order to be

25 consistent with the strength of evidence from two adequate

1 and well-controlled trials. That's a p value of .00125.

2 When I look at these data and probe further, I

3 acknowledge that -- and I'm very reluctant to move away

4 from a prespecified primary endpoint except in those very

5 settings where I have a philosophical strong concern about

6 the appropriateness of the choice of that endpoint. To my

7 way of thinking, what we're looking at here is a

8 combination of loss of renal function and death, and we're

9 trying to best characterize that. I'm at a loss for

10 knowing why we have to use the component doubling in

11 creatinine time when it doesn't take that long to follow

12 people, if it really is going to translate into end-stage

13 renal disease, to end-stage renal disease. Hence, as some

14 of us at least argued last January, we were questioning the

15 persuasiveness of the triple endpoint.

16 If this study had had a triple endpoint of four

17 0's and a 1, and the double endpoint of end-stage renal

18 disease/death had been a .03 to .06, I would have called

19 that at best a study that translates into the strength of

20 evidence of a single positive study. I.e., I would have

21 discounted the surrogate.

22 As a result, I think it's logically

23 inconsistent for me, even though I'm a strong believer in

24 adhering to the primary endpoint, that if I would not have

25 given credence to that primary endpoint, I should focus on

1   what it is that really matters, particularly in a setting

2   such as this where I can't interpret the primary endpoint

3   because they didn't follow 267 people to the triple

4   endpoint. They did, to their credit, fortunately from my

5   perspective, followed everybody to what really to me

6   matters from a renal perspective, end-stage renal

7   disease/death. When you look at that endpoint, one gets

8   significance levels on the order of .002. That's for end-

9   stage renal disease; .009 for end-stage renal

10 disease/death.

11   That's not, by the way, what we saw in January.

12   When we looked away from the triple endpoint into these

13 elements last January, we were seeing less strength of

14 evidence, which for some of us was the concern. Here we're

15 seeing much more strength of evidence.

16   Furthermore, we asked, looking at a different

17 domain, last January please don't just show us the

18 clinically important renal endpoints. Also show us the

19 most important, clinically important cardiovascular

20 endpoints, which before I ever looked at these data, we had

21 specified as end-stage renal disease, MI, stroke, and

22 death.

23   When you look at those specific endpoints for

24 stroke and death -- granted, cardiovascular deaths are

25 notable as having 11 in excess in the wrong direction --

1   strokes and non-cardiovascular deaths are 11 in the right

2   direction. So, overall, there's no difference. I'm not

3   claiming as a result that I know that there's any benefit

4   here on anything related specifically to mortality, but

5   over and above those measures are the 47 excess deaths

6   prevented on end-stage renal disease and the 18 events

7   prevented on MI, which is a total of 65 events, which

8   statistically is at the .003 level.

9   So, now I'm looking at what in January we

10 called the clinically most important events which, by the

11 way, are the ones we can interpret because that's where

12 they had complete follow-up. What we see are significance

13 levels on the order of .002, .009, .003 before there's any

14 adjustment for an issue of baseline imbalances, which is

15 another area that causes many of us to be greatly cautious.

16   Nevertheless, I've been persuaded that there's something

17 here of real relevance, and when adjusts for imbalances in

18 proteinuria, there's another log reduction in these

19 significance levels.

20   Now, is there persuasive data here when you

21 start subdividing into two groups? Well, let's subdivide

22 the Asian into the non-Asian populations. Now, that's in a

23 certain sense not particularly optimal for this

24 intervention because we did so specifically having seen the

25 greatest signal coming from the Asian population.

1   But when we do so, if you go with me for the

2   moment to what's the most important endpoint, which I don't

3   believe is the triple endpoint -- it's the double endpoint

4   -- when you look at the double endpoint and you adjust for

5   proteinuria, it must be significant. Clearly the Asian

6   subgroup is significant even without adjusting for

7   proteinuria. The sponsor showed us the double endpoint in

8   the non-Asian patients had a lower confidence interval. It

9   was very close to 0 even before adjusting for proteinuria.

10   So, if you focus on what really matters, end-

11   stage renal disease and death, and account for what is a

12   pretty strong case for an imbalance at baseline adjusting

13   for that, even if you simultaneously also adjust for the

14   systolic blood pressure differences, you'll find subgroups

15   in the Asians and the non-Asians that I strongly suspect

16   and can ask the FDA to validate will, in fact, be

17   significant in both of those groups.

18   So, as I look through these criteria, I am

19   seeing statistically persuasive findings that are on the

20   level of .00125, and we are seeing, across the endpoints

21   that really matter, the renal endpoints alone or the renal

22   and cardiovascular endpoints that last January we

23   designated as the most important, there's a significant

24   difference there as well.

25   What about the consistency across subgroups?

1 That is certainly a relevant concern. There are some

2 uncertainties, but the analysis that I was just giving of

3 the Asian/non-Asian on the dual endpoint I think does show

4 that there's benefit across both groups.

5   What about hyperkalemia? It's harder for me to

6 assess that. We're seeing, over 3 to 4 years, a difference

7 in 10 to 12 percent against 25 percent. But unless you

8 would believe that that would translate into influencing

9 negatively these hard clinical endpoints long term and, if

10 anything, if we're going to project out long term, I'm

11 thinking we have every reason to think the effects here are

12 going to be even greater. These curves are diverging. I

13 hate to put emphasis on what we haven't seen, but if we're

14 going to extrapolate what the adverse effects of

15 hyperkalemia may be that we haven't yet seen, and if you're

16 going to take the liberty to do that extrapolation, you

17 should take the liberty to extrapolate what these effects

18 are. They're growing over time. The separation between

19 these curves in ESRD-free survival are actually growing

20 over time.

21   The last issue is the issue of how to address

22 the ACE inhibitor. At least my understanding is if we

23 assumed that we knew the ACE inhibitor was effective and we

24 have a placebo-controlled trial and if in fact you look at

25 these data and say that this is establishing that losartan

1   is effective, it seems to me the question isn't whether you

2   approve losartan. The question is can we motivate the

3   conduct of a trial following the approval of losartan that

4   would allow us to establish whether we should be using an

5   ACE inhibitor or an ARB or the combination thereof. That

6   seems to me the relevant follow-up question if there is in

7   fact some uncertainty.

8   So, when I look at these FDA criteria, I find

9   very strong evidence to suggest that what we are looking at

10   as those factors that need to be met for this study to be

11   viewed as adequate for approval are in fact met.

12   DR. BORER: Since we've been asked for a vote,

13   let me translate that into simple terms. Is RENAAL alone

14   an adequate basis for approval of losartan? Tom?

15   DR. FLEMING: Do you want my vote?

16   DR. BORER: Yes.

17   DR. FLEMING: Yes.

18   DR. BORER: Let's start at the other end of the

19   table because we haven't given them too much of a chance,

20   and then we'll come back around. Yes or no and give a

21   reason.

22   DR. BREM: I guess yes, after that compelling

23   discussion.

24   (Laughter.)

25   DR. BREM: I was going to say it's equivocal,

1 but I've been certainly swayed by your arguments. So, I

2 vote yes.

3   DR. BORER: Dr. Kopp?

4   DR. KOPP: Yes, I have a problem here too that

5 I was of the belief that the great sin was to do other than

6 what was laid out initially, and I think coming from a

7 statistician, what you have said has been swaying me. I

8 actually would have preferred to vote last and see what

9 other people were saying.

10   (Laughter.)

11   DR. KOPP: But since I'm going at this point, I

12 would have to say yes. And I guess the reason is because I

13 am swayed that ESRD is important, that there was a

14 significant difference.

15   DR. BORER: Bob?

16   DR. TEMPLE: Well, just to be sure. I'm

17 certainly not trying to influence the answer. But

18 alternative analyses are always persuasive to the people

19 who like them. It's just worth remembering. I think Tom

20 is very sensible, but he's presenting you an analysis that

21 he finds persuasive for reasons that he gave. But subgroup

22 analyses and alternative analyses and covariate analyses

23 that we see all the time are always persuasive. Just don't

24 forget that.

25   (Laughter.)

1   DR. BORER: Paul, are you persuaded?

2   DR. ARMSTRONG: I'm not allowed to vote with

3   the knowledge of the field and taking other things into

4   account. It's only on this data. And if I knew nothing

5   else about the field, I would be optimistic but reserved

6   and would probably vote no.

7   DR. BORER: Do you want to state for the record

8   a couple of reasons?

9   DR. ARMSTRONG: Just the strength of the

10 analysis and the fact that it's a positive trial, and I

11 think it's effective. But it's one trial and the evidence

12 isn't of the usual standard. But clearly we haven't heard

13 the end of this discussion today.

14   DR. BORER: Beverly, I think you already gave

15 all your reasons, but if you have any more to add, go ahead

16 and give your vote.

17   DR. LORELL: I would still vote no. I think

18 Tom Fleming's discussion is very persuasive, but

19 nonetheless, it's not our job to redesign the trial and the

20 primary and secondary endpoints that were predefined. So,

21 using the predefined endpoints of this trial, I would vote

22 no.

23   DR. BORER: Susanna?

24   DR. CUNNINGHAM: Well, I've been challenged all

25 day as I've listened to all the discussion and been going

1 back and forth and thinking about what does this mean to

2 the person who has renal disease and what does this mean to

3 the person who is going to be developing renal failure. I

4 think after listening to Tom's very persuasive presentation

5 and thinking about what it would mean perhaps to have 6

6 months less of renal failure, I would say yes in this case.

7   DR. BORER: Steve?

8   DR. NISSEN: I think I've already stated my

9 reasons, and actually, Tom, although you are very

10 persuasive, I was not persuaded.

11   (Laughter.)

12   DR. NISSEN: A lot of what I know you taught

13 me, and I still think to go beyond the primary prespecified

14 endpoint of the trial, you've got to have very compelling

15 reasons to look at what you're looking at.

16   I do also agree with what Bob Temple said,

17 which is I can take data and I can contort it almost any

18 way I want and come to a conclusion.

19   But I look at the primary efficacy endpoint,

20 and I really believe that it was marginal and that it was

21 really troubling to see that it all came basically from one

22 subgroup. I just don't think that's the compelling

23 evidence that a single trial needs to have. And the word

24 is "compelling," and it's just clearly to me not there from

25 this single trial. And I reserve the right to vote

1 otherwise based upon other information today, but on this

2 trial alone, I don't think it comes even close.

3   DR. BORER: I would vote no also. I think that

4 these are very suggestive data, that it's a positive trial,

5 but I'm concerned about the lack of robustness as judged by

6 the different results across different groups. Things tend

7 to go the same way, but the magnitude is highly variable.

8 There are a lot of confounders that I can't interpret

9 fully. There are inadequate data to draw firm conclusions

10 about cardiovascular events, although that is not a show

11 stopper, and there are some concerns about safety that also

12 aren't show stoppers but I would like to see some

13 confirmatory evidence before I would vote yes. So, I will

14 vote no for this trial as a single trial to be sufficient

15 for approvability.

16   Alan?

17   DR. HIRSCH: The last three speakers have

18 mostly summarized most of my reasons for voting no.

19   But having the microphone on, this really was a

20 visionary trial design when it was created. It's landmark

21 in its ability to show a definitive, clear change in ESRD

22 in this particular population studied.

23   But I really do believe it's important for us

24 to stick to the true trial, high significance design with

25 no homogeneities that are evident with robust, overlapping

1 positive outcomes, especially -- and I'm bring to the table

2 another issue -- in an era when I think all of us are

3 seeing an effort for us to reach to molecules and to study

4 them in a global design, bringing in multiple countries in

5 a way that ultimately that, besides our USA mandate, will

6 be used for global marketing.

7   When we have a single trial of what I think is

8 sort of borderline significance, I think the standard has

9 to be very high, and I'd like to caution all of us not to

10 lean on single trials, ignoring everything else that we

11 might know about ARBs and ACE inhibitors, before we set a

12 new de facto standard. These standards should have the

13 very highest level of knowledge. We're not there with a

14 single trial.

15   DR. BORER: Blase?

16   DR. CARABELLO: Yes, I agree. I think that

17 we've made mistakes based on single small trials. If this

18 were 30,000 patients, that might be one thing, but I do

19 agree that single trials are dangerous. But my major

20 reason for voting no here is I can't get away from the fact

21 that almost the entire benefit was concentrated in a tiny

22 subsection of the study without even a trend in the other

23 subpopulations.

24   DR. BORER: JoAnn, as our committee reviewer,

25 you have the last word.

1   DR. LINDENFELD: I would say again no for the

2   reasons that have been stated. I think this study by

3   itself is not quite convincing enough. Also, by itself I

4   don't think it gives us as much assurance that this isn't

5   just a blood pressure effect.

6   DR. BORER: So that means we can go on to the

7   subsequent questions.

8   A drug with a related mechanism of action,

9   captopril, has an indication for diabetic nephropathy in

10   patients with type I diabetes. The primary basis of that

11   approval was the demonstration in a 409-subject, 2-year

12   study, of 51 percent reduction (p equals .004) in risk of

13   doubling of serum creatinine alone, and a 50 percent

14   reduction (p equals .006) in risk of mortality or end-stage

15   renal disease. Both effects were manifest in the first few

16   months of treatment. Captopril also reduces the

17   progression of microalbuminuria to overt proteinuria.

18   Are the results with captopril germane to a

19   discussion of losartan? In particular, 6.1, is nephropathy

20   in type I diabetes enough like type II diabetes? 6.2, are

21   the pharmacological effects of captopril and losartan

22   adequately similar?

23   JoAnn?

24   DR. LINDENFELD: We discussed this in January

25   with the same question, and I think at that time we felt

1 that the nephropathies in these two were very similar. The

2 patients are more different perhaps than the nephropathies

3 in some of their other covariates.

4   And the pharmacologic effects, while not the

5 same, are similar.

6   DR. BORER: So, then you think the results of

7 captopril are germane to the discussion.

8   DR. LINDENFELD: Yes. Sorry. I do.

9   DR. BORER: Does anybody disagree with that?

10 Steve?

11   DR. NISSEN: Yes, I guess I don't agree. While

12 the drugs affect the same enzyme system, they attack it at

13 different points. Gosh, I could give you innumerable

14 examples of drugs. Even within a class, it's tough to know

15 whether an effect is held across the class. There are some

16 very good examples of drugs where one drug in the class

17 actually is effective and the other drug isn't.

18   Now we're asked to look across two classes of

19 drugs. The minute you broaden it to that point, I think

20 it's a terribly slippery slope. I've had a lot of time to

21 think about this since January, and I feel more strongly

22 than ever that you can't extrapolate ACE inhibitor data to

23 ARBs and you can extrapolate ARB data to ACE inhibitors.

24 And you really shouldn't try. Even in the ACE inhibitors,

25 there are issues of tissue selectivity, et cetera. We

1   don't know if they're important or not, Bob, but the point

2   is that's even within an individual class, let alone across

3   two classes. So, I really do think this is dangerous.

4   DR. BORER: Paul?

5   DR. ARMSTRONG: In the same way that I'm unable

6   to transfer the effects of ACE inhibitors to ARBs in

7   cardiovascular disease, which I know more about than this

8   subject, I would not be prepared to do it with the subject

9   matter at hand.

10   DR. BORER: Dr. Brem?

11   DR. BREM: I would say the question before us

12   really, is there some similarity and can you draw from that

13   similarity -- I don't pretend to say that they're

14   equivalent and I don't thinks that's the question before

15   us. We're just asked is there some relevance from one to

16   the other, and I think the answer to that is probably yes,

17   there is. They do have some potential common modes of

18   action.

19   And diabetic pathology, the actual structural

20   changes and so on are quite similar from one to another.

21   Many of the pathologic mechanisms involving glycosylated

22   end-stage products and proteins and so forth are quite

23   similar.

24   So, I think there is a similarity, but it's not

25   equivalence. I think we should recognize that.

1   DR. BORER: That's with regard to type I and

2   type II diabetes.

3   DR. BREM: And the captopril and losartan, that

4   there are similarities that you might be able to draw upon,

5   but they're not equivalent.

6   DR. BORER: I'd like to comment on that too. I

7   agree with those who would not accept the captopril data as

8   particularly germane. That is, I agree with Dr. Brem that

9   there is something there. We are affecting the same

10 system, and therefore at the very least, the effects of

11 captopril would, for me, support the generation of a

12 hypothesis that ARBs work in patients with diabetes to

13 protect the kidneys. But beyond that, I'd have a hard time

14 going because there are, I think, potentially important

15 differences in pharmacologic effects between the two

16 classes.

17   I agree absolutely with Steve. Among the

18 molecules within a class, I think we've seen many examples

19 of different pharmacologic effects besides the primary ones

20 that we think about and therefore I would want to see more

21 information than merely the captopril information to

22 support losartan effectiveness.

23   On the other hand, I say again that I agree

24 with Dr. Brem, that there's something here that supports at

25 least the hypothesis that ARBs work, and then we have to

1   study them.

2   Alan.

3   DR. HIRSCH: One more extrapolation of that.

4   Obviously, there are relationships between these drug

5   classes that let us form hypotheses to lead to new clinical

6   trials and there are similar effects. Let's ask the

7   question. How would we all know on this panel or how would

8   we know designing if they were similar or not? What it

9   would take would be comparative trial data in humans. So

10   far, what we're doing on this panel I think is taking

11   monotherapy versus placebo in trials from different

12   populations and different investigators and then trying to

13   make comparisons. That's not how we'll decide if they're

14   similar or not.

15   DR. BORER: Beverly?

16   DR. LORELL: I agree, Jeff, with your summary

17   on this issue.

18   DR. BORER: Tom?

19   DR. FLEMING: I largely agree as well, Jeff.

20   The FDA in a number of instances in the past, as I

21   understand, has followed a strategy that I think makes a

22   lot of sense. If they're working with the sponsor in

23   setting up a development program and recognizing that we

24   need confirmatory studies that a strategy has been at times

25   to have two studies of the agent done in

1 pathophysiologically related settings and if the studies

2 are both positive, they reinforce each other and we obtain

3 the confirmatory evidence in that manner.

4   If one level of germaneness would be is this in

5 fact a study of that nature that could reinforce the RENAAL

6 study -- and my sense is not at all -- in fact, if we

7 believed that the captopril study provided evidence that

8 was that relevant, I would wonder why this committee or the

9 FDA in general hasn't approved captopril in type II

10 diabetes, step one.

11   Step two is it's a different class, as has

12 already been mentioned by my colleagues, and my clinical

13 colleagues can address this much better than I.

14   So, my own sense is at a certain level it is

15 germane, but I would consider it a pretty modest level

16 because it is in fact a related, but still different,

17 setting with a different class.

18   DR. TEMPLE: Jeffrey?

19   DR. BORER: Bob.

20   DR. TEMPLE: Just to be clear, we anticipated

21 that people might find the single study standing on its own

22 not a million miles away from sufficient but fairly close.

23 This was an invitation to think about whether something in

24 a closely related pharmacologic class tipped you over.

25   DR. BORER: And you've heard that it wasn't so

1   far.

2   DR. TEMPLE: Yes. This was to offer you that

3   opportunity.

4   DR. BORER: On the remaining four questions, we

5   need to have a formal vote with reasons.

6   First, if the results with captopril are

7   relevant to losartan, are the results on -- well, we've

8   actually said what we needed to say. Do you want a formal

9   vote on 7 now?

10   DR. THROCKMORTON: 7 has been answered to our

11   satisfaction. If you would just go to 8, that would be

12   terrific.

13   DR. BORER: Let's go to 8. Are the results of

14   RENAAL and prior expectations derived from the captopril

15   database an adequate basis for approval of losartan for the

16   treatment of -- I think we've answered that one as well,

17   but we can give a formal vote, if you like.

18   DR. THROCKMORTON: Yes, if you wouldn't mind.

19   DR. BORER: Okay. Why don't again we start at

20   the far end of the table here. Dr. Brem?

21   DR. BREM: Sticking my neck out first, yes, I

22   would vote for approval. My thinking is that while both

23   classes are clearly different, I absolutely agree with

24   that, and there are perhaps subtle mechanisms of action

25   which may be different, and when we argue that type II

1   diabetes and type I diabetes aren't exactly the same

2   either, there's enough supporting evidence, in terms of

3   direction and efficacy, that I would use those two together

4   to make a story that it's worth approval.

5   DR. BORER: Dr. Kopp?

6   DR. KOPP: Well, I earlier said that RENAAL

7   alone was sufficient, so obviously I have to say that A

8   plus B are sufficient. I don't actually find that the ACE

9   inhibitor data adds much.

10   DR. BORER: Paul?

11   DR. ARMSTRONG: No.

12   DR. BORER: Beverly?

13   DR. LORELL: No.

14   DR. BORER: Susanna?

15   DR. CUNNINGHAM: Yes and no.

16   (Laughter.)

17   DR. BORER: We need a comment there.

18   DR. CUNNINGHAM: I already said yes for the

19   first, so that's my statement. But I don't believe that

20   captopril is the same thing. I believe it has a different

21   action, so I can't say yes to the whole thing.

22   DR. BORER: Steve?

23   DR. NISSEN: No.

24   DR. BORER: And I vote no.

25   Alan?

1   DR. HIRSCH: I'd like to keep some suspense

2   going here for a while.

3   The previous question was more theoretical, and

4   I gave a very vigorous theoretical answer. When we come to

5   practical gestalt sense of things, I am swung a bit,

6   although I will tell you I haven't quite swung over, so I'm

7   still a close no.

8   DR. BORER: Blase?

9   DR. CARABELLO: No.

10   DR. BORER: JoAnn?

11   DR. LINDENFELD: No.

12   DR. BORER: Tom?

13   DR. FLEMING: I've already said yes based on

14   RENAAL. I would agree.

15   DR. BORER: The record should show that Tom

16   agreed to yes/no.

17   Okay, we're up to number 9. Let's go through

18   number 9 and then I want to ask a question. Number 9. In

19   considering the approval of irbesartan for diabetic

20   nephropathy, the advisory committee expressed interest in

21   the program for losartan, which we did. The respective

22   sponsors now have reciprocal agreements allowing reference

23   to IDNT and RENAAL in support of one another's programs.

24   Do the findings of IDNT support the

25   effectiveness of losartan for diabetic nephropathy? Why

1 don't we start with that and then we'll go to 9.2

2 separately. JoAnn, do you want to start with that?

3   DR. LINDENFELD: I believe the IDNT results do

4 support RENAAL, and I think a doubling of creatinine was

5 the primary finding there. But doubling of creatinine in

6 my own mind -- and we discussed this last time -- is more

7 than just a surrogate. Doubling of creatinine is a real

8 result that I think we can see in the clinic that applies

9 to patients. Yes.

10   DR. BORER: Tom?

11   DR. THROCKMORTON: Jeff?

12   DR. BORER: I'm sorry. Yes.

13   DR. THROCKMORTON: I wondered if we could maybe

14 get just a little more discussion around this question.

15 Maybe it wasn't worded quite as well as we could have.

16 Part of this was what's your level of comfort about

17 thinking of two drugs from pharmacologically related

18 classes as supporting efficacy. You can imagine some

19 people might be uncomfortable doing that in the same sense

20 that we heard some uncomfort about the ACE inhibitor data

21 informing your decisions about an ARB. Maybe that's a

22 foregone. Maybe that's easy. There's no question that

23 it's informative and could be supportive, but if there is

24 anything short of that, it would be interesting to hear

25 some thoughts along those lines.

1   DR. BORER: Okay. I thought you wanted that in

2   the context of 9.2, but that's fine. Bob?

3   DR. TEMPLE: Whenever. This is a slightly

4   radical concept for us. That's why we sent you the

5   evidence document which discussed it. Give me a minute to

6   just say something about that document.

7   One of the things it did was describe all the

8   circumstances -- it was our attempt to describe all the

9   circumstances in which we would accept a single study of a

10   particular drug and a particular use as sufficient

11   evidence. You already referred to one. If it's really

12   strong and the p value is out to the end of your arm and

13   there's internal consistency, fine, we've all done that,

14   and that's fine.

15   We also defined a whole bunch of situations in

16   which one would draw further support from other controlled

17   trials. Now, you can say that's a Bayesian prior or you

18   can say you really have another study and it doesn't really

19   matter. We give a whole list, studies of different doses,

20   other regimens. There is one thing toward the end of that

21   list that talks about pharmacologic and pathophysiologic

22   endpoints.

23   Although the words aren't as clear about the

24   present situation as one might have liked, because we

25   didn't really think of it, there is a suggestion that when

1   knowledge of the pharmacology, coupled with clinical

2   evidence that that pharmacology is relevant, is present,

3   that you might be able to rely on a single study, not no

4   studies. We're not talking about class labeling or

5   anything like that.

6   The main difference between the past cases that

7   we considered and this one is what we had in mind when we

8   wrote it is, oh, you've got 12 studies of ACE inhibitors.

9   Maybe now one more might do.

10   In this case, there isn't any approval of any

11 of them. So, there's a certain simultaneity that we hadn't

12 really come to grips with. You're thinking about one study

13 is supporting a drug, coupled with another study supporting

14 another drug, and vice versa, sort of a crossover, where

15 there isn't any established track record, approved drug.

16 But we thought that was close enough to the situation we

17 had contemplated to invite you to think about it, and we're

18 thinking about it internally too.

19   It's something of a novelty, although as we've

20 pointed out when we looked at it, we've been approving new

21 heart failure claims for ACE inhibitors based on single

22 studies with p values between .05 and .01 right along. We

23 have not identified that as being based on the prior

24 experience, but there's no other good explanation. We have

25 not insisted on p values at .00125 or anything like that.

1   So, we've been engaging in this without making it

2   particularly explicit. So, this time we're making it

3   explicit and giving you hard work.

4   DR. BORER: Well, we're explicitizing here. I

5   guess that given that preamble, JoAnn, you may want to

6   discuss 9.1 and 9.2 together.

7   DR. LINDENFELD: Yes. Again, I think the

8   findings of IDNT do support the effectiveness of losartan.

9   The captopril helps just a tiny little bit I think for

10 several reasons. We've seen a pathophysiology here and a

11 biologic plausibility that's consistent. We've seen a

12 doubling of creatinine in both studies that's relatively

13 similar, although we didn't see the end-stage renal disease

14 in IDNT I think we've seen in this, and for all the reasons

15 Tom said, I think we see a consistency of overall benefit

16 here and no specific differences in the drugs that I can

17 see that make me concerned that we're dealing with some

18 sort of different mechanism among the single class of

19 drugs. So, for all these reasons, I do think that IDNT

20 supports RENAAL.

21   DR. BORER: So, going to 9.2.1, are the

22 findings of IDNT as persuasive for losartan as would be a

23 replication of RENAAL?

24   DR. LINDENFELD: No. I think a replication of

25 the same study with the same drug would be more persuasive,

1   but a little bit more. I can't put a number on that.

2   Let me just get the next one. A second study

3   demonstrating losartan and slows progression I don't think

4   would be as persuasive as IDNT. We've said that

5   proteinuria alone we're not willing to consider as an

6   endpoint in itself. So, 9.2.3, a study demonstrating

7   progression to microalbuminuria would not be as strong.

8   And beating an active control arm in RENAAL, I

9   think I'd have to understand exactly what you meant by

10   that.

11   DR. THROCKMORTON: That was a reference to the

12   IDNT trial where, if you remember, there was an active

13   control arm.

14   DR. LINDENFELD: Yes. I think for all the

15   reasons we said there, because it's hard to tell if an

16   active control arm might cause some problems, that that

17   would not be as strong either.

18   DR. BORER: So, it sounds as if -- I'm trying

19   to pin you down here so we can move on to the next one with

20   real confidence -- that IDNT is supportive of RENAAL but

21   not quite as supportive as a second trial would have been.

22   DR. LINDENFELD: Right.

23   DR. BORER: And we'll get to the next question

24   about whether it's supportive enough.

25   Tom, what do you think about that?

1   DR. FLEMING: I think I largely agree point by

2   point with JoAnn's answers. My sense is clearly here what

3   we're dealing with now is an agent from the same class and

4   a study in the exact same setting, which adds to the

5   relevance, but to my way of thinking clearly is not as

6   persuasive as if we had a second trial of losartan in type

7   II diabetes. So, it is certainly addressing some of the

8   concerns that at least I had in the previous question, but

9   it's less persuasive than another trial would be of

10 losartan.

11   I think it's relevant here because at least

12 some of us viewed that the IDNT trial provided a strength

13 of evidence consistent with, just barely, one positive

14 study. At least some of us argued that was one positive

15 study, just barely, but not the greater strength of

16 evidence that we would think you would have to have had to

17 base an approval on that.

18   And the surrogate, microalbuminuria, study that

19 was presented in that setting, if it were presented in this

20 setting, as JoAnn said, I would view to be of relatively

21 low persuasiveness. That's the type of study that adds to

22 the sense of biological plausibility, but I want to see it

23 confirmed with a clinical endpoint trial.

24   So, it's not necessarily symmetric here. Maybe

25 I need to clarify that, but in essence what I'm viewing is

1   that with RENAAL in hand and with IDNT being viewed as a

2   single positive trial, it doesn't really provide the

3   strength of evidence of a full separate trial, but it

4   certainly is relevant and provides some additional strength

5   of evidence to RENAAL.

6   DR. BORER: Blase?

7   DR. CARABELLO: You're asking for comment or a

8   vote?

9   DR. BORER: We're asking for a vote and a

10   reason.

11   DR. CARABELLO: I would vote yes.

12   First of all, I want to point out that being

13   from Philadelphia, I thought IDNT was a word, like "IDNT a

14   nice day," using it in a sentence.

15   (Laughter.)

16   DR. CARABELLO: I think these two agents are

17   extremely close together. I think they constitute two

18   confirmatory trials, that they are effective in type II

19   diabetes, and I would vote yes for approval.

20   DR. BORER: It wasn't the approval issue.

21   (Laughter.)

22   DR. CARABELLO: I vote that they're

23   complementary.

24   DR. BORER: Alan?

25   DR. HIRSCH: Can I make this simple? I think

1 they are clearly complementary, but as Tom has said,

2 ultimately it would be nice to have a single molecule

3 studied definitively before we create a new precedent. The

4 reason for that is, again, that we tend in our

5 pharmacologic era to try to differentiate products even

6 within the same class when that's to our benefit, and now

7 we're trying to lump them when it's to our benefit. At

8 some point, we need secure knowledge again. But they

9 clearly are supportive.

10   DR. BORER: I would vote that IDNT is certainly

11 supportive of the effectiveness of losartan. As JoAnn and

12 Tom and everybody else said, I find the persuasiveness

13 somewhere short of replication of RENAAL and forget about

14 the other two. I'll tell you why.

15   There are some outstanding safety issues that

16 we want resolved here, and while I can accept IDNT as

17 sufficiently supportive of efficacy of a drug that does the

18 things that both of these drugs do in common, so that

19 that's nicely supportive, the safety issues are harder for

20 me to understand. Small differences in pharmacologic

21 effects based on molecular structure might well alter the

22 safety profile a little bit. The magnitude of hyperkalemia

23 that occurs, what have you.

24   Since those issues weren't really adequately

25 resolved or completely resolved -- I shouldn't say

1 adequately -- for losartan in this one trial, I am

2 concerned that they're still not resolved when I have the

3 IDNT data. The cardiovascular protection issues remain

4 again. Here too, I'm not sure that two drugs of the same

5 class do exactly the same thing.

6   So, if I were to, ultimately at the end of the

7 day, say that the concordance of evidence is sufficient so

8 that we should approve losartan for the indication that's

9 being sought, I would write the label very carefully to

10 indicate what we don't know and what's left out here.

11   I think that I would reemphasize what I said

12 earlier, particularly in view of what I've just said, that

13 if we vote to approve the drug, that the FDA should cause

14 something to be written into the label that makes it clear

15 that we are not in any way suggesting the data are

16 sufficient to mandate that this drug should be used in

17 preference, say, to ACE inhibitors or whatever else we may

18 be doing. That's hard to do. I understand, but I think

19 that that's important because of the paucity of information

20 we have.

21   And finally, I think it's very important that

22 if we believe this as a committee that we go on record

23 saying that we do not believe that if we choose to vote for

24 approval, that we're suggesting in any way that that

25 mandates class labeling for ARBs. It may be that the FDA

1   was never thinking of that. I'm sure the FDA never was

2   thinking of that, but I personally would like to say that I

3   don't think that that would be right.

4   DR. TEMPLE: Yes. I really wanted to make that

5   clear. We're talking about when a single study of ordinary

6   persuasiveness as opposed to superior persuasiveness would

7   be enough. We're not talking about a no-study standard.

8   We're more risk-averse than that.

9   DR. BORER: Well, so having said that, again in

10 summary, I believe that IDNT supports losartan. I have

11 concerns. I don't think it's the same as a replication of

12 RENAAL or a second study with losartan. Where we end up on

13 that depends on some of the ancillary issues about labeling

14 that I raised.

15   Steve?

16   DR. THROCKMORTON: Jeff, but what I'm hearing

17 is most of your concerns have to do with safety exposure.

18 And I heard some of the same things from Alan. Is that

19 what you're suggesting?

20   DR. BORER: Well, I am concerned about safety.

21   Let me say also that with regard to efficacy, I would

22 prefer to have a second study of losartan. However, I

23 would be willing to accept the concordance of evidence from

24 IDNT and RENAAL as sufficiently demonstrating efficacy for

25 diabetic nephropathy. The issue of approvability, however,

1 relates to efficacy as related to safety, and there I have

2 some concerns and I just want to express those.

3   DR. THROCKMORTON: Yes, but the only reason I

4 was saying that is here we have a large safety database of

5 the two compounds because they are approved. You might

6 imagine a place where two unapproved compounds --

7   DR. BORER: True. Well, the fact is we're

8 talking here about people with near end-stage renal

9 disease, which changes the ball game a little bit, and it

10 may be that within the dossiers that have been submitted,

11 there's a lot of information about that. That may resolve

12 the issue. I don't know those data because they weren't

13 presented.

14   DR. FLEMING: Just one more clarification

15 before we go on.

16   DR. BORER: Tom.

17   DR. FLEMING: A comment that Bob just made I

18 think, at least from my perspective, it would be

19 appropriate to just have a quick follow-up. I think what

20 Bob was pointing out was this is the type of consideration

21 that's especially relevant when you have a single study and

22 it provides -- I think your words were -- an ordinary level

23 of or what I would call just an adequate level of strength

24 of evidence to meet what we would think of as the standard

25 for this to be called a single positive trial. And does

1   this evidence reinforce it at a level that would lead you

2   to say, now we can approve, as opposed to where you might

3   say you don't need this if you viewed that that single

4   trial was of the strength of evidence of two positive

5   studies.

6   I would just point out that I don't disagree

7   with that. I would just point out that those of us -- and

8   some of us have said so, that we view this IDNT trial as

9   relevant but less than the strength of evidence that you

10 would have had by another study, technically speaking,

11 would argue that you could readily have a single positive

12 trial of the agent in hand that just barely is adequate to

13 be judged as a single positive study and, hence, a

14 companion trial that together doesn't make it because the

15 second study is less than the same strength of evidence.

16   By the way, one last point is keeping this in

17 mind, to be consistent, if that other trial goes in the

18 wrong direction, we would equally be weighing that; i.e.,

19 if it's relevant, it's relevant whether it's positively

20 reinforcing or negatively reinforcing.

21   DR. TEMPLE: I think that's true.

22   We haven't asked you to compare the two studies

23 here, but I just want to remind you the other guys beat two

24 drugs, including one where the effect on blood pressure was

25 almost the same. So, it has its own strengths too, but

1   each one has somewhat different strengths.

2   DR. BORER: It's interesting. I think, though,

3   I want to add something to what I said earlier in light of

4   Tom's comment. I'm persuaded by IDNT in part because of my

5   interpretation of RENAAL. Even though I wouldn't have

6   accepted it as a single study that is dispositive for

7   judgment or for approval, I do think it's better than the p

8   equals .022 for the primary endpoint because I too am

9   persuaded, as Tom is, that the hard endpoints are more

10 important.

11   So, I give a little bit higher bounce to RENAAL

12 than it might have had nominally and a little bit lower

13 bounce to IDNT than anybody else might. But you put the

14 two together, and that makes me feel reasonably comfortable

15 about the effectiveness. And then I have the other issues

16 that I mentioned.

17   Steve?

18   DR. NISSEN: I don't think we should go here.

19 I want to dissent a little bit on what's been said, and let

20 me see if I can articulate why.

21   First of all, I think there's a danger when

22 looking across two different trials involving two different

23 drugs. I would just point out to you there's a lot of

24 precedent here. We have drugs, HMG CoA reductase

25 inhibitors. Everything looked like it was going to go in

1   the right direction, and it pops up that cerivastatin has a

2   huge problem. Nobody anticipated that.

3   DR. TEMPLE: Not an effectiveness problem.

4   DR. NISSEN: No, not an effectiveness problem,

5   but a safety problem. I'm just pointing out that there are

6   examples. There are many examples where there is

7   heterogeneity here.

8   DR. TEMPLE: No one would ever argue that you

9   learn about the safety of a member of a class from the

10 previous members.

11   DR. NISSEN: I understand.

12   DR. TEMPLE: Beta blockers have been

13 carcinogenic occasionally and done other things. We don't

14 think that for a minute.

15   DR. NISSEN: No. I understand.

16   But just to say that I think we set up a

17 precedent here if we're not careful that we may regret. I

18 guess I want to be careful about that precedent.

19   Let me point out something else. If you're

20 going to combine the data in your mind from IDNT and

21 RENAAL, you have to combine all the data. And I would

22 point out to you that in RENAAL, there was about a 12

23 percent excess of cardiovascular death, not significant,

24 compared to placebo. Isn't that right? Wasn't it 1.12?

25   DR. TEMPLE: In RENAAL.

1   DR. NISSEN: Yes, in RENAAL. And in IDNT,

2   there was a 36 percent excess in comparison to active

3   control, in this case amlodipine. So, the cardiovascular

4   deaths went in the wrong direction in both trials. So, if

5   you're going to combine the two trials, you got to combine

6   them on the plus and on the minus side.

7   Again, what it does tell me is that the when

8   you combine those two trials, looking for cardiovascular

9   benefit, you're now looking at 3,000, 4,000 patients.

10   You're not looking at such a small study. So, now we're

11   sitting here in a post-HOPE era and with all the data we

12   have and now we've got two trials, both of which failed to

13   show the cardiovascular events going in the right

14   direction. In some cases like IDNT, they went in the wrong

15   direction for one of the arms. And now I'm troubled by it

16   all.

17   I don't think you can combine it for the

18   efficacy side without looking at both the pluses and the

19   minuses of combining the two trials, and I really do think

20   there's a lot of risk here in taking two different drugs in

21   the same class and saying, well, we've got trials with each

22   of these, we're going to use them to support each other

23   because it's going to come up again and again, unless you

24   really want to make the standard a lot lower. So, that's

25   my dissent.

1   DR. BORER: Susanna?

2   DR. CUNNINGHAM: I think a yes and a no. I

3 think they could support each other, but I don't think it's

4 as good as replication. But I think all the other points

5 that have been made are good ones. So, it's not exactly a

6 real clear-cut picture.

7   DR. BORER: Beverly?

8   DR. LORELL: I think that having looked at

9 these two trials very close together is almost more

10 troublesome than helpful. I think I agree more with Steve.

11   Let me see if I can articulate why that is true.

12   I think the evidence in aggregate from both of

13 those trials and other smaller studies compellingly argues

14 that there is a biologic real effect of interfering with

15 the renin-angiotensin system on progression of renal

16 disease. However, I think there are a couple of problems

17 when you actually look at these two trials together, and I

18 think we can't help but do that on this panel.

19   One is that they are remarkably congruent in

20 the modest nature of the effect on the primary endpoint,

21 and in fact they're quite congruent that for the primary

22 composite endpoint, the p value for both was .02. So, if

23 anything, that would suggest that the effect is a fairly

24 modest one and not a robust one.

25   If one tries to dissect and sort of redesign

1 the trials, going back to Tom's analysis of the hard

2 endpoint of end-stage renal disease, here we actually have

3 a bit of a problem because in this trial, if one pulls that

4 out not as the primary endpoint, it looks highly

5 significant. In fact, if I recall my data notes correctly

6 from a month ago, it was not significant in the other

7 trial.

8   DR. TEMPLE: They didn't have the same kind of

9 follow-up here.

10   DR. LORELL: I agree.

11   DR. TEMPLE: Up to the time of the endpoint,

12 the results were the same.

13   DR. LORELL: In fact, in pulling it together,

14 we have somewhat discordant data.

15   I share Steve's concern that we have two data

16 sets with the very worrisome hint of actually a negative

17 effect on the hard endpoint of cardiovascular death which

18 was the major cause of all deaths in this trial.

19   So, if anything, I think yes, it supports an

20 effect on the biology, but I think that putting them

21 together actually is somewhat dissuasive for approval of

22 this for the endpoint.

23   DR. TEMPLE: Can I just ask? The previous

24 study showed no difference versus placebo on mortality, and

25 there was a trend or maybe more than a trend, favoring the

1   calcium channel blocker. So, are you saying that suggests

2   a negative effect on mortality, or are you suggesting that

3   everybody ought to be on a calcium channel blocker?

4   DR. LORELL: No, I didn't say that at all. Far

5   be it for me to suggest that all these patients should be

6   on calcium channel blockers.

7   DR. TEMPLE: I didn't think so.

8   DR. LORELL: That was not what I said. I agree

9   with Steve's point that there is a worrisome signal

10 regarding an event that is of immense clinical importance.

11   DR. THROCKMORTON: But it's just worth thinking

12 so we understand. In the IDNT trial -- and I can be

13 corrected if I'm wrong -- the irbesartan mortality was, in

14 fact, lower on irbesartan than it was on placebo, 16

15 percent versus 14.9 percent. You're right. Amlodipine had

16 a point estimate that was lower than irbesartan, but versus

17 placebo, which was the comparison we had today, in fact it

18 trended in the correct and better direction. So, it would

19 be a wash if all you were doing was adding the two of them

20 up.

21   DR. FLEMING: Just as a quick statistical

22 clarification, Steve and Beverly, I think you raise very

23 relevant issues about looking at each of these components,

24 and cardiovascular death certainly is a key component.

25 Just as a reminder, the 90 versus 79 deaths translates into

1   an absolute 1.5 percent increase or a relative increase of

2   about 14.5 percent, and for an event that occurs at 10 to

3   12 percent in the population to be able to detect that

4   relative risk, i.e., to reliably sort out whether this is a

5   true 15 percent increase or it's purely noise, would take

6   20,000 to 25,000 people. It is more of a concern seeing it

7   in two trials of size 1,500 apiece, but even those two

8   together are still one-eighth of the size that we would

9   need to say anything reliable about whether that's a true

10   increase or it's consistent with random variability.

11   DR. TEMPLE: Tom, let's be clear we've got the

12   facts right. We don't think you do see it in the

13   irbesartan trial. What you see is a comparison with a

14   different drug, but against placebo it was actually

15   slightly but irrelevantly better.

16   DR. LINDENFELD: Yes. I think just the placebo

17   group was 16 percent in IDNT and I think 14.9 in irbesartan

18   and 14.1 in amlodipine.

19   DR. TEMPLE: So, that's not seeing the same

20   thing twice.

21   DR. LINDENFELD: Overall deaths, total

22   mortality.

23   DR. FLEMING: I thought what Beverly --

24   DR. LORELL: My concern was cardiovascular

25   deaths explicitly.

1   DR. BORER: Let me ask before we go on to Paul,

2   we want for the record, Beverly, a vote on 9.1. Do the

3   findings of IDNT support the effectiveness of losartan for

4   diabetic nephropathy. Forget out the magnitude of the

5   support which you've already answered in detail. But can

6   you look at these data in looking for support for RENAAL?

7   DR. LORELL: I think they provide soft support

8   in aggregate.

9   DR. BORER: Paul?

10   DR. ARMSTRONG: I side with JoAnn and I do so

11   in the context of reassurance about ARB versus placebo in a

12   broader pattern of evidence than what's been provided. So,

13   when I take that into context, I'm comforted.

14   DR. BORER: Do you want to go to the specifics

15   of 9.2 in addition to having voted yes on 9.1?

16   DR. ARMSTRONG: Just to reiterate what JoAnn

17   has said all the way down the line.

18   DR. KOPP: Yes. I think the findings from IDNT

19   are supportive.

20   I guess I'd like to make a point about

21   cardiovascular mortality to remind ourselves that once

22   somebody starts dialysis, the first-year mortality is

23   something like 20 to 25 percent and the two-year mortality

24   is something like 40 percent. So, if this drug is able to

25   postpone dialysis for even 6 months, it may gain more lives

1   because people don't start dialysis and die from

2   cardiovascular death potentially caused during that 6

3   months or 2 years of treatment.

4   DR. NISSEN: That's why I was so disturbed by

5   the fact it didn't go in the right direction. I would have

6   expected that a drug that would delay renal failure would

7   have an effect on death, and the fact that it didn't was

8   very bothersome to me in both trials.

9   DR. KOPP: Yes, that's a fair point.

10   I guess one issue would be is the dialysis

11 follow-up sufficient to see the full benefit, but I take

12 your point.

13   DR. BORER: Dr. Brem?

14   DR. BREM: To 9.1, I think they are supportive

15 in several ways. One, there is a dose dependence to the

16 effect in the IDNT trial which we have not been able to

17 demonstrate in this trial. Also, the blood pressure was

18 more comparable in the IDNT trial. There was, in other

19 words, less of a difference. So, it would support the view

20 that if you gave enough of a sartan drug, that it would

21 have some beneficial effect on the progression of diabetic

22 nephropathy.

23   The other point that I would make is I think

24 that the irbesartan trials now are more supportive in light

25 of ancillary or perhaps less relevant endpoints and that is

1   the progression of proteinuria. In this particular study,

2   there is a clear demonstration that proteinuria is

3   associated with the progression of renal disease. That was

4   not able to be demonstrated on the IDNT trial

5   satisfactorily. So, if one uses that information in

6   context, that's further information to me that would

7   support its beneficial effects.

8   So, yes, I think the two studies together are

9   complementary. They aren't additive, but they are

10 complementary.

11   DR. BORER: Having said that, why don't we

12 start with you again. I think we know the vote because

13 you've already given it. Should losartan be approved for

14 the treatment of nephropathy in patients with type II

15 diabetes?

16   DR. KOPP: Yes.

17   DR. BORER: Do you need more reasoning given

18 everything we've heard, or can he just vote yes?

19   DR. THROCKMORTON: No.

20   DR. BORER: Okay.

21   Dr. Kopp?

22   DR. KOPP: Yes.

23   DR. BORER: Paul?

24   DR. ARMSTRONG: Yes.

25   DR. BORER: Beverly?

1   DR. LORELL: No.

2   DR. BORER: Susanna?

3   DR. CUNNINGHAM: Yes.

4   DR. THROCKMORTON: Jeff, I'm sorry. If for any

5   reason that you don't -- well, no, that's fine. I take it

6   back.

7   DR. BORER: Steve?

8   DR. NISSEN: No.

9   DR. BORER: I vote yes, but I want to expand a

10 little bit. I think that the drug should be approved for

11 diabetic nephropathy in patients with type II diabetes.

12 I've already talked about my views of RENAAL, that I think

13 it's a pretty good trial, better than the nominal p value

14 on the primary endpoint, but not as good as two. I thought

15 IDNT supported it to some extent, sufficient so that I'm

16 willing to accept the effectiveness. But I'll say again I

17 believe that there are multiple safety issues that have to

18 be dealt with in labeling, that the mandated use of this

19 drug has to be dealt with in labeling, the fact that it

20 shouldn't be mandated.

21   And I am concerned about cardiovascular death,

22 but I'm less concerned than some of my colleagues because

23 we haven't looked at this population before, and I just

24 don't know what happens to cardiovascular events in people

25 who have end-stage or near end-stage renal disease. So,

1 I'm really not willing to delay the drug because of my

2 concerns, which are very real, about the cardiovascular

3 event issue. I won't say cardiovascular death because I

4 agree with Dr. Kopp about the tradeoff there.

5   Having said all that and having voted yes, I

6 have to say that if another ARB comes to this committee

7 tomorrow for the same indication, I may say no because I

8 may not find the totality of data from all these trials

9 that we've seen now -- that's two, RENAAL and IDNT --

10 together with whatever is presented for the new molecule

11 sufficient to weigh me in favor of the new molecule even if

12 the study turns out to be nominally positive for the new

13 molecule. So, this is not a precedent. This is a specific

14 issue.

15   Alan?

16   DR. HIRSCH: Well, I would vote no, but that's

17 in the guise that I don't believe a disapproval, if the

18 committee goes that way, will deprive a single patient with

19 diabetic nephropathy of access to a molecule that's

20 available. However, if approval is recommended, then like

21 my colleague to my left, I believe that the safety issue --

22 yes, sir?

23   DR. TEMPLE: Well, I guess we would hope, as a

24 general matter, that you not consider such practicalities.

25   DR. HIRSCH: Okay, I won't.

1   DR. TEMPLE: We want your answer and your

2   answer is no.

3   DR. HIRSCH: It remains the same.

4   DR. TEMPLE: But if your answer would be

5   different if somehow they weren't available --

6   DR. HIRSCH: No. I hear you. My answer, Bob,

7   is the same in the sense that I've been all day, including

8   at the last meeting, trying to be consistent between the

9   two meetings, like Bev, trying to look at the data from

10 single trials, even the two trials together, and decide,

11 fine, if this weren't available, do I have adequate data at

12 this point to bring it to approval. I would like not to

13 have to change my vote the next time an ARB comes. I'd

14 like to make sure the evidentiary standard persists.

15   DR. TEMPLE: But I guess we hope the votes will

16 be as if it wasn't available. Otherwise, it's sort of --

17   DR. HIRSCH: Well, I answered that. You may

18 have to ask the others who aren't here to revote.

19   DR. TEMPLE: No. You were the only one who

20 indicated that was influencing you. It's hard not to face

21 reality and know that it doesn't really matter whether we

22 approve it or not. People can use it anyway because they

23 can read the New England Journal. But we like to try to do

24 it completely abstractly and on an evidentiary basis and

25 not do that because, you know, fair is fair.

1   DR. HIRSCH: Fair is fair.

2   DR. THROCKMORTON: Was your reason for raising

3   the issue of it being available your concern with the

4   safety?

5   DR. HIRSCH: Yes. My hesitation is deep and

6   long and I'm not sure that the whole room has to hear a

7   rehash of what you've heard, but it does get attributed to

8   what I would see if I were merging the two trials. I'd

9   still believe there is a safety blip that is of some

10   concern and efficacy standards that are not quite achieved.

11   So, it's that risk/benefit analysis we always follow here

12   on prima facie evidence.

13   DR. BORER: Blase?

14   DR. CARABELLO: I vote yes.

15   DR. BORER: I think you already gave your

16   reasoning.

17   JoAnn?

18   DR. LINDENFELD: I vote yes. Just two quick

19   comments.

20   Again, as has been said before, I think we need

21   to try to say something that this doesn't imply superiority

22   over ACE inhibitors, just something in there.

23   And the other thing in terms of safety is that

24   I think we need to make it clear that the risk of

25   hyperkalemia is cumulative with this drug over the course

1   of the drug and probably always needs to be monitored

2   ongoing over time. That's a little bit different I think

3   than in other situations.

4   DR. TEMPLE: I do have to say commenting that

5   it's not better than ACE inhibitors or that that hasn't

6   been studied would be a very unusual thing for us to do

7   when there's no data showing that ACE inhibitors work in

8   this setting.

9   DR. LINDENFELD: That's right.

10   DR. TEMPLE: That's tough to support.

11   DR. LINDENFELD: That is tough, but maybe we

12   can think about that. But it would be nice to not have

13   this supplant the use of ACE inhibitors I think or not have

14   this be a reason to do that. Maybe that's not possible,

15   but I share that concern.

16   DR. TEMPLE: Also, if either of you have

17   specific suggestions or little phrases that you think will

18   do this, please.

19   DR. BORER: Off-line we can do that. I think

20   what JoAnn is saying is the same thing that I am, that

21   there has to be some kind of language that says we are not

22   saying that this is the be all and the end all. Now, how

23   to say that, I think we can figure out, make some

24   suggestions, and you can improve upon them, and something

25   can be done.

1   DR. TEMPLE: Again, though, for reasons that

2   are not known to us, no one has bothered to study ACE

3   inhibitors in this setting. I don't know why that is.

4   Maybe because they're all going to go off patent soon or

5   whatever the reason is, but nobody has studied it.

6   DR. BORER: Right. No, I'm not suggesting that

7   we can say anything about the relation to ACE inhibitors.

8   What I'm saying is we must say that we don't know what the

9   story is with cardiovascular morbidity and mortality here,

10   and therefore we can't say that this is necessarily the way

11   that one must go in the individual patient.

12   DR. TEMPLE: We would certainly give the

13   results that show no benefit on those endpoints. That

14   would be part of the trial.

15   DR. BORER: Okay, well, I don't want to take up

16   everybody's time, but we can write down some suggestions.

17   Tom?

18   DR. LORELL: Mr. Chair, are we really giving

19   two votes here? One is a yes/no vote if we get to have a

20   conditional labeling, and one is a yes/no vote if we don't

21   have any influence on labeling?

22   DR. BORER: No. I think we're saying we think

23   that the drug should be approved or it shouldn't be

24   approved and then we're giving caveats about how we think

25   that ought to happen. We're only an advisory committee and

1   the law is sitting across the table from us.

2   DR. TEMPLE: No, but suggestions on what you're

3   thinking of are welcome. I'm just trying to signal that

4   saying something like we don't know whether you're better

5   than ACE inhibitors, when they don't even have that claim,

6   would be very difficult to support against -- well, it

7   would be difficult to convince me to do that, much less the

8   company.

9   DR. BORER: I was going to make the suggestion

10 off-line, but sometimes we have meetings or sections of

11 meetings about issues rather than about drugs. I think

12 this issue in so many areas may have risen to the point of

13 needing some kind of open discussion at some other time.

14   Tom, I think you already voted on

15 approvability, but do you want to restate it?

16   DR. FLEMING: Sure. Yes, I vote approval. And

17 maybe I could just add one additional clarification and

18 that is I wanted to reinforce the wisdom that I have heard

19 today that one has to be extremely cautious when one is

20 analyzing data in putting particular focus on primary

21 endpoints. I want to strongly endorse that as extremely

22 important. From a statistical perspective, when we're

23 using a trial as a confirmatory trial, if one wants to

24 assess strength of evidence in a confirmatory fashion, it

25 is extremely important that we prespecified our primary

1   hypothesis with primary analysis methods so that we can

2   really interpret strength of evidence in that context.

3   Having said that, as strongly as I think

4   statistical procedures are extremely useful in making these

5   assessments, as to whether or not studies adequately

6   establish favorable benefit to risk, any statistical

7   approach must be viewed with the broadest assessment,

8   bringing in clinical judgment.

9   In my own sense in this particular trial, if

10   one views, as I do in this particular case, that the

11   primary endpoint that was set up here has as an important

12   component, at least a component that I view to be a

13   surrogate, which in particular in this setting isn't

14   intrinsically necessary to rely on because the clinical

15   endpoints are occurring so rapidly, it's my own assessment

16   that the evidence that I would have looked for in this

17   trial -- even though the primary endpoint had the triple

18   component, I would have relied on the double component

19   anyway.

20   Essentially, at least in my own perspective,

21   what one needs to avoid is a situation where you don't see

22   what you had hoped to see in the primary endpoint and you

23   start looking around for other ways of getting a more

24   favorable conclusion. Clearly that's hazardous.

25   What I'm trying to sort through here, though,

1   is in my own assessment, at least speaking for myself,

2   that's not the issue. As we discussed in January, some of

3   us had argued very strongly that in a setting such as this,

4   the primary endpoint ought to be based on those elements

5   that are truly the clinical elements, especially when they

6   can be addressed in a timely way and especially in a

7   setting such as this where it's somewhat problematic how to

8   interpret the triple endpoint because there wasn't a

9   complete follow-up. It creates a situation, at least for

10 me in my own judgment, that the primary endpoint would not

11 have been persuasive even if it had been meeting the

12 standards for strength of evidence of two positive trials.

13   So, I guess what I'm trying to articulate here

14 is just to reinforce that there is great wisdom in stating

15 that one needs to be extremely cautious about the strength

16 of evidence and the focus that you give to the primary

17 endpoint, but there clearly needs to be judgment and you

18 clearly need to look at the totality of results. So, I

19 would like to make it clear that, at least in my own case

20 where my view of what is clinically relevant leads me,

21 independent of what these data would have shown, to focus

22 on the dual endpoint shouldn't be viewed as an endorsement

23 of readily deviating from the primary endpoint.

24   DR. BORER: What we've said in summary is that

25 the majority of the committee favors approval of this drug

1   for the requested indication. I think it's important to

2   remember that there have been many important concerns

3   raised and that, though the vote was clearly and decisively

4   in favor of approval, the magnitude of the difference

5   between those who voted yes and those who voted no may be

6   relatively small and, therefore, that there's no binding

7   precedent based on this vote for how this committee would

8   view other drugs if they come with similar credentials for

9   similar indications.

10   Finally, I think I can say for all of us that

11   we voted the way we did without the expectation that

12   another trial is going to be performed because the data

13   didn't satisfy everybody. We voted based on what we have.

14   Bob?

15   DR. TEMPLE: I just wanted to thank you. This

16   was another difficult session, just like the one in January

17   was. You grappled with it.

18   I have to tell you it's hard not to allow

19   people to draw inferences from the fact that we're making

20   use of data from another drug of the same class, and they

21   will. You are, of course, free to be as situation-

22   appropriate as you want.

23   But this was very helpful to us and it was a

24   good discussion. So, we thank you.

25   DR. BORER: Thank you.

1   If there are no other questions from the FDA,

2   I'll call the meeting adjourned.

3   (Whereupon, at 4:47 p.m., the committee was

4   adjourned.)

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