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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS
ADVISORY COMMITTEE

Thursday, March 27, 2014
8:01 a.m. to 4:06 p.m.

FDA White Oak Campus
Building 31, The Great Room (Room 1503)
White Oak Conference Center
Silver Spring, Maryland

1 **Meeting Roster**

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

3 **Kristina A. Toliver, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7
8 **CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE**

9 **MEMBERS (Voting)**

10 **James DeLemos, MD**

11 Cardiology Service Chief, Parkland Memorial

12 Hospital

13 Sweetheart Ball-Kern Wildenthal, MD, PhD

14 Distinguished Chair in Cardiology

15 Professor of Medicine

16 University of Texas Southwestern Medical Center

17 Dallas, Texas

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Julia B. Lewis, MD

Professor of Medicine
Department of Nephrology
Vanderbilt University School of Medicine
Nashville, Tennessee

Jennifer S. Li, MD, MHS

Division Chief, Pediatric Cardiology
Director, Pediatric Research
Duke Translational Medicine Institute
Beverly C. Morgan Professor of Pediatrics
Professor of Medicine
Duke University School of Medicine
Durham, North Carolina

1 **A. Michael Lincoff, MD**

2 ***(Chairperson)***

3 Vice Chairman, Department of Cardiovascular
4 Medicine

5 Director, C5Research (Cleveland Clinic

6 Coordinating Center for Clinical Research)

7 Professor of Medicine, Cleveland Clinic

8 Cleveland, Ohio

9
10 **Vasilios Papademetriou, MD**

11 Professor of Medicine, Georgetown University

12 Chief Cardiovascular, VA Medical Center

13 Division of Cardiology

14 Washington, District of Columbia

15

16

17

18

19

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22

1 **Stuart Rich, MD**

2 Professor of Medicine

3 University of Chicago Pritzker School of Medicine

4 Attending Physician

5 Center for Pulmonary Hypertension

6 Section of Cardiology

7 University of Chicago Hospitals

8 Chicago, Illinois

9

10 **Philip Sager, MD**

11 Consulting Professor of Medicine

12 Stanford University School of Medicine

13 Chair, Scientific Programs Committee

14 Cardiac Safety Research Consortium

15 San Francisco, California

16

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18

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20

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1 **CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE**

2 **MEMBER (Non-Voting)**

3 **Rob Scott, MD**

4 *(Industry Representative)*

5 Vice President Global Clinical Development

6 Cardiovascular Therapeutic Area Head

7 Amgen

8 Thousand Oaks, California

9
10 **TEMPORARY MEMBERS (Voting)**

11 **Ralph D'Agostino, PhD**

12 Professor of Mathematics/Statistics,

13 Biostatistics, and Epidemiology

14 Boston University

15 Boston, Massachusetts

16
17 **Susan Leighton**

18 *(Patient Representative)*

19 Huntsville, Alabama

20

21

22

1 **Michele J. Orza, ScD**

2 *(Acting Consumer Representative)*

3 Washington, District of Columbia

4

5 **Michael Proschan, PhD, MS**

6 Mathematical Statistician

7 Biostatistics Research Branch

8 National Institute of Allergy and Infectious

9 Diseases

10 National Institutes of Health (NIH)

11 Bethesda, Maryland

12

13 **FDA PARTICIPANTS (Non-Voting)**

14 **Robert Temple, MD**

15 Deputy Director for Clinical Science

16 CDER, FDA

17

18 **Ellis Unger, MD**

19 Director

20 Office of Drug Evaluation I (ODEI)

21 Office of New Drugs (OND), CDER, FDA

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

2 (8:01 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. LINCOFF: Good morning, everyone. If
6 everyone can take their seats, we can get started.
7 I'd like to remind everyone present to please
8 silence your cell phones, BlackBerrys, and other
9 devices if you've not already done so.

10 I'd also like to identify the FDA press
11 contact for this meeting, Ms. Sandy Walsh. If
12 you're here, please stand.

13 My name is Michael Lincoff. I'm the
14 chairperson for the Cardiovascular and Renal Drugs
15 Advisory Committee. I'll now call this meeting of
16 the Cardiovascular and Renal Drugs Advisory
17 Committee to order.

18 We'll start by going around the table and
19 introducing ourselves. Let's start down at the
20 right.

21 DR. SCOTT: Good morning. My name is Rob
22 Scott. I'm the head of cardiovascular development

1 at Amgen, and I'm the industry representative.

2 MS. LEIGHTON: I'm Susan Leighton, and I am
3 from Huntsville, Alabama. And I'm the patient
4 representative.

5 DR. RICH: I'm Stuart Rich. I'm a
6 cardiologist at the University of Chicago.

7 DR. SAGER: Philip Sager, cardiologist at
8 Stanford University.

9 DR. LI: Good morning. I'm Jennifer Li.
10 I'm a pediatric cardiologist at Duke University.

11 DR. LINCOFF: I'm Michael Lincoff. I'm an
12 interventional cardiologist at the Cleveland
13 Clinic.

14 MS. TOLIVER: Kristina Toliver, designated
15 federal official, Cardiovascular and Renal Drugs
16 Advisory Committee.

17 DR. DELEMONS: James DeLemos, cardiologist,
18 UT Southwestern in Dallas.

19 DR. LEWIS: Julia Lewis, nephrologist,
20 Vanderbilt.

21 DR. PROSCHAN: I'm Michael Proschan. I'm a
22 statistician from the National Institute of Allergy

1 and Infectious Diseases.

2 DR. D'AGOSTINO: Ralph D'Agostino,
3 statistician from Boston University and the
4 Framingham Study.

5 DR. UNGER: Ellis Unger, director, Office of
6 Drug Evaluation I, Office of New Drugs, CDER, FDA.

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

17 In the spirit of the Federal Advisory
18 Committee Act and the Government in the Sunshine
19 Act, we ask that the advisory committee members
20 take care that their conversations about the topic
21 at hand take place in the open forum of the
22 meeting.

1 We are aware that members of the media are
2 anxious to speak with the FDA about these
3 proceedings. However, FDA will refrain from
4 discussing the details of this meeting with the
5 media until its conclusion.

6 Also, the committee is reminded to please
7 refrain from discussing the meeting topics during
8 breaks or during lunch. Thank you.

9 **Conflict of Interest Statement**

10 MS. TOLIVER: The Food and Drug
11 Administration is convening today's meeting of the
12 Cardiovascular and Renal Drugs Advisory Committee
13 under the authority of the Federal Advisory
14 Committee Act of 1972.

15 With the exception of the industry
16 representative, all members and temporary voting
17 members of the committee are special government
18 employees or regular federal employees from other
19 agencies and are subject to federal conflict of
20 interest laws and regulations.

21 The following information on the status of
22 this committee's compliance with federal ethics and

1 conflict of interest laws covered by, but not
2 limited to, those found at 18 USC Section 208 is
3 being provided to participants in today's meeting
4 and to the public.

5 FDA has determined that members and
6 temporary voting members of this committee are in
7 compliance with federal ethics and conflict of
8 interest laws. Under 18 USC Section 208, Congress
9 has authorized FDA to grant waivers to special
10 government employees and regular federal employees
11 who have potential financial conflicts when it is
12 determined that the agency's need for a particular
13 individual's services outweighs his or her
14 potential financial conflict of interest.

15 Related to the discussion at today's
16 meeting, members and temporary voting members of
17 this committee have been screened for potential
18 financial conflicts of interest of their own as
19 well as those imputed to them, including those of
20 their spouses or minor children and, for purposes
21 of 18 USC Section 208, their employers. These
22 interests may include investments, consulting,

1 expert witness testimony, contracts, grants,
2 CRADAs, teaching, speaking, writing, patents and
3 royalties, and primary employment.

4 Today's agenda involves biologics license
5 application 125468, serelaxin injection, submitted
6 by Novartis Pharmaceuticals Corp., as a treatment
7 to improve the symptoms of acute heart failure
8 through reduction of the rate of worsening heart
9 failure.

10 This is a particular matters meeting, during
11 which specific matters related to Novartis' BLA
12 will be discussed.

13 Based on the agenda for today's meeting and
14 all financial interests reported by the committee
15 members and temporary voting members, no conflict
16 of interest waivers have been issued in connection
17 with this meeting.

18 To ensure transparency, we encourage all
19 standing committee members and temporary voting
20 members to disclose any public statements that they
21 may have made concerning the products at issue.

22 With respect to FDA's invited industry

1 representative, we would like to disclose that
2 Dr. Rob Scott is participating in this meeting as a
3 nonvoting industry representative, acting on behalf
4 of regulated industry. Dr. Scott's role at this
5 meeting is to represent industry in general and not
6 any particular company. Dr. Scott is employed by
7 Amgen.

8 We would like to remind members and
9 temporary voting members that if the discussions
10 involve any other products or firms not already on
11 the agenda for which an FDA participant has a
12 personal or imputed financial interest, the
13 participants need to exclude themselves from such
14 involvement, and their exclusion will be noted for
15 the record.

16 FDA encourages all participants to advise
17 the committee of any financial relationships that
18 they may have with the firm at issue. Thank you.

19 DR. LINCOFF: We have two additional
20 members. If you could just introduce yourselves
21 into the record, please.

22 DR. PAPADEMETRIOU: Vasilios Papademetriou,

1 Washington, D.C.

2 DR. TEMPLE: Bob Temple, deputy director.

3 DR. LINCOFF: We'll now proceed with the FDA
4 opening remarks from Dr. Ellis Unger. I would like
5 to remind public observers at this meeting that
6 while this meeting is open for public observation,
7 public attendees may not participate except at the
8 specific request of the panel.

9 Dr. Unger?

10 **Opening Remarks - Ellis Unger**

11 DR. UNGER: Thank you, Dr. Lincoff, and good
12 morning, everyone. First let me welcome the
13 committee members as well as the patient, consumer,
14 and industry representative. I'd also like to take
15 a moment to thank in advance individuals who are
16 registered to participate in the open public
17 hearing this afternoon. Your comments are very
18 important to us, and we appreciate your effort in
19 coming here today to White Oak.

20 You're all aware that this meeting was
21 originally scheduled to be the 13th of February,
22 which was a snow day. And we rescheduled, I think

1 to the relief of many of you, maybe to the
2 consternation of some. But we appreciate your
3 flexibility in allowing us to reschedule the
4 meeting.

5 Dr. Stockbridge, the director of the
6 Division of Cardiovascular and Renal Products, took
7 a vacation, which is unusual, so he's not here this
8 week.

9 Okay. So as you know, we're here to discuss
10 a biologics license application for serelaxin,
11 which was submitted by Novartis Pharmaceutical
12 Corporation. Serelaxin is a recombinant form of
13 the hormone relaxin-2, and the proposed indication
14 sought is to improve the symptoms of acute heart
15 failure through reduction of the rate of worsening
16 heart failure.

17 Later this morning Dr. Melanie Blank, the
18 medical officer, and Dr. Steven Bai, the biometrics
19 reviewer, will give a detailed presentation of the
20 issues we're concerned about. But I'd like to give
21 just a high-level overview of the issues as seen
22 from our vantage point and for your orientation.

1 In support of the proposed indication, the
2 applicant submitted the results of a large
3 randomized, double-blind, placebo-controlled trial
4 called RELAX-AHF, and that would be your focus
5 today.

6 The trial enrolled 1161 patients with acute
7 heart failure. The patients had been treated prior
8 to their screening for the study, and the patients
9 had to be in reasonable shape. They had to have a
10 good blood pressure, at least 125 millimeters of
11 mercury systolic, at the time of screening.

12 They were excluded if there was planned use
13 of IV dilators or inotropes or vasopressors. IV
14 nitrates were allowed under some circumstances.
15 And you'll hear that these patients were by no
16 means in extremis. The mean baseline vital signs
17 were as follows.

18 The mean systolic blood pressure was 142,
19 which is well above 125 and pretty high. The heart
20 rate was only 82, and the respiratory rate was
21 only 22. So these are not very high values for a
22 patient in acute heart failure. So they weren't

1 extremely decompensated by the time they were
2 entered in the study. They were largely out of the
3 woods, I would say, when they were enrolled.

4 As you'll hear, the study had two primary
5 endpoints, both of which assessed patient-assessed
6 dyspnea. The first was a change in dyspnea from
7 baseline through day 5, as measured using a visual
8 analog scale.

9 This is a type of scale where a patient
10 is presented with a piece of paper with a
11 100-millimeter scale on it, and they're asked to
12 put pen to paper to rate their dyspnea at that
13 point in time. And they're not necessarily aware
14 of what they reported their dyspnea to be at
15 baseline. The endpoint was assessed by joining all
16 of those dots and summing the area under the curve
17 through 5 days.

18 The second endpoint was more conventional.
19 It was a 7-point Likert scale, also designed to
20 assess dyspnea as reported by the patient. And the
21 endpoint was the proportion of patients with
22 moderately or markedly better dyspnea relative to

1 the start of the study. This was assessed at 6,
2 12, and 24 hours. It had to be positive at all
3 three.

4 The statistical approach controlled type 1
5 error at a two-sided .05 level using the Hochberg
6 procedure. And with that procedure, either
7 endpoint could be successful but only at a two-
8 sided p-value of .025, or both endpoints had to be
9 statistically successful at a two-sided p-value of
10 .05.

11 Although the endpoint on the Likert was not
12 successful, you'll hear the endpoint on the visual
13 analog scale was statistically significantly
14 positive at a p-value that was better than .025.
15 So on its face, the trial succeeded.

16 But you'll hear that the successful results
17 were driven by an imputation rule for worsening
18 heart failure, as assessed by physicians at the
19 bedside. And this imputation scheme severely
20 penalized patients who were reported as having had
21 worsening heart failure, and it affected the
22 calculation in a very great way.

1 Conversely, the imputation scheme had little
2 or no effect on the Likert analysis because of the
3 way that analysis was conducted. The Likert
4 analysis was basically dichotomized as either doing
5 moderately or markedly better at the three time
6 points or not.

7 So patients who were not doing moderately or
8 markedly better were categorized as losers, so to
9 speak, and it didn't matter if they were ranked in
10 the worst because they had worsening heart failure.
11 So it didn't have much effect on that endpoint.

12 One of the intriguing findings here, as you
13 all have read, is a beneficial effect on mortality.
14 Vital status was assessed through 180 days. There
15 were 64 deaths in the placebo group and 41 in the
16 serelaxin group, for a hazard ratio of .63, which
17 was statistically significant.

18 We had considerable discussion and debate
19 about the meaning of this over the last several
20 months. It's very difficult to conceptualize how
21 a drug that's given for 48 hours could affect
22 mortality over the next 178 days when it's long

1 been gone from the bloodstream, and not clear to us
2 whether the results represent play of chance or an
3 actual treatment effect. So we'll be asking you to
4 discuss this.

5 There are several other points we're going
6 to be asking you to consider. We'll be asking you
7 to consider how the imputation scheme affected the
8 positive findings on the dyspnea endpoint, the
9 positive endpoint of the trial, and whether that
10 imputation scheme was reasonable or not.

11 We'll be asking you to consider the clinical
12 meaningfulness of the effect size on dyspnea. The
13 mean effect size through 5 days was about
14 4 millimeters on that zero to 100 millimeter scale,
15 4 out of 100 millimeters.

16 We'll be asking you to consider whether one
17 trial is enough. If you deem the results of
18 RELAX-AHF to be positive, are the findings
19 sufficiently persuasive to obviate the need for
20 substantiation from another trial? In other words,
21 are there sufficient additional findings here,
22 evidence of serelaxin's effectiveness, that

1 together could merit an approval? And maybe the
2 mortality results help somehow. We'll be asking
3 you to think about that.

4 Finally, we will ask you the approval
5 question. But I'll stress that we particularly
6 value your discussions and insights. And so the
7 comments the committee makes are at least as
8 important as the voting for or against approval.

9 One final point. We've included a number of
10 individual and joint reviews in our background
11 package, and they include assessments and
12 conclusions written by the individual FDA
13 reviewers. And as noted in the disclaimer in the
14 FDA briefing package, I want to assure the
15 committee and the audience that we've not made any
16 final decisions on this application.

17 Clearly, we've asked you to convene today
18 because we believe we cannot make a final decision
19 without your input and advice. And you should know
20 that there may be other issues on approvability
21 that are beyond the scope of the committee and the
22 discussion today.

1 So you have your charge. And with that
2 introduction, I'd like to thank you for the
3 considerable work you've already done in
4 preparation for the meeting, and thank you in
5 advance for all of your efforts today. And with
6 that, hand the microphone back to the chairman,
7 Dr. Lincoff. Thank you.

8 DR. LINCOFF: Thank you, Dr. Unger.

9 We will now proceed with the sponsor
10 presentation. Both the Food and Drug
11 Administration and the public believe in a
12 transparent process for information-gathering and
13 decision-making. To ensure such transparency at
14 the advisory committee meeting, FDA believes that
15 it is important to understand the context of an
16 individual's presentation.

17 For this reason, FDA encourages all
18 participants, including the sponsor's non-employee
19 presenters, to advise the committee of any
20 financial relationships that they may have with the
21 firm at issue, such as consulting fees, travel
22 expenses, honoraria, and interests in the sponsor,

1 including equity interests and those based upon the
2 outcome of this meeting.

3 Likewise, FDA encourages you at the
4 beginning of your presentation to advise the
5 committee if you do not have any such financial
6 relationships. If you choose not to address this
7 issue of financial relationships at the beginning
8 of your presentation, it will not preclude you from
9 speaking.

10 Now if we could begin with the sponsor's
11 presentation.

12 **Sponsor Presentation - Ameet Nathwani**

13 DR. NATHWANI: Good morning, Mr. Chairman,
14 members of the advisory panel, representatives of
15 the FDA, ladies and gentlemen. My name is Ameet
16 Nathwani, and I am the global head of critical care
17 for Novartis. And it is my pleasure to introduce
18 the overview of the BLA for serelaxin and its role
19 in the management of acute heart failure.

20 As the panel is well aware, acute heart
21 failure is a life-threatening condition with a
22 prognosis worse than many cancers. It represents

1 the largest cause of hospitalization in
2 over-65-year-olds and associated with a mortality
3 of between 20 and 35 percent at one year.

4 The main treatment goals are to improve the
5 acute clinical status, prevent clinical worsening,
6 and if possible, to reduce the risk of death
7 subsequent to the event.

8 Despite what appear to be simple goals for a
9 condition, which is so common, unlike in acute
10 coronary syndrome where there has been tremendous
11 progress over the last few decades, the treatment
12 for acute heart failure has remained largely
13 unchanged for at least the last 30 years.

14 Serelaxin is the recombinant form of
15 endogenous human relaxin, the hormone which is
16 elevated during pregnancy and is believed to be
17 responsible for the adaptive, systemic,
18 hemodynamic, and renal changes that occur. And it
19 was these observations which led to the
20 conceptualization of serelaxin as a potential tool
21 for the treatment of acute heart failure.

22 Relaxin binds to its cognate G-coupled-

1 protein receptors, the so-called relaxin family
2 peptides. Within the cardiovascular system, these
3 are located in the systemic, coronary, and renal
4 vasculature, as well as cardiac tissue and renal
5 epithelium.

6 Relaxin primarily stimulates rapid and
7 sustained nitric oxide-mediated vasodilatory
8 pathways via the release of nitric oxide. The net
9 physiological effect appears to be an increase in
10 arterial and venous compliance as well as renal
11 blood flow.

12 This chart outlines some key milestones in
13 the development of serelaxin. The acute heart
14 failure program was initiated in 2007 by Corthera,
15 who carried out the Pre-RELAX study and who also
16 initiated the phase 3 RELAX-AHF study. Novartis
17 acquired Corthera in 2010, when the RELAX-AHF study
18 was still ongoing.

19 Following the intriguing mortality data
20 observed across the RELAX program, we have
21 initiated a confirmatory mortality study, RELAX-
22 AHF-2, in 2013. Both the findings and the study

1 are the basis of the breakthrough therapy
2 designation granted by the FDA in 2013.

3 We will review two key studies today, the
4 dose-ranging efficacy study, Pre-RELAX, and the
5 pivotal phase 3 study, RELAX-AHF. These studies
6 were unusual in that they had near-identical
7 designs and enrollment criteria, enhancing the
8 ability to explore data for consistency and
9 concordance. While we will not present the data of
10 the hemodynamic study, we'll be very happy to take
11 questions during the Q&A.

12 The proposed indication we are seeking
13 approval for is to improve the symptoms of acute
14 heart failure through reduction of the rate of
15 worsening heart failure. I emphasize the word
16 "through" deliberately to help focus your attention
17 on the intent we are trying to convey during the
18 presentation of our data.

19 The recommended dosing requirement is
20 weight-based, delivering approximately 30
21 micrograms per kilogram per day, with the infusion
22 initiated as soon as possible after hospital

1 admission.

2 Following my introduction, Dr. Milton Packer
3 will provide a view of the changes of drug
4 development in acute heart failure. He'll be
5 followed by Dr. Olga Santiago, who will review the
6 primary clinical trial results.

7 Dr. Thomas Severin will then follow with a
8 review of the additional efficacy and safety, and
9 the presentation will conclude with Dr. Packer
10 providing a final commentary and clinical
11 perspective of the results.

12 In addition to the presenters named, we also
13 have a panel of several external experts, who will
14 help to join us in the Q&A. And just to include
15 Dr. Barry Greenberg, who has served on the
16 executive committee for the RELAX-AHF study.

17 With that, thank you. Dr. Packer?

18 **Sponsor Presentation - Milton Packer**

19 DR. PACKER: Thank you very much, Ameet.

20 Dr. Lincoff, members of the advisory
21 committee, Drs. Unger and Temple, members of FDA,
22 ladies and gentlemen, before I start I want to

1 mention that my time and travel has been
2 compensated by the sponsor, Novartis. I also would
3 like to mention that I am a special government
4 employee, but I have received permission from FDA
5 to participate on behalf of the sponsor this
6 morning.

7 Now, today's focus is on the treatment of
8 acute heart failure. But my introductory remarks
9 are not focused on the epidemiology of the disease,
10 the limitations of treatment, or the unmet needs of
11 patients. Instead, I will focus on the challenges
12 that clinical investigators and regulatory agencies
13 face in designing and interpreting clinical trials
14 of new drugs in this disease.

15 Now, traditionally there have only been
16 three clinically relevant measures of benefit in
17 trials of heart failure. We seek to make patients
18 feel better, we aim to maintain clinical stability
19 by preventing clinical events that represent
20 worsening of clinical status, and we want to reduce
21 the risk of death. These are, in fact, the only
22 valid measures of benefit for all cardiovascular

1 drugs, regardless of their indication.

2 Now, in patients with chronic heart failure,
3 these three clinically relevant measures of benefit
4 have been reflected in the endpoints used in the
5 design of clinical trials. In the past, we used a
6 variety of symptom-focused metrics in measuring
7 improvements in clinical status.

8 Now, each of these endpoints carried its own
9 challenges, but they all suffered from the fact
10 that they were assessed at arbitrary, protocol-
11 defined time points and did not consider the
12 clinical course of patients between visits.
13 Patients who experienced worsening of their
14 clinical status or died were typically omitted from
15 the analysis, or if they were included, the
16 occurrence of an interval event was ignored.

17 However, in recent years, symptom-focused
18 metrics have begun to incorporate the occurrence of
19 major fatal and nonfatal clinical events occurring
20 between study visits into their analyses.

21 Specifically, they have incorporated the occurrence
22 of hospitalization for heart failure as the key

1 measure of morbidity and all-cause or
2 cardiovascular death as the key measure of
3 mortality.

4 Now, the inclusion of these events into a
5 clinical evaluation of a new drug is important
6 because by doing so, one is effectively shifting
7 the focus from one that looks only at symptoms at
8 one point in time to one that looks at the clinical
9 course of patients over time.

10 Now, one approach that has been used now for
11 about 10 to 15 years is known as the clinical
12 composite, and it has been used to look at changes
13 in symptoms and clinical status in an increasing
14 number of clinical trials in heart failure.

15 Now, this slide shows the structure of the
16 clinical composite. The composite classifies
17 patients as either improved, shown in blue,
18 unchanged, shown in white, or worse, shown in red,
19 usually at the end of the study.

20 But the key to the clinical composite is
21 that if the patient dies or experiences worsening
22 heart failure requiring hospitalization between

1 protocol-specified visits, then the patient is
2 classified as having the worst possible outcome and
3 is not classified as improved, regardless of any
4 other clinical assessments.

5 Now, the same evolution of thought is now
6 taking place in our evaluation of drugs for the
7 treatment of acute heart failure. Initially,
8 trials in acute heart failure focused only on
9 symptoms such as dyspnea scores, various types of
10 global assessment, which were assessed at fixed
11 time points.

12 But such an approach has created major
13 difficulty for investigators who design trials of
14 new drugs for acute heart failure. And the reason
15 is that despite the limitations of current therapy,
16 most patients who are admitted to the hospital with
17 acute heart failure show improvement in symptoms
18 within hours or a few days, such that nearly all
19 patients show some significant improvement, as
20 shown in this schematic.

21 Therefore, if we focus only on the relief of
22 symptoms, the most that we can expect from a new

1 drug is that symptoms will be improved maybe a
2 little faster than they would with current
3 conventional therapy.

4 However, since the majority of patients
5 experience meaningful improvement, the magnitude of
6 this expected benefit will be small and treatment
7 will be intensified, presumably more in the placebo
8 group, if patients do not improve.

9 As a result, at the end of 5 or 7 days or
10 so, the two curves can be expected to converge.
11 The situation is rather similar to that in acute
12 coronary syndromes, where most patients who survive
13 eventually become pain-free.

14 Consequently, as has occurred in the field
15 of chronic heart failure, investigations of new
16 drugs in acute heart failure have begun to shift
17 from an endpoint that focuses only on symptoms to a
18 symptom endpoint that also incorporates morbidity
19 and mortality. And in focusing on morbidity, we
20 have begun to focus on the occurrence of worsening
21 heart failure during the index hospitalization as
22 an important clinical event.

1 A large number of clinical trials and
2 registries have now demonstrated that a meaningful
3 proportion of patients with heart failure
4 hospitalized with acute heart failure improve
5 initially on their prescribed treatment, but then
6 experience meaningful worsening of symptoms.

7 Instead of progressive stabilization and
8 rapid conversion to an oral outpatient regimen,
9 some patients unexpectedly become clinically worse.
10 From the available data, in-hospital worsening
11 heart failure occurs in about 15 to 30 percent of
12 patients within the first 7 days following
13 admission to the hospital for heart failure.

14 Now, the occurrence of in-hospital worsening
15 heart failure has the same significance in trials
16 of acute heart failure as hospitalization for heart
17 failure has in trials of chronic heart failure.
18 Both represent clinically meaningful, nonfatal
19 worsening of clinical status.

20 In capturing the occurrence of these events
21 in clinical trials, we use a similar approach. For
22 both types of events, we require the patient

1 demonstrate worsening of symptoms or in clinical
2 status, and we require that these be sufficiently
3 severe that the clinician responds by the immediate
4 intensification of therapy.

5 Now, you might ask, why do we need to focus
6 on the occurrence of in-hospital worsening heart
7 failure? I'd like to give you three reasons.

8 First, the occurrence of in-hospital
9 worsening heart failure represents a meaningful
10 change in clinical status signifying instability in
11 the clinical course of patients. These episodes
12 are typically unexpected. They may be slow or
13 rapid in onset. They can persist for hours or
14 longer.

15 The patient reports worsening symptoms, and
16 the physician decides that the change in clinical
17 status is unlikely to resolve on its own and thus
18 requires the immediate intensification of rescue
19 therapy. In essence, the occurrence of in-hospital
20 worsening heart failure represents a treatment
21 failure, specifically, the failure of the patient's
22 prescribed therapy to maintain clinical stability.

1 Second, because the occurrence of worsening
2 heart failure leads physicians to intensify
3 background therapy, this intensification,
4 especially if it occurs differently in the two
5 treatment groups, can be expected to distort the
6 trial's ability to identify, quantify, and
7 interpret the benefit of a new drug.

8 Because of the greater intensification of
9 background therapy, patients with worsening events
10 improve and may eventually get almost to the same
11 place as patients who did not experience these
12 worsening events.

13 As a result, if the study protocol specified
14 an evaluation of symptoms at 6 hours and at 48
15 hours, but worsening heart failure occurred between
16 these two time points, then the preplanned symptom
17 assessments would be unable to discern that the
18 clinical course of these two types of patients had
19 been meaningfully different between these two time
20 points.

21 Any analysis that focused only on the
22 measurements taken at preplanned study visits would

1 effectively ignore the fact that the patients had
2 experienced substantial interval worsening of
3 symptoms and a different clinical course.

4 Now, you may be thinking, if intensification
5 of therapy brings the two groups of patients to the
6 same place, why should we care about the interval
7 event? The reason is that the occurrence of in-
8 hospital worsening heart failure appears to have
9 important clinical consequences.

10 In the first hours, its occurrence has been
11 associated with the release of cardiac troponin.
12 Its occurrence necessitates the need for more
13 prolonged intravenous therapy and slows the
14 conversion to outpatient oral therapy, and thus it
15 prolongs the duration of a patient's hospital stay.
16 And its occurrence has been associated with a
17 meaningful increase in the risk of cardiovascular
18 death.

19 Now, of all of these, the one that I would
20 emphasize is the direct relationship between
21 in-hospital worsening of heart failure and the
22 prolonged use of intravenous medications and the

1 lengthening of hospital stay.

2 Therefore, for all the reasons that I've
3 just presented, trials in acute heart failure are
4 now routinely incorporating meaningful interval
5 worsening of clinical status into the analysis of
6 the primary endpoint.

7 Specifically, in most of the recent trials
8 in acute heart failure, patients with interval
9 worsening have been assigned the worst possible
10 score or rank in the analysis of their clinical
11 course. This reflects their status as treatment
12 failures.

13 Now, the committee will hear a great deal of
14 discussion today about the assignment of worst
15 score or worst rank to patients with in-hospital
16 worsening of heart failure. So before that
17 discussion begins, I would like to present a
18 framework for understanding what we are trying to
19 achieve here.

20 Our goal is to accurately describe the
21 clinical course of patients. Now, this slide
22 represents a schematic that illustrates four

1 hypothetical patients with four different clinical
2 courses from the point of randomization.

3 The patient shown in blue has a
4 progressively favorable course. The patient shown
5 in green doesn't change very much but remains
6 clinically stable. The patient shown in red
7 experiences multiple episodes of clinical worsening
8 and is stabilized only because of the
9 intensification of background therapy. And the
10 patient in black deteriorates and dies during the
11 trial.

12 Now, if we look only at the clinical status
13 at the end of the study, we might not see much of a
14 difference amongst these three patients who
15 completed the study even though they had very
16 different clinical courses.

17 To make matters worse, the patient who died
18 would have been excluded from the analysis
19 entirely. Therefore, to fully describe the actual
20 clinical course of these patients, we have been
21 using two approaches.

22 One approach is to carry out numerous

1 clinical assessments during the study period and
2 combine them in time into a single numerical value.
3 To account for the unfavorable events that occur
4 between planned study visits, patients with an
5 unfavorable clinical course are assigned the worst
6 possible score. And I'm going to refer to this
7 approach as the numerical approach.

8 Now, this approach was adopted in the
9 serelaxin program, which assessed the clinical
10 course of patients using a visual analog scale,
11 area under the curve, with worst numerical score
12 assignment for patients with an unfavorable
13 clinical course. The use of numerical scores in
14 this approach is both an advantage and a
15 disadvantage.

16 On the one hand, it provides considerable
17 granularity to the range of clinical responses.
18 But on the other hand, it is challenging to know
19 what numerical score should be assigned to patients
20 with an unfavorable clinical course.

21 A second approach is to describe the
22 clinical course of patients by assigning ranks

1 rather than numerical scores. Now, patients who
2 die or have worsening heart failure are assigned
3 the worst ranks, and those who have marked
4 improvement without worsening are assigned the best
5 rank.

6 Now, this is largely based on the work of
7 Finkelstein and Schoenfeld, who proposed in 1999
8 that the effect of a new drug on the clinical
9 course of a disease could be identified by
10 comparing the distribution of ranks in two
11 treatment groups.

12 Now, this approach is less granular than the
13 first, but it minimizes the need to prespecify and
14 justify a numerical score for the patients with an
15 unfavorable clinical course. Now, this is the
16 approach that has been used in trials that have
17 adapted the clinical composite, originally
18 developed in chronic heart failure, for use in
19 acute heart failure.

20 Remember, the clinical composite defines
21 three ranks. Patients who improve substantially
22 without clinical instability are assigned the best

1 rank. Patients who die or experience clinical
2 instability, as evidenced by in-hospital worsening
3 heart failure or death, are assigned the worst
4 rank, regardless of the level of symptoms assessed
5 following the event.

6 Now, I do want to emphasize that these two
7 approaches, one based on numerical scores on the
8 left and one based on ranks on the right, are not
9 that different from each other. Both approaches
10 assign the worst possible outcome to patients who
11 die or experience clinical instability, as
12 evidenced by in-hospital worsening heart failure.

13 In fact, the visual analog scale that you
14 will hear about today that was used in the
15 serelaxin trials is as much a composite endpoint as
16 the clinical composite used in heart failure
17 trials. In essence, it's a composite of three
18 components, death, in-hospital worsening heart
19 failure, and the visual analog scale. And in the
20 synthesis of this composite, clinical events
21 appropriately supersede changes in symptoms at the
22 time of occurrence.

1 The development of the endpoints I've
2 discussed reflects the fact that our goal in
3 patients with acute heart failure cannot simply be
4 the relief of the presenting symptom since this
5 resolves in most patients following admission.
6 Rather, our goal must focus on the maintenance of
7 clinical stability and the prevention of clinical
8 worsening because doing so favorably affects the
9 in-hospital clinical course of these patients.

10 I'd now like to ask Dr. Olga Santiago to
11 come and present the primary endpoint results of
12 the RELAX trial.

13 **Sponsor Presentation - Olga Santiago**

14 DR. SANTIAGO: Thank you, Dr. Packer. Good
15 morning, Mr. Chairman, members of the advisory
16 committee, representatives of the FDA, ladies and
17 gentlemen. I am Dr. Olga Santiago, the global
18 program head for serelaxin from Novartis. Today I
19 will present the design and primary efficacy
20 results of the RELAX-AHF trial.

21 RELAX-AHF, together with the preceding
22 study, Pre-RELAX-AHF, comprise the two main

1 placebo-controlled trials that support the efficacy
2 of serelaxin in the treatment of patients with
3 acute heart failure.

4 Both trials had identical entry criteria,
5 very similar study designs, and nearly identical
6 endpoints. This allows us to look at consistency
7 of results across these two trials, and Dr. Severin
8 will do so later in the presentation.

9 This slide lists the main entry criteria,
10 which were identical in the two trials. I would
11 like to highlight a few key points.

12 First, all patients were hospitalized for
13 acute heart failure and had dyspnea at rest or
14 minimal exertion with evidence of increased left
15 ventricular filling pressures both on chest X-ray
16 and by levels of natriuretic peptides. They were
17 present despite treatment with intravenous
18 diuretics.

19 In contrast to earlier trials in acute heart
20 failure, patients were randomized early, within
21 16 hours of clinical presentation, in both trials.
22 Furthermore, to reduce the risk of hypotension,

1 patients were enrolled with an entry systolic blood
2 pressure of greater than 125 millimeters of mercury
3 and had a dose reduction for a meaningful decrease
4 in blood pressure.

5 Neither trial enrolled patients who required
6 or were likely to require treatment with
7 intravenous vasodilators, positive inotropic drugs,
8 vasopressors, or mechanical ventilation or
9 circulatory support at the time of randomization.
10 Eligible patients could be on an infusion of
11 intravenous nitrates if the systolic blood pressure
12 was elevated, but only at a dose of 0.1 milligrams
13 per kilogram per hour or less.

14 In both trials, patients were randomized to
15 placebo or one or more doses of serelaxin. Placebo
16 or serelaxin was infused for 48 hours, efficacy
17 assessments were carried out for up to 5 days,
18 patients were discharged when clinically
19 appropriate, and all patients were followed for
20 180 days post-randomization. The only difference
21 was that four doses were evaluated in Pre-RELAX-AHF
22 and only one dose of serelaxin was evaluated in

1 RELAX-AHF.

2 Both trials specified the same efficacy
3 endpoints. These included short-term assessments,
4 which were carried out during the index hospital
5 stay. Long-term assessments were also performed
6 and were carried out post-discharge.

7 In the confirmatory trial, RELAX-AHF, two
8 in-hospital assessments were designated as primary
9 endpoints and two post-discharge assessments were
10 designated as secondary endpoints. I will focus
11 the remainder of the presentation on the two
12 primary endpoints.

13 One of the primary endpoints used the visual
14 analog scale shown on the left, which asked
15 patients to identify their current level of dyspnea
16 at prespecified time points during the first
17 5 days. This endpoint was designed to be sensitive
18 to both improvement and worsening over time.

19 If the in-hospital clinical course of
20 patients was particularly poor, specifically if the
21 patient died or experienced worsening heart
22 failure, the worst observed score was assigned from

1 the time of occurrence of worsening heart failure
2 through to day 5, and this worst score superseded
3 any recorded subsequent assessment.

4 The other primary endpoint used a Likert
5 scale, shown on the right. This scale asked
6 patients to compare their symptoms to their
7 baseline status. The analysis of this endpoint
8 focused only on patients who considered themselves
9 markedly or moderately improved at all prespecified
10 time points during the first 24 hours. Therefore,
11 this endpoint was designed to be sensitive only to
12 early responders. The alpha for the study was
13 divided equally across these two different
14 endpoints.

15 The difference between the two primary
16 endpoints can also be depicted graphically. As
17 just noted, the Likert endpoint, shown in brown and
18 pink in the upper left, focused only on patients
19 who showed moderate or marked improvement at all
20 time points during the first 24 hours. And since
21 the first planned assessment was at 6 hours,
22 patients had to show improvement at 6 hours to be

1 included as a responder.

2 In contrast, the visual analog scale-area
3 under the curve was sensitive to the entire range
4 of patient responses through to day 5, including
5 worsening.

6 In order for the visual analog scale to be
7 sensitive to the entire range of patient responses,
8 it was constructed as a composite endpoint with
9 three components: death, the occurrence of
10 in-hospital worsening heart failure, and change in
11 the dyspnea score.

12 Composite endpoints are typically designed
13 to be analyzed in a hierarchical manner, and for
14 this composite, the occurrence of death or in-
15 hospital worsening heart failure superseded the
16 change in dyspnea score. This was prespecified in
17 the protocol and in the statistical analysis plan.

18 Prior to presenting the results, I would
19 like to briefly review the baseline characteristics
20 of the study population. The 580 patients in the
21 placebo group and 581 patients in the serelaxin
22 group were well-balanced at the time of

1 randomization and were typical of patients with
2 heart failure.

3 About half of the patients had a preserved
4 left ventricular rejection fraction, and the
5 patients were appropriately treated with neural
6 hormonal antagonists. Of note, the average time
7 from initial presentation to randomization was
8 about 8 hours.

9 The effects of placebo and serelaxin on the
10 visual analog scale-area under the curve composite
11 through to day 5 are shown here. The visual analog
12 scale values in the placebo group, shown in green,
13 were approximately 20 percent better than the
14 values in the placebo group, shown in gray.

15 The p-value for the difference was 0.0075,
16 which was smaller than the prespecified threshold
17 of 0.025. Hence, the RELAX-AHF trial achieved its
18 primary endpoint, as defined in the protocol, below
19 the prespecified threshold for statistical
20 significance.

21 The effect of serelaxin on the visual analog
22 scale was consistent across subgroups, and the

1 magnitude of the effect did not vary according to
2 any baseline characteristic. This was true of the
3 baseline variables shown on this slide as well as
4 the more disease-related baseline variables shown
5 on this slide.

6 The effects of placebo and serelaxin on the
7 second primary endpoint, the Likert scale analysis
8 of early responders, are shown here. Although the
9 proportion of responders was slightly higher in the
10 serelaxin group than the placebo group at all three
11 time points, this endpoint, which required a very
12 favorable response at all three points, was not
13 met.

14 The reason why one primary endpoint was
15 achieved while the other was not is apparent from
16 this graphic. The Likert scale was sensitive only
17 to early responders and was designed not to be
18 influenced by patients with a poor in-hospital
19 clinical course. In contrast, the visual analog
20 scale was designed to be sensitive to the full
21 range of patient responses and for a far longer
22 period of time.

1 To show that these differences were
2 responsible for the results of the RELAX-AHF trial,
3 we performed two analyses.

4 First we took the values recorded for the
5 Likert scale, and instead of focusing only on this
6 small square, where assigning score for patients
7 with a poor in-hospital clinical course is not
8 expected to have an impact, we analyzed the full
9 range of values for the Likert scale over the
10 entire 5-day primary endpoint evaluation period,
11 again assigning worst score for patients with a
12 poor in-hospital clinical course, and found a
13 statistically significant difference between
14 placebo and serelaxin using the Likert scale, just
15 as we had seen with the visual analog scale-area
16 under the curve composite endpoint.

17 We then carried out the complementary
18 analysis using the visual analog scale. The visual
19 analog scale responses, with the worst score
20 assignment, are shown as hatched lines. And the
21 responses without worst score assignment for
22 patients with a poor in-hospital clinical course

1 are shown in the superimposed solid lines. There's
2 very little difference between placebo and
3 serelaxin.

4 Therefore, these two additional analyses
5 show, in a complementary manner, that the RELAX-AHF
6 trial achieved its primary endpoint primarily
7 because of a favorable effect of serelaxin on the
8 number of patients who died or experienced
9 worsening heart failure and were assigned the worst
10 observed score.

11 The incidence of a poor in-hospital outcome,
12 worsening heart failure through to day 5, was
13 markedly reduced in the serelaxin group compared to
14 placebo. The risk reduction was evident early
15 during the first 48 hours, which was the time when
16 the study drug was infused.

17 At the end of the 5-day primary endpoint
18 evaluation period, serelaxin reduced the risk of a
19 worsening event by about 50 percent. The effect is
20 the basis of our proposed indication for serelaxin,
21 which indicates that the benefit of serelaxin in
22 patients with acute heart failure was achieved

1 through a reduction in the short-term risk of
2 worsening heart failure.

3 Now, as you can tell from the documents you
4 received, the FDA and Novartis agree that the
5 effect of serelaxin in the RELAX-AHF trial is
6 achieved through a reduction in the risk of
7 worsening heart failure. However, in the FDA
8 review, several questions about worsening heart
9 failure as a clinical event were raised, and I
10 would like to address each of those questions in
11 the remainder of my presentation.

12 First, the agency asked whether in-hospital
13 worsening heart failure was adequately defined and
14 documented as an event in the case report form.
15 There should be no doubt that worsening heart
16 failure was clearly defined in the RELAX-AHF study.
17 Here is a verbatim from the study protocol.

18 "Worsening heart failure is defined for this
19 study as worsening signs and/or symptoms of heart
20 failure that require an intensification of
21 intravenous therapy for heart failure or mechanical
22 ventilatory or circulatory support." The specific

1 types of interventions are also described.

2 It is important to note that it is not the
3 use of these interventions that defines the
4 occurrence of a worsening heart failure event.
5 Instead, it is the meaningful adverse change in the
6 patient's clinical course that defines the event.
7 The use of these specified interventions simply
8 provides evidence that the physician took the event
9 seriously.

10 The case record form was specifically
11 designed to capture these events. Every 24 hours
12 for the first 5 days, the investigator was
13 specifically asked to report whether the patient
14 had or had not experienced a worsening heart
15 failure event since the last assessment. And if
16 the answer was yes, the investigator was asked to
17 identify the intervention that was used to treat
18 the event.

19 In addition, nearly all in-hospital
20 worsening heart failure events -- 98 out of 102,
21 which I will show next -- were also documented by
22 the investigator as adverse events along with a

1 descriptive phrase, the time and date of onset and
2 offset, and the prescribed treatment. Treatments
3 for worsening heart failure were also documented on
4 the medication pages of the case report form.

5 The terms used to describe the occurrence of
6 worsening heart failure events are shown here. In
7 nearly all cases, the worsening heart failure event
8 was recorded and described as an adverse heart
9 failure-related event.

10 The rescue intervention used to respond to
11 the occurrence of worsening heart failure events
12 was also captured. In about half of the events,
13 the physicians relied on intensification of
14 intravenous diuretics, and in the other half, the
15 physicians administered intravenous vasodilators,
16 intravenous positive inotropic agents, intravenous
17 pressors, ultrafiltration, mechanical ventilation,
18 or other forms of circulatory support. Regardless
19 of the type of intervention, such use was less
20 common in the serelaxin group than in the placebo
21 group.

22 Second, the FDA asks whether in-hospital

1 worsening heart failure is really a clinically
2 meaningful event. While it is true that the
3 physician makes the diagnosis and decides the
4 treatment for the worsening heart failure event, it
5 is also true that these events reflect a distinct
6 and meaningful deterioration in the patient's
7 clinical status despite ongoing treatment, and thus
8 represents the occurrence of a treatment failure,
9 which requires immediate therapy with a rescue
10 intervention.

11 As might be expected, physicians treated
12 these two groups of patients very differently. On
13 the left you can see that patients without
14 worsening heart failure were tapered from
15 intravenous diuretics rapidly, which reflects a
16 quicker conversion to oral diuretics. In contrast,
17 as shown on the right, patients with worsening
18 heart failure events required persistent treatment
19 with intravenous diuretics, and consequently were
20 not rapidly converted to an outpatient regimen.

21 As a result, patients with worsening heart
22 failure events remained in the intensive care unit

1 and in the hospital longer than patients without
2 worsening heart failure. Specifically, as shown in
3 the right panel, patients with worsening heart
4 failure stayed in intensive care about 5 days
5 longer, and as shown on the left panel, stayed in
6 hospital for the index event about 8 days longer
7 than patients without worsening heart failure.

8 Therefore, as a result of their unstable
9 clinical course and slow conversion to an
10 outpatient regimen, the occurrence of worsening
11 heart failure was accompanied by about a doubling
12 of the duration of medical care.

13 It is also noteworthy that during the first
14 5 days, patients with worsening heart failure had
15 higher levels of cardiac biomarkers, specifically
16 NT-proBNP and troponin, than patients without
17 worsening heart failure. And during long-term
18 follow-up, patients with worsening heart failure
19 events had about a doubling of the risk of death
20 during the following 6 months when compared to
21 patients without worsening heart failure.

22 The third point raised by the FDA asks

1 whether worst score should be assigned to patients
2 with in-hospital worsening heart failure from the
3 time of its occurrence. We prospectively assigned
4 worst score to patients with in-hospital worsening
5 heart failure because it is a clinical event that
6 represents the occurrence of a treatment failure
7 which trumps any subsequent symptom assessment.

8 Following initial improvement, the patient
9 experiences recurrence of worsening heart failure
10 which requires immediate rescue treatment. In the
11 absence of rescue treatment, the clinical status of
12 the patient is unlikely to improve by itself and
13 instead, if left untreated, the patient's clinical
14 state is likely to deteriorate.

15 To the degree that the rescue treatments are
16 successful, any subsequent clinical assessments
17 will be meaningfully altered by the effects of
18 rescue therapy. This is the reason why in all
19 trials of acute heart failure, worst score or rank
20 has been routinely assigned to patients who die or
21 experience in-hospital worsening heart failure.

22 Now, if relaxin were effective in preventing

1 treatment failures, we would expect treatment with
2 the drug to reduce the risk of worsening heart
3 failure and also to delay its onset in those who
4 experience these events.

5 Such an effect is conventionally displayed
6 as a Kaplan-Meier time-to-event plot, which is
7 shown in this slide. This is an actual
8 time-to-event Kaplan-Meier plot as opposed to the
9 time of event recording, which is presented in your
10 briefing document.

11 In the RELAX-AHF trial, the curve for
12 worsening heart failure events in the serelaxin
13 group was shifted downward and to the right from
14 placebo, indicating both a reduction in the risk
15 and a delay in onset of these events. And as can
16 be seen, the effect of serelaxin was highly
17 significant.

18 Now, you may also hear that the occurrence
19 of in-hospital worsening heart failure was not a
20 primary endpoint, but instead was an exploratory
21 endpoint in the study protocol. I want to make
22 sure that there is no confusion on this issue.

1 While the protocol specified worsening heart
2 failure as an exploratory endpoint, more
3 importantly, it also specified the occurrence of
4 worsening heart failure events as an integral
5 component of the visual analog scale primary
6 endpoint.

7 Our emphasis on worsening heart failure
8 events today does not reflect its designation as an
9 exploratory endpoint, but instead reflects its
10 importance as the component that drove success on
11 the primary endpoint. We are focusing on worsening
12 heart failure to show why the primary endpoint was
13 met.

14 Finally, you may also hear the question, was
15 the effect on serelaxin on the risk of in-hospital
16 worsening heart failure robust? And clearly, that
17 is the critical question for today's discussion.

18 In that regard, it is important to note that
19 serelaxin not only reduced the first worsening
20 heart failure event, shown in the top row, it also
21 reduced the risk of recurrent worsening events,
22 which occurred in 15 patients in the placebo group

1 and in only 4 patients in the serelaxin group, a
2 near fourfold difference, shown in the middle row.

3 If one totals all worsening events and
4 deaths occurring during the 5-day primary endpoint
5 period, there were 85 events in the placebo group
6 and only 41 events in the serelaxin group. The
7 finding of a more than 50 percent reduction in the
8 rate of worsening events, based on an analysis of
9 more than 120 events, shown on the bottom row, is
10 very unlikely to represent a chance finding.

11 I do not think that the FDA questions the
12 importance of the difference. But the review does
13 ask whether all worsening heart failure events
14 should be considered equal; specifically, whether
15 worsening heart failure, treated with intravenous
16 diuretics only, should be grouped together with
17 events that are treated with intravenous
18 vasodilators, intravenous positive inotropic
19 agents, or mechanical interventions; and whether
20 worsening heart failure events, treated with
21 intravenous diuretics only, should be assigned the
22 same worst score as events that were treated more

1 aggressively.

2 Earlier I made the point that the occurrence
3 of worsening heart failure was a clinically
4 meaningful event because it prolonged the use of
5 intravenous diuretics and slowed the conversion to
6 an outpatient oral regimen, and thus prolonged the
7 duration of intensive care and index hospital stay.

8 The data that I showed you to support these
9 findings was based on all patients with worsening
10 heart failure. So you may ask, are these features
11 also characteristic of worsening heart failure
12 events treated with intravenous diuretics only? I
13 will show that the answer is yes.

14 On the left, you can see that patients with
15 worsening heart failure were converted from
16 intravenous diuretics to oral diuretics rapidly.
17 In contrast, as shown on the right, patients with
18 worsening heart failure events treated with
19 intravenous diuretics only required persistent
20 treatment with intravenous diuretics and were not
21 rapidly converted to an outpatient regimen.

22 Similarly, you have already seen that

1 patients with worsening heart failure events remain
2 in intensive care and in the hospital longer than
3 patients without worsening heart failure events.

4 Now I will superimpose upon this the
5 findings in patients with worsening heart failure
6 treated with intravenous diuretics only. These
7 patients also stayed in intensive care about 3 days
8 longer and stayed in hospital about 5 days longer
9 than patients without worsening heart failure.

10 Therefore, using the same criteria we use
11 for all patients with worsening heart failure, we
12 can see that worsening heart failure treated with
13 intravenous diuretics only also is a clinically
14 meaningful event.

15 Despite these findings, the reviewer
16 speculates that many worsening heart failure events
17 were mild and responded to a single small dose of
18 intravenous diuretics or an increase in the rate of
19 an ongoing infusion of nitroglycerin. Some
20 verbatim statements are listed here.

21 Specifically, the main difference between
22 the groups was a difference in relatively mild

1 worsening heart failure treatable with increased
2 diuretic use. So we must ask, does serelaxin
3 primarily influence mild events managed by small
4 changes in ongoing treatment? I will show that the
5 answer is no.

6 The investigator's assessment of the
7 severity of worsening heart failure-related adverse
8 events, together with the interventions used to
9 treat these events, are shown here.

10 In the columns showing the placebo and
11 serelaxin response, you see a consistent reduction
12 in worsening heart failure events through day 5 in
13 the serelaxin group compared with placebo across
14 the mild, moderate, and severe events, as well as
15 across rescue interventions. This shows that
16 serelaxin reduced mild as well as moderate and
17 severe worsening heart failure-related adverse
18 events, including events treated with the most
19 aggressive rescue interventions.

20 We will also address this question by
21 looking at worsening heart failure events whose
22 treatment represented a meaningful departure from

1 ongoing therapy. This includes patients who died
2 or were rehospitalized for worsening heart failure,
3 patients whose event was treated with IV positive
4 inotropic drugs or mechanical interventions,
5 patients whose event was treated with new
6 initiation of IV nitroprusside or IV nitroglycerin,
7 and finally, patients whose events was treated with
8 a doubling of their daily dose of diuretic or who
9 had intravenous diuretics reinitiated after having
10 been converted to an oral regimen.

11 These events, which required more intensive
12 rescue interventions, comprised two-thirds of the
13 total worsening heart failure events during the
14 first 5 days. And importantly, for three of the
15 four categories, the incidence in the placebo group
16 was twice that of serelaxin.

17 Therefore, the difference in the number of
18 worsening events in the primary endpoint analysis
19 is driven not by events that were followed by minor
20 changes in ongoing treatment, but by the difference
21 in the number of events that were followed by very
22 meaningful changes in treatment, namely, 49 in the

1 placebo group versus 24 in the serelaxin group.
2 This difference is statistically significant. And
3 importantly, the difference remained significant
4 even when the analysis focuses only on patients who
5 died or required intravenous positive inotropic
6 drugs or mechanical interventions.

7 Despite these findings, the reviewer still
8 questions whether the assignment of the same worst
9 score is justified for all worsening heart failure
10 events. As a result, Novartis performed many
11 sensitivity analyses that assigned different
12 numerical values to different types of worsening
13 heart failure events.

14 Although these sensitivity analyses all
15 yielded small p-values that were consistent with
16 the p-value calculated using the primary analysis
17 approach, the FDA points out that many of these
18 were nominally greater than 0.025.

19 Novartis feels that all sensitivity analyses
20 that assign different numerical values to different
21 types of worsening heart failure events suffer from
22 the fact that they are post hoc and thought any

1 numerical assignment for a worsening heart failure
2 event is necessarily arbitrary.

3 To address this concern, we carried out a
4 sensitivity analysis that made no arbitrary
5 numerical assignment to patients who died or
6 experienced worsening heart failure. Instead,
7 using the approach described by Dr. Packer in his
8 opening remarks, clinical judgment was used to
9 characterize, in a hierarchical manner, the
10 clinical course of patients during the first
11 5 days.

12 In fairness to the FDA, we only recently
13 completed these analyses, so they have not had the
14 opportunity to review these results presented in
15 the addendum.

16 In these additional analyses, based on
17 clinical ranks, patients who died during the first
18 5 days were assigned the worst rank. Patients who
19 experienced worsening heart failure but did not die
20 were assigning next-to-worst rank, with sub-ranks
21 based on the type of event. And patients who did
22 not experience a worsening event were ranked

1 according to their values for the visual analog
2 scale-area under the curve.

3 Once each patient was assigned a rank that
4 reflected their clinical course, the distribution
5 of ranks in the placebo group was compared with the
6 distribution of ranks in the serelaxin group using
7 a log-rank test.

8 Such an approach eliminates the need for
9 assignment of any arbitrary numerical value.
10 Instead, this approach only requires that clinical
11 judgment be applied to characterize the clinical
12 course of patients during the first 5 days.

13 Four approaches were used to distinguish
14 among patients with different types of worsening
15 heart failure events. First, all patients with
16 worsening heart failure were assigned the same
17 rank. Second, the patients with earlier worsening
18 heart failure were assigned a worse rank than
19 patients with later worsening heart failure.

20 Third, patients with recurrent worsening
21 events were assigned a worse rank than patients
22 with only a single worsening event. And finally,

1 and I think important to the question in hand,
2 patients whose worsening event was treated with
3 intravenous positive inotropic agents or mechanical
4 interventions were assigned a worse rank than
5 patients treated with intravenous vasodilators, who
6 were assigned a worse rank than patients treated
7 with intravenous diuretics.

8 As you can see, regardless of approach, the
9 p-values obtained were consistent with the
10 protocol-specified analysis, were consistent with
11 each other, and were all smaller than the protocol-
12 specified threshold of 0.025.

13 Taken together, these analyses demonstrate
14 that the achievement of success on visual analog
15 scale-area under the curve primary endpoint
16 composite in the RELAX-AHF trial did not depend on
17 the assignment of an arbitrary numerical value to
18 patients with an unfavorable clinical course.

19 If the clinical course of patients in the
20 trial was characterized and ranked only according
21 to clinical judgment, a favorable effect of
22 serelaxin was consistently identified, and the

1 strength of evidence for this effect was very
2 similar to the protocol-specified analytical
3 approach.

4 Therefore, in response to the FDA questions
5 about the analysis of the primary endpoint, we
6 would like the committee to consider:

7 Worsening heart failure was a prespecified
8 component of the primary endpoint and drove the
9 treatment difference;

10 Worsening heart failure was a fully
11 documented event;

12 Worsening heart failure, regardless of
13 rescue therapy, led to prolonged use of intravenous
14 medications and longer ICU and hospital stay for
15 the index event; and importantly,

16 Serelaxin reduced the risk of first and
17 recurrent events; reduced the risk of treatment
18 failures regardless of severity, including
19 worsening events treated with more intensive rescue
20 interventions; and finally, analysis of the
21 clinically ranked outcomes without numerical
22 assignment for worsening events confirmed the

1 primary endpoint results.

2 In summary, one of the two primary endpoints
3 in the RELAX-AHF trial was a composite endpoint
4 consisting of death, in-hospital worsening heart
5 failure, and the change in the dyspnea score. The
6 RELAX-AHF trial met its primary endpoint, as
7 specified in the protocol, with a p-value of
8 0.0075, which is well below the prespecified
9 threshold of 0.025.

10 Success on the primary endpoint was driven
11 not primarily by an effect on death or change in
12 the dyspnea score, but by an improvement in the
13 clinical course of patients through an effect on
14 the occurrence in-hospital worsening heart failure.
15 This effect was large and highly significant.
16 Serelaxin reduced the rate of worsening heart
17 failure by reducing the risk of first events and
18 preventing the recurrence of these clinical
19 meaningful worsening events.

20 Thank you for your attention, and I will now
21 ask Dr. Severin to complete the efficacy and safety
22 presentation.

1 **Sponsor Presentation - Thomas Severin**

2 DR. SEVERIN: Thank you, Olga.

3 Good morning, Mr. Chairman, members of the
4 advisory committee, representatives of the FDA, and
5 ladies and gentlemen. My name is Thomas Severin.
6 I'm the global program medical director for
7 serelaxin at Novartis.

8 Today I would like to review additional data
9 from trials with serelaxin and provide an overall
10 perspective based on the totality of evidence from
11 the serelaxin program. First, let us review the
12 effects of serelaxin on the two secondary efficacy
13 endpoints in the RELAX-AHF trial.

14 Treatment with serelaxin did not affect
15 significantly the endpoint of days alive and out of
16 the hospital to day 60. Serelaxin treatment did
17 also not affect the secondary endpoint of time to
18 cardiovascular death or rehospitalization for
19 either heart failure or renal failure through day
20 60.

21 This secondary endpoint is shown on the
22 left-hand of the slide, and on the right-hand side,

1 the two endpoint components are displayed. There
2 were 8 fewer cardiovascular deaths at day 60 in the
3 serelaxin group, and there were 10 more
4 rehospitalizations, as displayed in the second
5 paragraph. However, these differences were not
6 statistically significant.

7 But it is worth noting that this analysis
8 ignores the early occurrence of worsening of heart
9 failure. And therefore, we conducted a
10 prespecified analysis, which included the
11 occurrence of in-hospital worsening heart failure,
12 together with death and together with
13 rehospitalization for heart failure, in a time to
14 first event analysis to day 14. And treatment was
15 serelaxin resulted in a hazard ratio of .7, or a
16 30 percent reduction in the risk of all such
17 relevant events.

18 At this time point, there were 91 episodes
19 of worsening of heart failure or rehospitalizations
20 or deaths in the placebo group and only 66 such
21 events in the serelaxin group. And if we extend
22 the same combined endpoint to day 30, which was

1 also a prespecified analysis, the hazard ratio now
2 is .79, representing a 21 percent risk reduction in
3 the serelaxin group.

4 If we extend this analysis back to
5 day 60 -- this is a post hoc analysis -- and if we
6 look at the Kaplan-Meier curve on the left-hand
7 side and at the endpoint components of this
8 composite endpoint on the right side, now including
9 worsening heart failure, we see that the hazard
10 ratio overall is .85. The results still favor
11 serelaxin, and the imbalance on morbid events is no
12 longer apparent.

13 I would now like to review other
14 prespecified efficacy analyses, such as the use of
15 intravenous diuretics, the length of the stay in
16 the hospital, the length of stay in the intensive
17 care unit, and also talk about cardiac and renal
18 biomarkers.

19 It's important to note that in RELAX-AHF,
20 the physicians were free to administer any
21 intravenous therapy after randomization as
22 clinically indicated, and patients in the serelaxin

1 group received lower doses of IV diuretics on each
2 of the first 5 days of the study, as shown on the
3 left-hand side. Also, the patients on serelaxin,
4 they were tapered off intravenous diuretics more
5 rapidly than patients in the placebo group.

6 On the right-hand side, we see that the
7 cumulative dose of IV diuretics during the first
8 5 days is 24 percent lower in the serelaxin group
9 when compared with placebo.

10 The duration of stay in the hospital both
11 for the index hospitalization, as shown on the
12 left, and for the time in the intensive care unit,
13 shown on the right, were both significantly shorter
14 in those patients treated with serelaxin.
15 Serelaxin-treated patients spent almost a full day
16 less in the hospital when compared with placebo
17 patients.

18 In this analysis, the longest length of stay
19 plus 1 day was assigned to patients who died.
20 There were no score assignments in this analysis
21 for worsening of heart failure.

22 Let me now show you cardiac and renal

1 biomarker data. The three panels on this slide
2 show the geometric mean changes in high sensitivity
3 troponin-T, a marker of cardiac injury, shown on
4 the left, NT-proBNP, a marker of cardiac wall
5 stress, displayed in the middle, and cystatin C, as
6 a sensitive marker of renal function.

7 When compared with patients in the placebo
8 group, patients in the serelaxin group showed
9 favorable changes in all three of these biomarkers,
10 with statistically significant differences at day 2
11 and longer for cystatin C.

12 Now, in order to explore the potential
13 relevance of these changes, we conducted post hoc
14 analysis of categorical changes for each of these
15 biomarkers. And for this categorical analysis, we
16 used published thresholds. For example, for
17 troponin, a threshold of a 20 percent increase was
18 selected, according to the WHO universal definition
19 for myocardial infarction.

20 In the top three panels, we see that
21 increases to day 2 in each of the markers shown
22 before were associated with a higher mortality,

1 which is seen in the red lines in these association
2 curves. In the lower three panels, the bar charts
3 indicate that the number of patients at day 2 in
4 each of these categories of higher risk was
5 favorable for serelaxin.

6 In summary of this section, the findings in
7 the RELAX trial show a consistent pattern of
8 benefit across multiple and across clinically
9 relevant endpoints. Serelaxin improves the
10 clinical course of patients through reduction of
11 the risk of worsening of heart failure which, as we
12 heard, reflects clinical instability.

13 The effect of serelaxin on worsening of
14 heart failure drove the success on the primary
15 endpoint using the visual analog scale, and on
16 signs and symptoms of heart failure. And, in
17 addition, the patients treated with serelaxin
18 received less intravenous diuretics, they were
19 tapered off diuretics more rapidly, had a shorter
20 index hospital stay, and favorable effects on
21 biomarkers, which are potentially indicative of
22 organ injury or dysfunction.

1 Now I would like to turn to the safety
2 results in the RELAX-AHF trial.

3 The overall rate of adverse events, which in
4 this study were recorded to day 5, and serious
5 adverse events, which were captured to day 14, was
6 comparable across the placebo and the serelaxin
7 groups, as shown in the blue bar at the top of the
8 table. And overall, the safety profile of
9 serelaxin was reasonably benign.

10 As serelaxin has an effect, among others, on
11 vasodilation, specific attention was paid to avoid
12 potential hypertension. Confirmed blood pressure
13 decreases were defined by the protocol, and rules
14 were implemented in the protocol to manage blood
15 pressure decreases and to protect the patient
16 safety.

17 If the blood pressure decreased by more than
18 40 millimeters of mercury from baseline or was
19 above 100 millimeters of mercury, the study drug
20 infusion rate was reduced by 50 percent. And if in
21 any case the blood pressure decreased to below
22 100 millimeters of mercury on two consecutive

1 measurements, the study drug infusion had to be
2 discontinued.

3 As we see in the blue bar and as we would
4 expect with a drug, which has a vasodilatory
5 effect, the blood pressure decreases were reported
6 more frequently on serelaxin than on placebo. But
7 importantly, while not shown on this slide, the
8 confirmed blood pressure decreases resolved
9 spontaneously without further treatment, and the
10 dose adjustment rules to manage blood pressure
11 allowed the majority of patients in the RELAX-AHF
12 study to complete the 48-hour infusion.

13 It is also important in this safety section
14 to mention an analysis where we looked at all
15 events, adverse events and also serious adverse
16 events, in any way potentially related to cardiac
17 failure, and we carried this out to day 14.

18 As the committee already knows, standardized
19 MedDRA queries, or SMQs, are predefined. They are
20 validated sets of MedDRA terms. And the number of
21 patients who experienced such adverse events, which
22 can be classified into the standard MedDRA query

1 for cardiac failure, was smaller in the serelaxin
2 group than in the placebo group, as shown here in
3 the blue bar on the top. These findings are
4 consistent, indeed, with the reduction in the risk
5 of worsening heart failure.

6 If we look at the standardized MedDRA
7 queries for acute renal failure on this slide,
8 there were also fewer patients who experienced an
9 adverse event potentially related to renal
10 impairment. This finding is also consistent with
11 the observation that during the first 5 days of the
12 study, increases in blood urea and nitrogen, as
13 shown on the left, and notable increases of
14 creatinine, as shown on the right, were
15 consistently smaller and less frequent in the
16 serelaxin group than in the placebo group.

17 Now I would like to review the results on
18 cardiovascular and all-cause mortality.

19 Cardiovascular mortality was prespecified in
20 RELAX-AHF as an additional efficacy endpoint, and
21 treatment with serelaxin resulted in a hazard ratio
22 of .63, representing a 37 percent reduction of

1 cardiovascular mortality to day 180.

2 Importantly, the analysis of all-cause
3 mortality shows a similar hazard ratio of .63, and
4 treatment with serelaxin was associated with a
5 similar 37 percent reduction of mortality to
6 day 180.

7 I should note that as described in your
8 briefing book, there were 14 patients whose vital
9 status was unknown at day 180. There were
10 7 patients in the placebo group and 7 patients in
11 the serelaxin group.

12 This slide now shows the prespecified
13 analysis for all-cause mortality in red at the top,
14 and two possibilities of handling data from the
15 patients where we have the missing vital status.

16 Even under the most conservative approach
17 possible, shown at the bottom, when we count to
18 7 patients on placebo, alive, and to 7 patients in
19 the serelaxin group, if we all count them as dead,
20 then the upper bound of the 95 percent confidence
21 interval for all-cause mortality remains below 1.1.

22 This additional analysis provides

1 substantial support for our finding that the 48-
2 hour infusion of serelaxin does not increase the
3 risk of death at 6 months, and it shows reassuring
4 evidence of no harm.

5 The clinical relevance and the robustness of
6 the effect of serelaxin to reduce the risk of
7 worsening heart failure was supported by the
8 finding of consistent benefits across multiple
9 endpoints within the RELAX trial, including
10 favorable effects on the use of diuretics, the
11 length of stay, cardiac and renal biomarkers,
12 cardiac and renal adverse events, and the effect on
13 cardiac and total mortality.

14 You will be asked today by the FDA whether
15 there are supportive findings in the Pre-RELAX
16 study. And therefore, I would like to show you
17 evidence from the Pre-RELAX trial, which was a key
18 supportive study, and this data support the
19 efficacy of serelaxin.

20 As noted earlier, the study population and
21 the design of Pre-RELAX-AHF were very similar to
22 the phase 3 study, RELAX-AHF. The Pre-RELAX-AHF

1 trial was designed as a dose-response study, and
2 therefore the results should be viewed from a dose-
3 response perspective rather than as a comparison of
4 individual doses versus placebo.

5 This slide now shows the results for the
6 visual analog scale AUC on the left and for the
7 Likert scale on the right. And with respect to
8 the visual analog scale, there was a consistent
9 improvement with all four doses of serelaxin when
10 compared to placebo.

11 In contrast, the response to serelaxin was
12 inconsistent across the doses on the Likert scale,
13 with a meaningful improvement seen only at the
14 30 micrograms per kilo per day dose, as shown in
15 the bar in green color.

16 As demonstrated on this slide, serelaxin was
17 associated with a reduction in the risk of
18 worsening heart failure, also in the Pre-RELAX
19 study. And this reduction of worsening of heart
20 failure was consistent across the doses of 30
21 micrograms per kilo per day or greater.

22 On the right-hand side, we also see

1 consistency for the reduction in the length of
2 hospital stay. This reduction was similar across
3 all four doses when compared with placebo.

4 Serelaxin treatment was associated with a
5 lower cardiovascular mortality and a lower all-
6 cause mortality to 180 days across all of the four
7 doses of serelaxin when compared to placebo, as
8 shown on this slide for cardiovascular mortality on
9 the left, where there was not one death in the 30
10 micrograms per kilo per day dose group, and for
11 all-cause mortality on the right.

12 It's important to note that nearly every
13 measure, when we directly compare the results of
14 RELAX-AHF and Pre-RELAX, were seen also in between
15 these both trials.

16 I want to emphasize that the confirmation in
17 the Pre-RELAX study is not based on p-values,
18 comparing a particular dose of serelaxin versus
19 placebo. This was not the way the study was
20 designed. Instead, the confirmation is based on
21 the consistency of effect, the consistency of
22 effect across multiple endpoints and the

1 consistency of the magnitude of the effect across
2 multiple doses.

3 So here the effect of serelaxin on the
4 visual analog scale in the relate trial was
5 replicated with nearly all doses of serelaxin in
6 the Pre-RELAX study. The effect of the drug on
7 worsening of heart failure, as we see in the
8 middle, and the length of stay at the bottom was
9 very consistent with multiple doses.

10 Inconsistency was observed for two
11 endpoints, days alive and out of hospital, and
12 cardiovascular death or rehospitalization. These
13 endpoints were actually favorably affected by
14 serelaxin in the Pre-RELAX study, but as we have
15 seen, were neutral in the phase 3 study, RELAX-AHF.

16 Importantly, serelaxin treatment was
17 associated with a reduction of mortality in both
18 studies, in RELAX-AHF and in Pre-RELAX, which I
19 compare on this slide side by side.

20 The cardiovascular mortality results in
21 RELAX-AHF are consistent with the reduction of
22 cardiovascular mortality in Pre-RELAX, where the

1 hazard ratio across the four doses was .25. The
2 curves show a similar pattern of early separation,
3 and the pooled analysis listed at the bottom of the
4 slide for cardiovascular and for all-cause
5 mortality result in highly significant p-values.

6 The evidence that we are presenting to you
7 today does not consist -- it does not consist only
8 of a single trial focusing only on symptoms. We
9 are presenting to you the results of two trials,
10 RELAX-AHF and the key supportive study, Pre-RELAX,
11 both studies with nearly identical design and
12 concordant results. And the efficacy of serelaxin
13 was not only seen across the two trials but across
14 multiple endpoints and across multiple doses.

15 Now that you have seen the totality of
16 evidence, I would like to conclude my part of this
17 presentation with a perspective on the benefit and
18 risk.

19 The effect of serelaxin on the improvement
20 of the in-hospital clinical course of patients, as
21 evidenced by the reduction in clinically relevant
22 events of worsening heart failure, which reflects

1 clinical instability; as evidenced by less use of
2 medications, more rapid conversion to oral therapy,
3 and a reduction in the length of hospital stay,
4 these results, they are consistent, they are
5 robust, and I think they are clinically relevant
6 for patients and physicians.

7 In addition, serelaxin has a favorable
8 safety profile, and the reduction of mortality
9 provides us reassuring evidence that serelaxin does
10 not adversely affect longer-term survival. And for
11 these reasons, the overall benefit to risk
12 assessment is favorable for the use of serelaxin in
13 the treatment of patients with acute heart failure.

14 In light of the consistent and after robust
15 demonstration of clinically relevant benefits
16 within and across trials, with minimal concerns
17 about short- or long-term safety, the totality of
18 evidence supports the proposed indication.

19 Serelaxin is indicated to improve the symptoms of
20 acute heart failure through reduction of the rate
21 of worsening of heart failure.

22 Thank you for your attention. I would like

1 to acknowledge the study committee and patients and
2 investigators who participated in the study, and
3 hand over to Dr. Packer.

4 **Sponsor Presentation - Milton Packer**

5 DR. PACKER: Thank you very much, Tom.

6 As you've already heard, the primary
7 endpoint used in both Pre-RELAX and RELAX trials
8 was formulated as a composite consisting of death,
9 the occurrence of in-hospital worsening heart
10 failure, and a change in dyspnea score, which were
11 analyzed in a hierarchical manner.

12 Now, if a trial demonstrates an effect on a
13 composite endpoint, it's important, one, to ensure
14 that the effects on each component are
15 directionally concordant, and two, to identify
16 which component drives the effect.

17 You've already seen that the RELAX trial
18 met its primary composite endpoint, that the
19 effects of serelaxin on each of the components was
20 directionally concordant, and that statistical
21 significance was driven primarily by the favorable
22 effect of serelaxin on the occurrence of in-

1 hospital worsening heart failure.

2 Now, if an effect on the risk of in-hospital
3 worsening heart failure can formulate the basis of
4 approval and labeling, then we need to make sure it
5 is both meaningful and robust. First, let's see if
6 the effect is meaningful.

7 I'm confident that the committee knows from
8 personal experience what in-hospital worsening
9 heart failure looks like. In-hospital worsening
10 heart failure represents the failure of prescribed
11 therapy to maintain clinical stability. Its
12 occurrence changes the in-hospital clinical course
13 of the patient.

14 Whereas patients without worsening heart
15 failure are generally tapered rapidly off of
16 intravenous medications, patients with worsening
17 heart failure continue to require intravenous
18 therapy for many days. As a result, patients with
19 in-hospital worsening heart failure have longer
20 stays in intensive care and longer overall stays in
21 the hospital.

22 Now, the FDA has raised the question as to

1 whether worsening heart failure treated only with
2 intravenous diuretics should be considered to be
3 clinically important, while the occurrence of
4 in-hospital worsening heart failure reflects
5 clinical instability regardless of how a physician
6 elects to treat it.

7 You've already seen that patients with
8 worsening heart failure treated with only
9 intravenous diuretics also continue to require
10 intravenous diuretics throughout the entire 5-day
11 primary endpoint period, and they stayed in the
12 hospital longer than patients without worsening
13 heart failure.

14 This shouldn't be surprising. Please
15 remember, it's the clinical event that matters to
16 the patient, not the treatment preferences of the
17 patient's physician. All that we should require is
18 the event be considered serious enough that the
19 treating physician decided to administer immediate
20 intravenous treatment. Frankly, I think it would
21 be a bit troublesome if we started including or
22 excluding events based on a treatment preference

1 rather than a patient experience.

2 In most trials in acute heart failure
3 carried out to date, the occurrence of in-hospital
4 worsening heart failure has been incorporated into
5 the primary endpoint of the trial and assigned the
6 worst possible result from the time of onset of the
7 event.

8 As I've noted earlier, these trials have
9 either used the numerical approach, shown on the
10 left, as exemplified by the visual analog scale-
11 area under the curve, or the ranked approach, shown
12 on the right, as exemplified by the clinical
13 composite.

14 Now, why do we assign worst rank or score to
15 these patients? Well, because of the patients'
16 clinical instability, the treating physician makes
17 every effort to stabilize the patient as quickly as
18 possible.

19 If rescue interventions were not
20 administered, the clinical instability would not
21 only be expected to persist, but would likely
22 worsen. So the assignment of worst rank or score

1 allows the occurrence of clinical instability to be
2 reflected in the assessment of the clinical course
3 of the patient.

4 Now, if we agree that in-hospital worsening
5 of heart failure is important and that its
6 prevention is meaningful, then we need to ask if
7 the effect of serelaxin on worsening heart failure
8 is robust. Well, I think you need to be the judge
9 of this.

10 But in thinking about this, it would be
11 relevant to consider the effect of treatment on the
12 frequency of first episodes, the time of onset of
13 these episodes, and the frequency of recurrent
14 episodes. Regardless how one measures or
15 quantifies worsening heart failure events, they
16 were favorably influenced by treatment with
17 serelaxin.

18 It would also be relevant to consider
19 whether treatment reduced the occurrence of events
20 that required rescue therapy that represented a
21 meaningful departure from ongoing therapy.

22 These types of treatments that I am showing

1 on this slide were reduced by serelaxin regardless
2 of whether we're talking about intravenous
3 inotropic drugs, mechanical intervention, or new or
4 aggressive treatment with intravenous vasodilators
5 and diuretics. And these differences were the
6 primary driver of the effect of the drug on the
7 occurrence of worsening events.

8 As you've already seen, serelaxin prevented
9 worsening events regardless of severity. The drug
10 did not just prevent mild events that responded
11 only to modest changes in ongoing treatment with
12 intravenous diuretics.

13 It would also be relevant to consider
14 whether the effect was consistent across trials.
15 The magnitude of the effect of serelaxin on
16 worsening heart failure in the RELAX trial was
17 similar to that seen with three different doses of
18 serelaxin in the Pre-RELAX trial. And this
19 consistency across trials and doses was also seen
20 with respect to the two endpoints most closely
21 linked to worsening heart failure, the visual
22 analog scale and the length of hospital stay.

1 Now, having seen all of this, you may still
2 be concerned by the fact that the effect on the
3 visual analog scale primary endpoint was achieved
4 by assigning a score of zero to all patients with
5 worsening heart failure, regardless of the gravity
6 of the event and the intensity and aggressiveness
7 of treatment.

8 In its review article, the FDA has wondered,
9 was this a reasonable approach to do? Would the
10 results differ if some other approach had been
11 used? Should patients with a worsening event have
12 been assigned a zero score? Should a zero score
13 have superseded future clinical assessments?
14 Should patients with all types of worsening events
15 have received this same zero score?

16 As a result of these questions, the
17 documents for this meeting, both from FDA and the
18 sponsor, contain numerous sensitivity analyses that
19 assign different numerical scores in different ways
20 to different types of worsening heart failure
21 events.

22 As I noted earlier in my presentation, it is

1 an inherent requirement of the numerical approach
2 to assign some very low score to patients with an
3 unfavorable clinical course. Unfortunately, once
4 the study is completed, it's always possible to
5 challenge the value of the score or the way it's
6 assigned.

7 Of course, regardless of the reasons given,
8 any assignment of any numerical score to patients
9 with an unstable clinical course is unavoidably
10 arbitrary. The least arbitrary approach to
11 evaluating the robustness of the effect of
12 serelaxin is to avoid the assignment of numerical
13 scores altogether.

14 This can be achieved by changing the
15 analytical approach from a numerical assessment to
16 a hierarchical ranking of the clinical course of
17 patients which, if you remember, is based entirely
18 on physician judgment rather than mathematical
19 assumptions. Importantly, an approach based on
20 ranks also allows us to do what the FDA suggests is
21 important to do, which is to rank certain types of
22 worsening events differently than others.

1 This slide shows the results of an analysis
2 of ranks. Now, no matter how the ranking is
3 carried out, no matter what criteria you use to
4 distinguish amongst the various types of worsening
5 heart failure events, the p-values are strikingly
6 similar to each other and to the p-value that is
7 achieved using the prespecified approach.

8 Now, this analysis that I am showing you on
9 this slide directly addresses the principal concern
10 that the FDA has raised about the robustness of the
11 effect of serelaxin. Please don't look at this
12 sensitivity analysis as a post hoc analysis being
13 done to make the primary endpoint statistically
14 significant. That is not the case here.

15 All of the sensitivity analyses that you
16 will see during this meeting are post hoc, and all
17 have been performed to determine if the
18 statistically significant effect on the primary
19 endpoint is robust. However, sensitivity analyses
20 vary in the degree to which they can provide
21 reassurance or raise doubts.

22 The major advantage of the sensitivity

1 analysis based on ranks is that it is based on
2 clinical judgment and not arbitrary numerical
3 assignments. And therefore, in my view, it has a
4 far stronger foundation than all the other
5 sensitivity analyses, and provides the needed
6 reassurance about robustness.

7 Furthermore, because Pre-RELAX and RELAX
8 were nearly identical trials, we can, in a post hoc
9 manner, combine the findings of the two trials
10 using the ranked approach to the analysis of the
11 primary endpoint. Please remember that the FDA
12 review suggests that given the similarity of these
13 two trials, combining their results is appropriate.

14 Well, if we were to do that, the resulting
15 p-values for the ranked approach are quite small.
16 And if we combine the two trials using the
17 numerical approach, adjusted for covariates or not
18 adjusted for covariates, the resulting p-value is
19 very small. Either approach would support a
20 finding with the strength of evidence of two
21 trials.

22 Viewed from the perspective of ranks,

1 treatment with serelaxin shifts the proportion of
2 patients with an unfavorable clinical course and
3 increases the likelihood of patients experiencing a
4 stable clinical course.

5 Now let's turn to one final question. If
6 the effect of serelaxin on in-hospital worsening of
7 heart failure is meaningful and robust, then we
8 should ask, is it distinctive? Is there something
9 noteworthy that should be considered by the
10 committee?

11 Well, I don't need to tell the committee
12 that currently available drugs for the treatment of
13 acute heart failure were largely approved based on
14 their effects on hemodynamic variables, and we know
15 little about whether any of these drugs truly
16 improves the clinical course of patients. We know
17 even less about what doses to use. And we have
18 concerns that the benefits of all of these drugs
19 have important limitations, if we are confident
20 that there are benefits at all.

21 The effects may be transient, in the case of
22 nitroglycerin. Some of these drugs are thought to

1 have adverse effects in heart failure, such as
2 intravenous positive inotropic drugs that may
3 increase the risk of death. None of the drugs
4 currently available in the United States has been
5 shown to have a favorable effect on the risk of
6 in-hospital worsening of heart failure.

7 Only one other drug, specifically
8 levosimendan, which is available in many European
9 countries but not in the United States, has been
10 shown to have an effect on in-hospital worsening
11 heart failure, but its use has been associated with
12 an increased risk of death.

13 In contrast, as you have seen, the available
14 data with serelaxin indicates we can be reasonably
15 confident that the drug does not increase the risk
16 of death. All of this means that we know more
17 about the benefits and risks of serelaxin than we
18 know about most drugs that we can use for the
19 treatment of acute heart failure. The totality of
20 evidence indicates that serelaxin reduces the risk
21 of in-hospital worsening heart failure without any
22 adverse effect on mortality.

1 Now, given the nature of this benefit, I
2 don't think it really matters whether this has been
3 shown, a reduction of the risk of in-hospital
4 worsening heart failure has been demonstrated in
5 one trial or two, although to be fair, the totality
6 of evidence, as you have seen, supports an effect
7 with the strength of evidence of two trials.

8 The only question is whether the finding of
9 the effect of serelaxin on in-hospital worsening
10 heart failure is robust and clinically important.
11 If the answer is yes, I think we have for the first
12 time the opportunity to expect that treatment of
13 patients with acute heart failure be based on the
14 use of drugs that have been shown to have a
15 favorable relation of benefit to risk. We simply
16 cannot do that with the drugs currently available
17 to us.

18 I will turn the meeting back over to
19 Dr. Lincoff. That concludes the sponsor's
20 presentation.

21 **Clarifying Questions to Presenters**

22 DR. LINCOFF: We thank the sponsor for a

1 very clear presentation. And now it's time for
2 clarifying questions to the presenters. Dr. Sager?

3 DR. SAGER: Thank you for a very interesting
4 set of presentations, and it really covered a large
5 amount of material. As I look at this, there were
6 two primary endpoints, the VAS and the Likert. The
7 VAS met statistical predetermined criteria; the
8 Likert didn't. And then there were two other
9 criteria, which were 60-day criteria, which were
10 both negative.

11 We look at the focusing in on the VAS and
12 used this imputation method, which included,
13 assigned to zero, anyone who had "clinical
14 worsening" independent of whether they had mild
15 worsening and then it got better. And even, as you
16 showed on your slides with the pictures, there were
17 people who got worse and then they got better, but
18 regardless, they would have been assigned zero
19 throughout.

20 I find that really difficult from a study
21 standpoint process. So I'd like you to, if you
22 could put up some of the -- and there are other

1 ways to look at this. And the FDA, in your
2 briefing document, apparently on table 7-20, I'd
3 asked you to look at some others. So if we could
4 look at that.

5 But while you're putting that up, I think
6 the other thing is, the clinical worsening, the
7 heart failure worsening, these are all interesting,
8 as well as many of the other types of analyses.
9 But I personally see these are exploratory, post
10 hoc. I think they are really fascinating for a
11 future study.

12 But I think we really today have to focus on
13 what was the primary endpoint to the study, which
14 the positive one we have is the VAS. So if we
15 could look at that table, that would be great, if
16 you have that in slide form.

17 DR. NATHWANI: Dr. Sager, thank you. You
18 asked a large of questions, and if you don't mind,
19 I'll try and break them down in series, if that's
20 okay. And then we can show you some of the data
21 that you've requested as well.

22 DR. SAGER: Actually, I only asked one

1 question. I made a few statements. If you want to
2 respond to the statements, I guess that's okay.

3 DR. NATHWANI: Right. You made some
4 statements that I'd like to clarify along the way.
5 If I could just ask Dr. Greenberg first just to
6 talk about the intent of the study and its design
7 to give some clarity as to how they were thinking
8 about it from the executive committee, and then we
9 can go down through some of the sensitivity.
10 Because it may address some of the issues.

11 DR. SAGER: Well, I'm really interested in
12 how the committee thought about the design. But
13 I'm more interested in what the protocol said and
14 what the endpoints were. And I feel that while
15 there was a desire to include clinical worsening in
16 the VAS, there are multiple ways to have done it,
17 and the way that was done, I think, was the
18 least -- it did not take into the physiologic
19 perturbations that these patients typically
20 exhibit.

21 DR. GREENBERG: I'm Barry Greenberg. I am a
22 member of the executive committee for RELAX-AHF.

1 And both my travel and time were supported by the
2 sponsor.

3 So when we were developing the initial
4 criteria for endpoints in this clinical trial, we
5 were aware of the fact that the patients would be
6 hospitalized for a period of days, and that this
7 was a very dynamic period. And we wanted to
8 capture the events that occurred during the
9 totality of this period.

10 We also recognized that worsening heart
11 failure was a substantial problem in this patient
12 population. We were informed, number one, by our
13 own clinical experience; all the members of the
14 executive committee were clinicians who saw
15 patients like this on a regular basis, and were
16 aware of the problem of worsening heart failure.

17 Number two, we were informed by Pre-RELAX in
18 which we saw worsening heart failure and saw an
19 opportunity for serelaxin to improve this outcome.
20 And then, number three, from other clinical trials,
21 worsening heart failure had been observed as an
22 important occurrence during this time.

1 It was also an occurrence that had
2 consequences associated with it. Some of those
3 you've heard about today -- longer use of diuretic
4 agents, prolonged time in the hospital. Because
5 of this we wanted to incorporate this into the
6 evaluation of serelaxin in this clinical trial.

7 Consequently, right from the get-go, this
8 was included as part of the composite, along with
9 the dyspnea assessment and death, considering this
10 was all part of the patient experience during the
11 hospitalization, and the worsening heart failure
12 was an important component.

13 DR. SAGER: Then let me ask you why you
14 didn't have a third endpoint of worsening heart
15 failure that was prospectively defined rigorous?
16 Sticking it inside of a very different measure
17 creates a lot of the problems we're having today in
18 looking at this. And obviously, how was put in I
19 feel is really problematic, unfortunately.

20 DR. GREENBERG: We felt this was all going
21 to be part of the primary endpoint and an important
22 component of it as we were looking at a composite,

1 which really tried to capture the totality of the
2 patient experience during the hospitalization.

3 We included the three components because we
4 felt that that really captured and gave us an
5 opportunity to put our arms around what the patient
6 was experiencing during that time, worsening heart
7 failure being part of that.

8 DR. NATHWANI: Dr. Sager, while we try and
9 pull up, can you just clarify which sensitivity
10 analysis you wanted? And then I'm going to ask
11 Dr. Packer for a comment as well.

12 DR. SAGER: The figure 7-20 from your
13 briefing book, page 82.

14 DR. NATHWANI: While we're pulling that up,
15 Dr. Packer?

16 DR. PACKER: Yes. Dr. Sager, if you want to
17 focus on the prespecified, protocol-specified
18 endpoint and protocol-specified analysis, the
19 protocol-specified endpoint, as prospectively
20 designed and analyzed according to the protocol,
21 was fulfilled in this trial.

22 The minute that the executive committee

1 decided to assign a worst score to patients with
2 in-hospital worsening of heart failure or
3 death -- and that, by the way, is what we routinely
4 do in acute heart failure trials -- the minute they
5 did that, they were effectively giving them worst
6 rank.

7 Now, really, as long as that's the concept,
8 as long as the concept is that clinical instability
9 is a bad thing and represents an unfavorable
10 course, then one can get around the dilemma of what
11 score was assigned by eliminating the numerical
12 scores altogether, because the sensitivity analysis
13 that --

14 DR. SAGER: I know that. But again, that
15 was not one of the primary analyses. Let me come
16 back --

17 DR. LINCOFF: Let's let the sponsors finish
18 their response.

19 DR. PACKER: But in all honesty, the
20 sensitivity analyses that you've seen were not the
21 primary analyses, either. All of these are
22 sensitivity analyses. The question is which

1 sensitivity analyses give you comfort or not. And
2 in that sense, the problem with all of the
3 sensitivity analyses that rely on numerical score
4 is that they're arbitrary. So the reason why I
5 think that the ranked approach -- it's post hoc,
6 but it's just as post hoc as the other sensitivity
7 analyses.

8 If one wants to go with the prespecified
9 approach, that was fulfilled and it was met. But
10 if one wants to go into why the worst score was
11 assigned to people with in-hospital worsening heart
12 failure and death -- and remember, that was
13 prespecified -- then the ranked approach alleviates
14 the concern about what score to assign.

15 DR. NATHWANI: Dr. Sager, we have the slide
16 that you were requesting.

17 Can I have C-24? Slide up. And can I
18 invite Dr. Lefkowitz to the microphone?

19 Is this the analysis that you were
20 requesting?

21 DR. SAGER: Yes.

22 DR. LEFKOWITZ: Martin Lefkowitz, Novartis

1 clinical. I could walk you through the different
2 assumptions on the analysis one by one. I think
3 the point being is that they are all directionally
4 consistent but not necessarily statistically
5 significant at the predefined p-value.

6 So on top in red, of course, is the primary
7 analysis we were assigned, worst observed test
8 score to the worsening heart failure. The first
9 requested analysis is we assigned worst score to IV
10 inotropes, mechanical ventilation. But patients
11 whose intensification was with diuretics and
12 nitrates, there is their observed score.

13 The second analysis is a variation on that,
14 where inotropes again are given zero, whereas those
15 with diuretics and nitrates are either given the
16 observed score or 50 percent of the median value,
17 whichever was worse, so a variation on that.

18 FDA analysis three is that we gave zero to
19 all scores during the worsening heart failure
20 event, and then following the event, worst
21 score -- rather, observed scores were given to all
22 patients.

1 So there, the request was to look at the
2 worsening heart failure during the episode, so
3 everybody -- I know these are a lot of different
4 variations, but everybody got worst score during
5 the episode, and then after the episode it was
6 their observed score.

7 I'll come back to four, which is a little
8 bit more complicated. And then five is where it
9 was zero again for all scores during the worsening
10 heart failure event, and then after the worsening
11 heart failure event, the diuretics got their
12 observed score.

13 Four is a bit more complicated. Four is
14 where patients with IV diuretics and nitrates are
15 given their observed score throughout, whereas
16 patients with inotropes are given zero during the
17 event and then their observed score after, which is
18 why that p-value is a little after.

19 If I could just add, if I may, as Dr. Packer
20 said, all of these analyses are somewhat arbitrary.
21 I think the purpose that we put forward, the rank
22 analysis, after we read the FDA comments, although

1 we had one of these analyses in our original
2 briefing book -- but the reason we put these out is
3 that FDA had raised points related to, should early
4 events count more than late events, should all
5 worsening heart failure events count the same, et
6 cetera.

7 The rank analysis follows the basic concept
8 of the protocol; that is, if you accept, based on
9 clinical judgment, that death and worsening heart
10 failure are bad things -- and that was the concept
11 of the study, it allowed us then to say, okay,
12 death, which I think we then agree in ranked
13 analysis would get the worst rank, and then
14 worsening heart failure gets the next rank, and
15 there we could vary the different worsening heart
16 failure: early/late, inotropes, early versus
17 not -- inotropes given more weight rather -- and if
18 I could have -- you've seen this before. Slide up,
19 please.

20 Just to show you again, so this just allowed
21 us to give all worsening heart failure the same
22 rank, to give earlier heart failure events a worst

1 rank. We also did recurrent events, giving worst
2 rank in patients without recurrent events. And
3 then finally, it allowed us to then rank the
4 worsening heart failure by intensification.

5 I think the point is if you accept the
6 clinical judgment of these rankings -- that is,
7 death, worsening heart failure, and then all other
8 patients get ranked according to their dyspnea
9 scores -- what this analysis shows is that there
10 is, I think, a clear treatment effect of the drug
11 with very significant p-values concordant with the
12 primary endpoint. And I think then the question
13 is, is this a clinically relevant effect, which we
14 strongly believe it is.

15 DR. NATHWANI: Dr. Sager, Dr. Packer has
16 requested just to come back and ask you --

17 DR. PACKER: What you've brought up now,
18 it's so important. It's so critical. And we just
19 want to make sure that we have addressed your
20 concern because the goal here is to obey the
21 principles that you've just described, which is
22 prespecification, what was put into the protocol in

1 advance, and what was the specified analytical plan
2 for that endpoint.

3 What you saw with a p-value of .0075 is
4 the result of that prespecified endpoint and
5 prespecified plan. All other sensitivity analyses
6 that you've seen are post hoc. And the reason that
7 they're done is to determine the robustness of the
8 finding because the finding met, as prespecified.
9 But the question is, is it robust?

10 The real clinical question -- it's not even
11 a regulatory or analytical question -- is, should
12 clinical instability be considered more important
13 than changes in the VAS score? The executive
14 committee in advance said yes. And when they said
15 yes, what they essentially did was put that as one
16 of the worst ranks.

17 By the way, that's what we do in every acute
18 heart failure trial now, whether we use the
19 numerical approach or the clinical composite. So
20 this is really important. And I just want to make
21 sure that we've addressed this to your satisfaction
22 because this is a question that everyone on the

1 committee has. The understanding why, what was
2 done in advance and how it was to be analyzed in
3 advance, and what the intent was, is very
4 important.

5 DR. LINCOFF: We're going to move to other
6 questions. Dr. Lewis?

7 DR. LEWIS: Okay. I have three; I'll try to
8 be brief.

9 First off, if worsening heart failure is so
10 integral to the study and so important, it is a
11 little concerning and I actually don't understand
12 why it was not better captured. In a study where
13 the primary outcome was renal, we had secondary
14 cardiovascular outcomes.

15 There was a much more detailed description
16 of what constituted worsening heart failure. Chest
17 X-rays, discharge summaries, echocardiograms,
18 et cetera, were collected, and they were
19 adjudicated by an independent committee. We have
20 none of that.

21 Dr. Packer has repeatedly -- and I don't
22 mean this critically, but has repeatedly said IV

1 diuretics were immediate treatment for some
2 dramatic worsening of heart failure. I don't know
3 if you have adjudicated and have other evidence
4 that you haven't shared with us. There are only
5 106 cases; they certainly could have been
6 adjudicated.

7 I have no reason to not believe this was
8 someone walked in, in the morning, someone had a
9 little worse edema, and their Lasix dose at the
10 next scheduled visit 8 hours later was slightly
11 higher, especially in people with renal failure who
12 might have not been on an appropriate dose to start
13 with.

14 So have you further information to confirm
15 these dramatic worsenings of heart failure with
16 immediate treatments? Do you have information like
17 that? Were these adjudicated? Can you share that
18 with us? That's my first question. Do you want to
19 answer that, and then I'll do my other ones?

20 DR. NATHWANI: Yes, please. And there were
21 two questions in that, so I'll take that in two
22 parts. One was why we didn't adjudicate those, and

1 then the second one was have we done the review
2 right now.

3 So if I can invite Dr. Greenberg just to
4 comment about the adjudication, and then I'll ask
5 Dr. Packer to comment on a review.

6 DR. GREENBERG: So the issue of adjudication
7 came up quite early when we were planning this
8 study, and we decided not to have adjudication
9 because we felt that these were un-adjudicable
10 events.

11 These were events that were going to be
12 clearcut. They were going to be made by clinicians
13 at the bedside for these patients. And not only
14 did the clinicians need to decide that the patient
15 had worsening heart failure, but that this was an
16 event that was actionable, and those actions were
17 an increase in the IV diuretic or the other
18 therapies.

19 When you have somebody that's admitted to
20 the hospital with decompensated heart failure, the
21 symptoms that these patients would develop, there's
22 a very narrow bandwidth for what that could be due

1 to. And we felt that any critical event committee
2 was not likely to overturn the clinical judgment by
3 the clinician at the time when they observed one of
4 these events.

5 DR. LEWIS: Yes. But you lost the ability
6 to be able to describe to us what the
7 characteristic of those events were. Did they have
8 pulmonary edema on chest X-ray and couldn't
9 breathe? Did they have slightly worse edema and
10 their Lasix was doubled 8 hours later? That would
11 have been very helpful information. But there
12 hasn't been an adjudication and you have --

13 DR. NATHWANI: Yes. There hasn't been an
14 adjudication. But if I can invite Dr. Packer,
15 who's had -- we've gone back to the sites to get as
16 many of the cases as possible. And Dr. Packer's
17 had a review.

18 DR. PACKER: Yes. This is really important.
19 I, like you, was concerned that we didn't have a
20 lot of information about the event at the time of
21 its occurrence, and there was no adjudication. And
22 so I said, look. Can you photocopy every patient

1 with worsening heart failure, the medical records?

2 I want to see those medical records.

3 Now, this is not adjudication. Okay? This
4 is one person looking at what happened during the
5 time that there were recorded worsening events
6 because I just wanted to make sure they were real.
7 And when I went through it -- and let me just say
8 that we had to have some of them translated; some
9 of them were in various languages, and not all of
10 them were in English. Actually, very few were in
11 English.

12 We were able to document, one, worsening
13 dyspnea, and the timely administration of
14 intravenous therapy directly from the medical
15 records in the vast majority of patients.

16 So that's not an adjudication, and it's one
17 person doing it after the fact. But if you want to
18 know whether these patients actually had the events
19 attributed to them, just based on my personal
20 review, I think the answer is yes.

21 DR. LEWIS: My second question is, so there
22 were the rehospitalization and death at 60 days.

1 Certainly rehospitalization is an important
2 clinically significant marker as well as important
3 to the healthcare system.

4 If you take the 8 people who died in the
5 placebo group more than your drug group and add
6 them and say, okay, all those people didn't die, if
7 you add them to say they were
8 rehospitalized -- it's 58 versus 60 -- you still do
9 not win in rehospitalization.

10 I would like you to comment on what -- that
11 to me seems like a disconnect. And I'll throw out
12 a devil's advocate hypothesis. Perhaps those
13 subjects in the placebo group who received
14 increased IV diuretics and did not get
15 rehospitalized because they actually got a primary
16 treatment, these patients with high blood pressure,
17 poor renal function, and probably volume overload.

18 Do you have any analyses of the
19 rehospitalization rates in the patients who
20 received increased IV diuretics versus those who
21 don't? And then I have one other question. It's a
22 safety question.

1 DR. NATHWANI: That's okay. I'll just take
2 that in two parts, if that's okay. I'd like to ask
3 Dr. Greenberg to comment on the patency in
4 rehospitalization first, and then take the second
5 question about the additional data.

6 DR. GREENBERG: Well, you can't be a heart
7 failure doc without considering rehospitalization.
8 We're getting beaten over our heads about it every
9 day by our hospitals.

10 Let me make two points about this. The
11 first is that there is no therapy currently
12 available that has been shown to have any impact on
13 rehospitalization in this patient population. I
14 think that this is much more of a systems issue,
15 the transition of patients from the in-hospital
16 setting to discharge, which determines the
17 rehospitalization rate.

18 I don't know if it's amenable to medical
19 therapy. And even if it is, there's so much noise
20 caused by all of the other issues going on that it
21 would be one that's very, very difficult to
22 determine in a clinical trial.

1 It was included as a secondary endpoint in
2 this clinical trial simply because we had to. It's
3 so topical. Everybody is asking about it. But I
4 don't think we really had a chance to show that.

5 DR. NATHWANI: May I just address the second
6 part of your question and invite Dr. Lefkowitz to
7 the microphone.

8 DR. LEFKOWITZ: Martin Lefkowitz, clinical.
9 We did not break down rehospitalization according
10 to intensification. What I can tell you of those
11 patients who were rehospitalized, 9 on serelaxin
12 had a previous episode of worsening heart failure
13 and 6 on placebo had a previous episode of
14 worsening heart failure. That's out of the 60 and
15 50 in the two groups.

16 If I may, though, Dr. Lewis, can I clarify a
17 bit more your first question in terms of what these
18 events were and were they just peripheral edema,
19 for example?

20 First off, this was a rigorous collection or
21 rigorous determination by the investigator. At
22 every visit, the investigator assessed for the

1 presence of worsening heart failure. If they
2 determined that it was, they entered the time that
3 the worsening heart failure started. They entered
4 the AE, which I will re-share with you in terms of
5 a description, start/stop time. They entered in
6 the concomitant medication page the intensification
7 therapy. And then they checked the relevant parts
8 of the CRF. So all that was done.

9 If I can share with you the AEs and then
10 share with you a bit more of what we have on
11 the --

12 DR. LINCOFF: You've got to keep this short,
13 though.

14 DR. LEFKOWITZ: Okay. Slide 343. Again,
15 you've seen this before. This is just the
16 symptoms. Now, much of these were just listed as
17 cardiac failure. There's some dyspnea. There was
18 only one peripheral edema.

19 If I could share two other slides with you,
20 then. We did not, as you know, collect symptoms at
21 the time of the event. These events could occur
22 any time, and we don't have that data. We did look

1 at symptoms at the visit immediately following the
2 worsening heart failure event. So patients have
3 already received their rescue treatment, and now
4 we've looked at symptoms.

5 So if I could have slide 202. This is a
6 somewhat complex slide. But in orange are patients
7 with worsening heart failure at the visit
8 immediately following their episode. Their
9 comparison group is all other patients with
10 worsening heart failure at the time.

11 On the left side is physician-assessed
12 dyspnea, and you can see moderate and severe
13 dyspnea. You can see at all visits it was
14 significantly more than those persons without
15 worsening heart failure.

16 In addition, when we broke it up, only in
17 the severe group on the right side you can see
18 again, especially at the early visits where there
19 was less separation on the left, at every visit
20 pretty much the patients with worsening heart
21 failure had more severe dyspnea at the visit after
22 the episode despite rescue therapy.

1 The last slide I show, 203, is the same
2 for -- 203, please, and slide up -- is the same
3 slide for orthopnea, patient-reported orthopnea,
4 giving the same sort of picture.

5 DR. LEWIS: Can I just ask my one last
6 safety question?

7 DR. DELEMOS: Can we just go back one slide?

8 DR. LEWIS: Sorry.

9 DR. NATHWANI: Okay. Just go back to that
10 slide, please, 203, C-203. Slide up. Marty, do
11 you want to return to the microphone?

12 Did you have a specific question on this or
13 just wanted to see it a bit longer?

14 DR. DELEMOS: I just make the point that
15 they're continuing to improve, just at a slower
16 rate, even though they're defined as clinically
17 unstable in terms of symptoms.

18 DR. LEFKOWITZ: Perhaps I didn't explain it
19 well enough. This is not patients over a time in
20 orange. Patients had worsening heart failure
21 throughout the 5 days. So in orange is the visit
22 immediately after that worsening heart failure

1 episode.

2 So it's not their course over time. This
3 is simply to demonstrate that these patients were
4 symptomatic. It was not simply peripheral edema.
5 And that's what we wanted to respond to here.

6 DR. LEWIS: Okay. I have one last safety
7 issue. And I know everybody kind of was just
8 passing on the safety here, but speaking as a
9 nephrologist, I guess, a 40-millimeter in systolic
10 blood pressure is very different in someone with a
11 blood pressure of 160, in whom it was actually
12 probably a benefit to lower their blood pressure.

13 Someone with 126 dropping their blood
14 pressure, I wonder what the safety of that is in
15 them. Do you have a breakdown of safety events as
16 well as efficacy based on maybe tertiles or
17 quartiles of baseline blood pressure?

18 DR. NATHWANI: Yes, we do. I'm going to
19 invite Dr. Rolli to the microphone.

20 DR. ROLLI: Melanie Rolli, drug safety. We
21 asked a similar question. We wanted to understand
22 if someone with a lower baseline blood pressure is

1 more likely to have an event than someone with a
2 higher blood pressure. Slide up, please.

3 What I would like to show you here -- it's a
4 little complex. I'll work you through. On the
5 upper part of the table, you see the placebo
6 patients, on the lower part, the serelaxin
7 patients. We cut them by baseline blood pressure
8 of below 130, then the middle group between 130 and
9 150, and above 152.

10 What you see is what we heard earlier, is
11 that the serelaxin patients are more likely, a
12 little more likely, than placebo to have those
13 events. However, there is not a huge increase on
14 the lower part -- actually, if patients were on the
15 lower part, around 130 or above 150 had a similar
16 chance to have the event, and the ones in the
17 middle are a little less likely.

18 I think it's important to note that the
19 consequence was different because this is how it
20 was determined. The criteria said if you were
21 dropping below 100, you would be discontinued. If
22 you were dropping first by 40 and then follow that

1 by 10, you could stay on drug. And yes, we had to
2 discontinue patients, but --

3 DR. LEWIS: This is very interesting. I'm
4 wondering not about how often this occurred in them
5 because I imagine -- I'm wondering about what
6 happened to them, someone with a blood pressure of
7 130 or less, when they dropped their blood
8 pressure. Did they get acute renal failure? Did
9 they have other adverse events in excess?

10 DR. ROLLI: Okay. For the outcomes, would
11 you like to continue?

12 DR. NATHWANI: Yes. I was going to ask
13 Dr. Lefkowitz just to address the outcomes for
14 these patients. Dr. Lefkowitz?

15 DR. LEFKOWITZ: Yes. So what I can show you
16 is more the longer-term outcomes with these
17 patients. If I could have slide 62, and slide up.

18 Here we looked at placebo versus serelaxin
19 in patients without or with a confirmed blood
20 pressure drop, and obviously, the concern that
21 those patients with a confirmed blood pressure drop
22 are at higher risk to begin with, but then may also

1 have a consequence.

2 DR. LEWIS: This is interesting. But again,
3 I'm concerned about the range of blood pressures
4 that you're asking us to indicate this drug for,
5 perhaps.

6 DR. LEFKOWITZ: Sure.

7 DR. LEWIS: I believe that when your blood
8 pressure is 160 or 180, probably dropping it by
9 40 millimeters is okay. 130, because your entry
10 criteria would allow this drug to be labeled,
11 theoretically, for someone with a systolic blood
12 pressure of 130, what happens to those patients who
13 are going to be a lot of them in the real world.
14 Right?

15 DR. LEFKOWITZ: Okay. I understand.

16 DR. LEWIS: This is a very interesting
17 subset that you've studied.

18 DR. LEFKOWITZ: Right. Can I have slide
19 C-54, please? Excuse me, the slide with --

20 DR. LEWIS: I mean, it's good you enrolled a
21 lot of them. It looks like you have about 118 less
22 than 130. Right? If I read that right. So you

1 have a fair number of them.

2 DR. NATHWANI: Just give us a moment. We'll
3 just call the right slide up.

4 DR. LEFKOWITZ: C-53.

5 DR. LEWIS: You can come back with it.

6 DR. LINCOFF: Yes. If you don't have it --

7 DR. LEWIS: Yes. Why don't you come back so
8 we don't take up time?

9 DR. LEFKOWITZ: We have it. No, we do. I'm
10 sorry. So, Tom, would you like to address it?

11 DR. SEVERIN: Tom Severin from the clinical
12 team. We looked at the results of the primary
13 endpoint VAS-AUC and also on the result of
14 mortality by baseline blood pressure. And I would
15 like to show -- slide up, please.

16 So here you see that the point estimate
17 favors serelaxin, no matter in which blood pressure
18 category patients entered the study, for the
19 VAS-AUC, shown in the upper half of this table, and
20 for 180-day all-cause mortality, shown on the left.
21 So the point estimates are always in favor of
22 serelaxin and consistent with the overall treatment

1 effect.

2 DR. LEWIS: How about the safety?

3 DR. NATHWANI: Yes. We'll come back
4 to -- Dr. Rolli? Did you want to comment further
5 on the safety in that particular group?

6 DR. ROLLI: Can I get the slide one more
7 time up, please, that we had previously so we look
8 at the numbers? Okay, 6. Slide up, please.

9 So what you see is that we had a dose
10 discontinuation or dose decrease. I think the
11 important thing is that the ones who did then in
12 that context need treatment, actually most of them
13 were okay with fluids and recovered within the next
14 2 hours, according to the narratives that we had.

15 If we then looked at -- we had 3 patients on
16 placebo, 2 on inotropes, that needed inotropes in
17 intervention to recover. And they were fine, too.

18 DR. LEWIS: Perhaps you can come back to us
19 with, actually, some actual data, that would be
20 great.

21 DR. NATHWANI: We'll come back with the
22 specific slides. We'll do that. Thank you.

1 DR. LINCOFF: All right. We're out of time
2 for now. We're scheduled for break. So we will
3 get to the people who are still on the list at some
4 point later.

5 So we'll take a short, 15-minute break.
6 Committee members, please remember there should be
7 no discussion of the meeting topic during the break
8 amongst yourselves or with any member of the
9 audience. We'll resume at 10:35 a.m.

10 (Whereupon, a recess was taken.)

11 DR. LINCOFF: All right. In the interests
12 of time, I'd like to get started.

13 So now we'll proceed with the presentations
14 by the FDA. It's my understanding that the FDA
15 wants to add some of their other slides in
16 response. That's fine, but I'd ask them to stay
17 within the time period for this talk.

18 **FDA Presentation - Melanie Blank**

19 DR. BLANK: Good morning, members of the
20 advisory committee, Novartis representatives, FDA,
21 ladies and gentlemen. I am Melanie Blank, and I am
22 one of the clinical reviewers who was assigned to

1 the serelaxin BLA.

2 I have with me Dr. Bai, who's sitting behind
3 me. The two of us will be sharing the podium.
4 Dr. Bai is the statistical reviewer. I also have
5 with me on the FDA side Dr. Tzu-Yun McDowell, who
6 was the safety reviewer. She did the clinical
7 review with me, and she will be available for your
8 questions regarding safety.

9 First we will talk about the regulatory
10 guidance on relying on a single trial for proof of
11 efficacy, and some of the discussions and
12 agreements that were made between the sponsor and
13 FDA prior to submission. Then we will discuss the
14 primary endpoints, primarily focusing on the VAS-
15 AUC.

16 Then there will be discussion of the
17 worsening heart failure imputation and how that
18 impacted the results. Finally, I will briefly
19 discuss the secondary endpoints.

20 Occasionally the FDA accepts a single trial
21 as a basis of approval. There are two possible
22 scenarios for this. One is when there is

1 independent confirmatory evidence of efficacy to
2 support it, and another case where there is not.

3 In the case of serelaxin, there is only
4 one phase 3 trial. And while there were many
5 interesting and encouraging exploratory findings
6 during the development program, in my opinion this
7 is an example of the second scenario, where there
8 is only one pivotal trial and no independent
9 confirmatory evidence of efficacy.

10 Independent substantiation of a favorable
11 result from a single study is important because it
12 protects against the possibility of erroneously
13 concluding that a treatment is effective based on a
14 chance occurrence. For this reason, the standards
15 are high for accepting approval on the basis of one
16 trial without confirmatory evidence.

17 The FDA guidance on evidence of
18 effectiveness states that FDA has relied on only a
19 single adequate and well-controlled efficacy study
20 to support approval generally only when a single
21 well-designed multi-center study provides
22 statistically strong evidence of an important

1 clinical benefit, such as an effect on survival,
2 and a confirmatory study would be difficult to
3 conduct on ethical grounds.

4 Generally speaking, for a symptomatic claim,
5 FDA requires evidence of efficacy from two
6 independent trials, both successful at a p-value
7 less than .05.

8 The end of phase 2 FDA advice reflects the
9 position that FDA was willing to be flexible about
10 the need for more than one trial for serelaxin even
11 though the prespecified endpoint was a symptomatic
12 endpoint as opposed to a benefit on the significant
13 mortality or morbidity.

14 FDA informed the applicant that a highly
15 persuasive p-value, specifically a value less than
16 .00125, on at least one of the primary endpoints in
17 RELAX-AHF would have been sufficient evidence of
18 efficacy, with the proviso that if only one of the
19 two primary endpoints was this successful, the
20 other endpoint would have to be trending favorably.

21 The applicant's agreement with the FDA's
22 advice was stated in the RELAX-AHF final

1 statistical analysis plan. It stated that, "A
2 result significant at the two-sided .05
3 significance level" -- which was the agreed-upon
4 standard for success -- "but not significant at the
5 two-sided .00125 level, will be confirmed in a
6 subsequent study."

7 Now I will move on to discuss the primary
8 endpoints in RELAX-AHF.

9 The applicant's stated objective and
10 hypothesis were that serelaxin has an effect on a
11 symptomatic benefit, namely, dyspnea, as measured
12 by patient-reported outcome tools that were
13 specifically designed to measure dyspnea. This is
14 an important point to keep in mind because of the
15 worsening heart failure designation that you've
16 heard so much about, that the sponsor in their
17 objective talked only about dyspnea.

18 One of the primary endpoints was the
19 proportion of subjects with moderate to marked
20 improvement on the Likert dyspnea scale at all
21 three of the earliest time points, 6, 12, and
22 24 hours, and the other primary endpoint was the

1 AUC over 5 days of the change from baseline in the
2 visual analog scale for dyspnea. This is what the
3 applicant calls the VAS-AUC.

4 For the primary endpoint, the Likert test
5 was carried out at baseline and at three subsequent
6 time points over a 24-hour test period by providing
7 the subjects with a paper questionnaire that asked
8 that subject to compare his or her breathing at the
9 present time to how it was at the time of
10 randomization, and then to circle the number next
11 to the description that best captured that
12 comparison.

13 This bar graph shows the results of the
14 Likert. The bars represent the proportion of
15 subjects who got moderately or markedly better over
16 time. As you can see by the similar bar heights at
17 each time point, there was little difference
18 between the treatment groups.

19 The set of bars that are on the far right of
20 the graph represent the primary endpoint, which was
21 the proportion of subjects who are moderately or
22 markedly improved at all three of those time

1 points. There was no difference between treatment
2 groups, and there was no favorable trend.

3 The VAS dyspnea score asked the subjects to
4 rate their breathing by drawing a hatch line on a
5 100-millimeter vertical scale, which compared their
6 breathing to the best it's ever felt or the worst
7 it's ever felt.

8 As straightforward as the VAS was, the
9 VAS-AUC calculation was far from straightforward.
10 Dr. Bai and I are going to explain it to you with a
11 series of graphs.

12 The VAS scores were reported at baseline,
13 6 hours, 12 hours, 24 hours, and then every day
14 after that for the next 4 days. If a time point
15 was missed, VAS was imputed using linear
16 interpolation or the last observation carried
17 forward.

18 The important aspect of the VAS-AUC
19 calculation that I will be spending quite a bit of
20 time on later is the imputation for the worsening
21 heart failure.

22 If a subject was designated by the

1 investigator as having worsening heart failure, the
2 worst observed VAS score in the whole trial was
3 used instead of the raw VAS, and then carried
4 forward for all future time points for that
5 subject.

6 The worst observed VAS score in the study
7 was zero. This imputation rule accounted entirely
8 for the success of the trial, and hence, as you
9 will see, made the endpoint difficult to interpret.

10 The mathematics of the calculation of the
11 VAS-AUC is presented here. Basically, each
12 interval between VAS score measurements has its own
13 AUC that could be calculated. The 5-day VAS-AUC is
14 the sum of all of the AUC intervals.

15 The AUC for each interval was calculated by
16 adding the change from baseline in the VAS score at
17 the beginning of the interval to the change in VAS
18 from baseline at the end of the interval,
19 multiplying by the number of hours in the interval
20 and then dividing by 2. Then all of these
21 different AUCs were added together to get you the
22 VAS-AUC.

1 Dr. Bai will now make this clearer by using
2 a hypothetical example.

3 **FDA Presentation - Steven Bai**

4 DR. BAI: Dr. Blank verbally described the
5 calculation of the VAS-AUC in the last slides. We
6 normally don't spend so much detail on how to
7 derive primary endpoints in AUC presentations, not
8 even or statistical reviews. However, we feel if
9 we can graphically display how to compute a VAS-
10 AUC, then you can understand why the imputation
11 rule has such a significant impact on the final
12 results.

13 These are the VAS scores and the change on
14 baseline scores of a hypothetical subject. At each
15 time course, the subject had a baseline VAS of 33,
16 and goes to 40 at 6 hours and 43 at 12 hours and so
17 forth. Hence, the change from baseline is zero at
18 the baseline and 7 at 6 hours, 10 at the 12 hours.

19 We connect each time point delta VAS with
20 next time point in this plot. The total area under
21 this curve is calculated by summing up the area of
22 each sections. We can see that except the first

1 section, rest of six sections are all trapezoid,
2 and the first section is a right triangle.

3 Let's focus on the first two periods as
4 examples. Please excuse me that I changed my mind
5 about the order of these two slides last night, so
6 it's too late for the change. You may find it
7 reasonable when I finish, or not.

8 Let's see the second section first, which is
9 between 6 hours and 12 hours. In order to compute
10 the area of this trapezoid, we need to know the
11 height of the left edge -- we'll call it height
12 1 -- and the height of the right edge is called
13 height 2. We know they are 7 and 10 millimeters
14 from the previous slides. The width is 6 hours.
15 It's from 6 to 12 hours, so the width is 6 hours.
16 So we plug these three numbers into the trapezoid
17 formula and we've got 51 millimeter/hour.

18 Now I'll go back to the first section, which
19 is the right triangle. But we can treat it as a
20 special trapezoid, with height 1 being zero. And
21 we can still plug in those three values used in the
22 same trapezoidal formula and get 21 millimeter/hour

1 for the area of this first section.

2 So if we sum up those two values, we get
3 72 millimeter/hour for the first two time periods.
4 And if we repeat this for the rest of five
5 sections, the total sum of area ended up to be 1554
6 millimeter/hour.

7 But for most of us, 1554 millimeter/hour is
8 not intuitive measurement. We have a hard time
9 conceptualizing what it means for a subject's
10 [indiscernible]. A better way to conceptualize
11 this result is to think in terms of average change
12 through 5-day period. So we divide 1554 by
13 120 hours, the number of hours in 5 days. We got
14 13 millimeter.

15 Basically, this hypothetical subject had a
16 time-weighted average change from baseline of
17 13 millimeter in 100-millimeter VAS scale over
18 5 days.

19 So now here are the results of the VAS-AUC
20 primary endpoint. This is same as the sponsor's
21 slide 56 you saw earlier, but we have this in a
22 tabular format; they had it in a graphical format,

1 but results are the same.

2 The time-weighted average treatment effect
3 is approximately 3.77 millimeter in the 100-
4 millimeter VAS scale. Again, we obtained by divide
5 by 120 hours.

6 Now I would hand the podium back to
7 Dr. Blank.

8 DR. BLANK: Now I'm going to shift your
9 attention to the mean change from baseline in VAS
10 scores at each assessment time by treatment to give
11 you a sense of how the results trended over time.
12 The data used to construct this graph are the
13 change from baseline in VAS scores, with the
14 imputation method substitutions at each of the
15 seven post-baseline measurements.

16 On the X axis are the post-baseline
17 assessment times, and on the Y axis, which I
18 intentionally shrunk so that you could see it more
19 clearly, is the change in VAS from baseline in
20 millimeters.

21 The red curve represents the mean change
22 from baseline in VAS scores through day 5 at each

1 assessment time point, with confidence intervals in
2 the serelaxin group. And the blue curve represents
3 the same for the placebo group.

4 You can see that there's just 1 millimeter
5 difference between groups in the change in VAS from
6 baseline at 6 hours, and that the largest
7 difference between the groups are at days 3 and 4,
8 where there is a 5-millimeter change from baseline
9 on a 100-millimeter scale.

10 By doing a responder analysis, we attempted
11 to look for an outlier subgroup that may have shown
12 a larger benefit, but didn't find one, at least at
13 day 5. On the X axis are the responder categories
14 labeled by the change in VAS from baseline in
15 millimeters, and the bars represent the percent of
16 subjects in each responder category.

17 The first set of bar on the left represent
18 the proportion of subjects who at day 5 had at most
19 a 10-millimeter change in VAS, but they could have
20 stayed the same or gotten worse. The second set of
21 bars, marked "More than 10," represents subjects
22 who had more than a 10-millimeter improvement from

1 baseline in the VAS score at day 5. The last set
2 of bars on the right are subjects who had more than
3 a change of 40 millimeters from baseline at the 5-
4 day time point.

5 The take-home points from this graph are
6 that at day 5, both treatment groups had about the
7 same percent of subjects at each responder
8 category, and that there were no difference in the
9 subjects who were the biggest responders between
10 groups.

11 Now I will speak more about the VAS
12 imputation rule and the effect it had on the
13 interpretability of the results.

14 I have already mentioned that the protocol
15 stipulated a rule for imputing the worst value
16 observed for any subject instead of the raw VAS
17 score when that subject had an episode of
18 investigator-designated worsening heart failure,
19 and then it was carried forward.

20 It's important for the advisory committee to
21 note -- this was not in my review and it was a
22 subsequent finding -- that only 4 subjects had

1 baseline values of zero so that the value of zero
2 was almost always lower, and often very much lower,
3 than the VAS score that the subject had at
4 randomization.

5 It is also interesting to note that only one
6 subject had a post-baseline score, a real VAS
7 score, of zero, and that subject happened to be in
8 the serelaxin group.

9 To evaluate whether the imputation method
10 was reasonable and to interpret the findings, it is
11 important to understand what worsening heart
12 failure was. So now let's turn to the protocol
13 definition of worsening heart failure.

14 The definition was primarily treatment-
15 oriented. The protocol defined it as, "Worsening
16 signs and/or symptoms of heart failure that
17 required an intensification of IV therapy for heart
18 failure or mechanical ventilatory or circulatory
19 support. Such treatments could include the
20 institution or up-titration of IV furosemide, IV
21 nitrates, other IV medications for heart failure,
22 institutional of mechanical support such as

1 mechanical ventilation, intra-aortic balloon pump,
2 et cetera.

3 "Note that there are no symptoms or signs of
4 heart failure specified, such as hypoxia, JVD,
5 orthopnea, dyspnea at rest, pulmonary edema on
6 chest X-ray, or elevation in BNP."

7 The applicant is making the case that
8 worsening heart failure was prespecified and should
9 therefore be considered to be a prespecified
10 endpoint. In response, I would like to point out
11 to the AC that the imputation rule specified in the
12 SAP defined worsening heart failure slightly
13 differently in that it included rehospitalization
14 in the definition of worsening heart failure for
15 the purpose of applying the imputation rule.

16 Another point that the AC should consider is
17 that the protocol did not include a spelled-out
18 definition of worsening heart failure, the one that
19 you see here, until the fifth amendment, when all
20 but 60 subjects had been enrolled.

21 Also, worsening heart failure was not
22 considered a topic for discussion during any of our

1 pre-submission meetings. So I don't believe that
2 the sponsor really had thought this as well out as
3 they seem to suggest. The FDA certainly did not
4 think that this was going to be driving the results
5 of the trial.

6 So not only were there no objective criteria
7 for defining worsening heart failure, there was no
8 capture of the signs, laboratory assessments, and
9 symptoms that were present at the time of worsening
10 heart failure.

11 Notice the case report form asks if the
12 subject, in the investigator's opinion, had
13 worsening heart failure in the last 24 hours, but
14 does not ask for a description of symptoms or
15 signs, nor does it ask for vital signs or labs,
16 just treatment.

17 Because worsening heart failure often
18 occurred between investigator assessments and there
19 was no place in the CRF to describe the signs or
20 symptoms of worsening heart failure, it is
21 impossible to know what really occurred to those
22 subjects that made the investigator come to his or

1 her conclusion that the subject had worsening heart
2 failure. All you have is the assessment of
3 treatments, which you can see spans the gamut.

4 So to recapitulate, worsening heart failure
5 was left to the investigator to decide. There was
6 no prespecified criteria, and the signs and
7 symptoms were not captured. All that was captured
8 was the treatment outcome, which encompassed a
9 large spectrum, some quite serious -- need for
10 mechanical ventilation -- but others mild and
11 easily treated, such a worsening heart failure that
12 required just a small increase in IV diuretic use.

13 Now Dr. Bai will show you the impact of
14 worsening heart failure on the VAS-AUC.

15 DR. BAI: Recall the hypothetical subject I
16 made up earlier who had a raw VAS-AUC score of
17 1554. Now suppose the subject developed worsening
18 heart failure at hour 10 and received 6 milligram
19 of furosemide.

20 For this reason, the VAS scores are imputed
21 to zero for all time points after 12 hours, the
22 change from baseline for all those time points

1 subsequently imputed to negative 33 because
2 difference between baseline and zero is
3 negative 33.

4 Now the curve goes under the X axis at this
5 point, which means for all the trapezoids after
6 this point will have negative heights. This
7 implies all those trapezoids will have negative
8 areas above the curve. We probably should call
9 this part of AUC AAC for area above the curve.

10 The result of her VAS-AUC is now negative
11 3621, which is 5175 millimeter/hour less than the
12 raw score. That's a pretty big penalty for what
13 seems like a minor episode of worsening heart
14 failure.

15 Now let's see an actual real subject in the
16 study. This subject also had VAS scores across all
17 time points. So subject's change from baseline in
18 AUC by the method described can be easily followed
19 in the third and fourth column.

20 However, subject had an episode of worsening
21 heart failure somewhere between 12 hours and day 1.
22 So day 1 through day 5 VAS scores are imputed to

1 zero. The last two columns are imputed VAS scores
2 and the imputed AUCs.

3 The discrepancies between the two AUCs are
4 getting larger and larger after imputation. We
5 see that by day 5, the subject's AUC had been
6 reduced by as much as fourfold.

7 I need to mention that this subject had the
8 most negative VAS-AUC in the entire trial, and
9 happened to be a placebo subject.

10 Now, if we translate this subject's data
11 into this figure, then the profile plot of the
12 subject's observed change from baseline VAS scores
13 are the curves underneath of this red Region A.
14 The profile of imputed values are the outer edge of
15 the entire figure.

16 Since this subject start off with a very
17 high baseline scores, all change from baseline
18 scores are all negatives. So the observed AUC only
19 consist of Region A; however, imputation rule
20 added, or you can say it's subtracted, the actual
21 Region B into the final AUC. So you can see the
22 imputation had drastically impacted the AUC for

1 this subject both numerically and graphically.

2 In this subgroup analysis, we see that a
3 total of 110 -- I need to say that we added 4 more
4 deaths into this subgroup, 2 in each treatment
5 group, so we have 110. The sponsor had 106. So
6 within this 110 subjects, the treatment difference
7 is nearly 1600 millimeter/hour; however, for the
8 remainder of the subject, there's no difference at
9 all.

10 We further evaluate the distribution of this
11 110 worsening heart failure patients. In this four
12 box plots, we compared the imputed and the raw AUCs
13 across both treatment groups. Statistics 101 -- a
14 box plot is a graphical tool for the summary data.

15 Suppose we look at the placebo imputed data,
16 the first one. This lower bar is the 25th
17 percentile, this middle bar is the median, and
18 there's the 75th percentile. The diamond is a
19 mean.

20 If you go from the 25th percentile down by
21 1 and a half times of the length of this rectangle,
22 you get to this point, it's got a lower whisker.

1 If you go from the 75th percentile up the same
2 distance to this point, that's the upper whisker.
3 Any calculations outside these two whiskers can be
4 considered as outliers or highly influential data.

5 As we can see from this figure, the
6 imputation rule reduced mean AUCs across both
7 treatment groups. Within placebo, the mean was
8 reduced from 1,080 to negative 3109, and for the
9 serelaxin, it was reduced from 1990 down to
10 negative 1512.

11 So the imputation exaggerated the difference
12 between the treatment and placebo from originally
13 of 900 up to 1500, roughly up to 1500 now. And
14 there's a bigger reduction in the placebo; there's
15 roughly 4000 millimeters reduction in the placebo
16 and about negative 3500 millimeter reduction in the
17 serelaxin.

18 Finally, this is a simple post hoc
19 exploratory analysis. I reported this analysis to
20 the review team during the early stage of the
21 review, and the imputation may not be reasonable
22 in the clinical perspective.

1 But I did the imputation based on my
2 statistical mind, so I basically left subject
3 without worsening heart failure as specified. And
4 for the subject with worsening heart failure, if
5 they have observed VAS scores, I do not impute them
6 to zero. I just use the value observed. For the
7 missing values, I impute them to zero.

8 Even though this is a simple analysis, I can
9 say this to be the birth mother of all those
10 imputation method sensitivity analyses you saw
11 earlier because this results was concerning for the
12 review team, and we asked the sponsor to perform a
13 number of different sensitivity analyses you
14 already saw earlier.

15 Now I'm going to turn the podium back to
16 Dr. Blank again.

17 DR. BLANK: Now I'm shifting your attention
18 back again to the change from baseline in VAS
19 scores of the different assessment time points.
20 This graph is the easiest way -- well, you've seen
21 this graph before, but I just want to show it to
22 you again to show the impact of worsening heart

1 failure on the VAS scores over time.

2 On the X axis is the VAS assessment time in
3 hours, and on the Y axis is the mean change in VAS
4 from baseline in millimeters, intentionally
5 shrunken as before. The red curved lines represent
6 serelaxin and the black represent placebo. The
7 mean baseline VAS scores for all subjects was about
8 44 millimeters.

9 I showed this graph earlier with only the
10 dotted curves, which used the imputed VAS values.
11 The solid upper lines represent the change from
12 baseline in both treatment groups over time using
13 raw VAS scores only, without any imputation for
14 worsening heart failure or missing values.

15 As you can see, they are practically
16 superimposable. This graph illustrates the absence
17 of a difference between groups when you only
18 consider patient-reported dyspnea. It also
19 illustrates that the difference in the VAS-AUC was
20 entirely caused by a difference in the incidence of
21 investigator-designated worsening heart failure.

22 So how many subjects got worsening heart

1 failure and how were they treated? A total of
2 110 of 1161 subjects, so less than 10 percent,
3 12.2 percent of placebo bono and 6.7 percent of
4 serelaxin, were determined to have worsening heart
5 failure by the investigators. The only way to
6 evaluate the severity of the episodes of worsening
7 heart failure is to look at how they were treated.

8 I did an exploratory analysis in which I
9 ordered the subjects with worsening heart failure
10 or death by their most aggressive treatment, or
11 death if they died. So for instance, if the
12 subject had IV milrinone and mechanical
13 ventilation, he would be counted as a case of
14 mechanical ventilation.

15 On the other hand, if the most aggressive
16 treatment was IV furosemide, the subject would be
17 reported as having IV diuretics unless he died, and
18 then he would be counted as a death. If he were
19 rehospitalized for heart failure and had any
20 treatment, he would be counted as having a
21 treatment, not rehospitalized.

22 You can see that most subjects were treated

1 with diuretics and nitrates. The number of
2 subjects in the more aggressive treatment
3 categories were quite small. From this, I
4 concluded that the main difference between the
5 groups was difference in relatively mild worsening
6 heart failure treatable with increased IV
7 diuretics.

8 After listening to the sponsor's
9 presentation, I would consider modifying my
10 conclusion to state that the main difference
11 between the groups was a difference in mild to
12 moderate worsening heart failure treatable with
13 increased IV diuretics.

14 You might wonder how much of a difference in
15 IV diuretic use there was between groups. As you
16 can see, there was an average difference of about
17 50 milligrams of furosemide between groups and a
18 median difference of 20 milligrams. But this was
19 in totality over 5 days.

20 This bin analysis shows the proportion of
21 subjects receiving different IV furosemide
22 equivalent doses by treatment over the 5-day

1 period. Serelaxin is represented by the red bars
2 and placebo by blue.

3 You can see from this graph that most of
4 the high and very high IV diuretic uses were given
5 to the placebo group. The handful of subjects in
6 the placebo group who received more than
7 2000 milligrams of IV furosemide equivalent doses
8 accounted for most of the discrepancy between the
9 mean and median IV diuretic doses.

10 Finding this, we asked the applicant to do
11 some sensitivity analyses using different
12 imputation methods to explore the impact of the
13 more aggressively treated cases of worsening heart
14 failure and deaths on the primary endpoint. Here
15 are three examples of the analysis that were done.
16 The first two are very similar.

17 The first exploratory imputation method was
18 to use the raw score or the median score, whichever
19 was lower, if the worsening heart failure was
20 treated with IV diuretic or nitrate, and for all
21 other cases of worsening heart failure, to use zero
22 and carry it forward.

1 The second exploratory imputation method
2 shown was to use the raw score if the worsening
3 heart failure was treated with IV diuretic or
4 IV nitrate or, for all other cases of worsening
5 heart failure, use zero and carry it forward.

6 The third method was to use zero for all
7 worsening heart failure, regardless of treatment,
8 but only during the episode, and then use the raw
9 score after the episode was over. None of these
10 imputation methods provided statistical success,
11 according to the prespecified criteria.

12 The recently submitted addendum ranked
13 subjects with the highest ranks given to subjects
14 who died, intermediate ranks to worsening heart
15 failure, and then low ranks to the subjects who did
16 not die or have worsening heart failure.

17 When you have more than 1000 subjects and
18 you take the 110 worsening heart failure subjects
19 and put them up at top, even if you subcategorize
20 their rank by intensity of treatment or time to
21 worsening heart failure, it's going to come out the
22 same as the primary analysis because of the 2 to 1

1 ratio between placebo and serelaxin in the subjects
2 who developed worsening heart failure.

3 In my opinion, this sensitivity analysis
4 does not address the issue that all worsening heart
5 failure was treated in the same way vis-a-vis
6 imputation, and also does not address the
7 possibility that increased worsening heart failure
8 in the placebo group could have been a chance
9 finding.

10 So to encapsulate the effect of worsening
11 heart failure on the imputation rule, the rule
12 drove the results of the trial and created a
13 successful outcome even though there was no
14 difference between groups in the primary
15 hypothesis, which was self-reported dyspnea. The
16 difference between groups stems mostly from an
17 increase in subjects in the placebo group who
18 required small increases in IV diuretics as their
19 most aggressive treatment.

20 What makes this problematic is two basic
21 factors: worsening heart failure was not well
22 defined or documented, and since it was not the

1 subject of the primary hypothesis, which is
2 improved dyspnea, there's a high likelihood that
3 it's a chance finding. Also, sensitivity analysis
4 using other imputation treatments for worsening
5 heart failure showed that the VAS-AUC success was
6 not as statistically robust as it seemed.

7 Another measure of acute heart failure
8 treatment is an improvement in respiratory rate.
9 This graph shows the different assessment time
10 points on the X axis and respiratory rate change
11 from baseline on the Y axis. It shows that there's
12 no difference in the change in respiratory rate
13 from baseline between groups, which is contrary to
14 what you would expect if there were a strong effect
15 of serelaxin on acute heart failure.

16 Now I will briefly discuss the secondary
17 endpoints.

18 The two prespecified secondary efficacy
19 endpoints were days alive and out of the hospital
20 at day 60 and cardiovascular death or
21 rehospitalization due to heart failure or renal
22 failure at day 60. These endpoints were an

1 opportunity for the sponsor to show confirmatory
2 evidence of efficacy of serelaxin, but neither of
3 these endpoints were successful.

4 So in summary, there is inadequate evidence
5 of efficacy for a single trial approval,
6 particularly since there is no independent
7 confirmatory evidence of efficacy.

8 Secondly, while there was statistical
9 success on the primary endpoint in the trial, it
10 wasn't due to a difference in dyspnea, which was
11 the hypothesis being tested. Instead, the
12 statistical success was due to a difference in
13 worsening heart failure cases between the two
14 treatment groups, and resulted because the
15 imputation rule assigned the worst case value to
16 all subjects with worsening heart failure.

17 Interpreting the results is problematic
18 because dyspnea, not worsening heart failure, was
19 the prespecified endpoint, making it possible that
20 worsening heart failure was a chance finding. It
21 was not well defined, and the case report forms
22 didn't document the basis for the designation. The

1 imputation method treated all cases the same,
2 regardless of severity.

3 In looking closer at the worsening heart
4 failure cases, it's apparent that what drove the
5 results of the trial was a minority of subjects who
6 were treated with relatively small increases in IV
7 diuretics. When looking at other more reasonable
8 imputation methods that considered severity of
9 worsening heart failure, the treatment effect did
10 not achieve the prespecified statistical values to
11 consider the trial a success.

12 I would like to acknowledge the other
13 members of the serelaxin review team. And if I
14 have a few more minutes -- a few more minutes?

15 DR. LINCOFF: Yes.

16 DR. BLANK: -- I would like to present some
17 slides that address some of the issues that the
18 sponsor raised. So if I could have slide 3.

19 Okay. So the Pre-RELAX trial is not
20 something I focused much on in my review. But I
21 had to present it here a little bit because I feel
22 like my review of it was different than how the

1 sponsor is presenting it. So it's just an area
2 that perhaps you want to question more.

3 In the protocol, there were a lot of
4 prespecified criteria that, when they finally did
5 the primary analysis, they used different criteria.
6 For instance, the analysis population was the
7 efficacy population; that was what was
8 prespecified. But they used the MITT for the
9 primary analysis, which was somewhat different.

10 The primary analysis, they stated during
11 this advisory committee that there was no
12 prespecified primary analysis. But in the protocol
13 that I saw, there was a prespecified primary
14 analysis, which was the proportion of subjects with
15 marked or moderate improvement on the Likert at
16 12 and 24 hours.

17 They were comparing the placebo plus
18 10 milligram to the other dose groups. And there
19 was a missing data rule that was slightly different
20 between what they prespecified and what they used.
21 And the statistic used was also different than what
22 was prespecified.

1 May I have the slide 4? This just really
2 recapitulates what the sponsor said, which was that
3 there were these five different groups. So I can
4 go on now to slide 5.

5 This is the primary endpoint that was stated
6 verbatim from the protocol. And as you can see, it
7 says that it was the proportion of subjects with
8 marked or moderate improvement in the 7-point
9 Likert dyspnea scale at both 12 and 24 hours, and
10 then it says here, "in the absence of worsening
11 heart failure symptoms and signs, between 3 and
12 24 hours following start of study drug infusion."
13 And then it did say it was underpowered for that.

14 Okay. And then slide 6. So the results of
15 Pre-RELAX on that prespecified primary endpoint was
16 .59. And they did the exploratory analyses that
17 they found encouraging, and that's what made them
18 decide on how they were going to design RELAX-AHF.

19 Then I'd like slide 7. So this is actually
20 the results of their primary endpoint. As you can
21 see, there's no difference in what they
22 prespecified as a primary endpoint, which was the

1 proportion with moderate to marked improvement on
2 the Likert between the placebo plus 10 and the
3 other doses.

4 Then the last slide that I want to show is
5 slide 8, which shows you that the 30-microgram-per-
6 kilogram dose did look better than the other doses.
7 And the way I would look at this is that this was a
8 trial that was really a dose-ranging trial that
9 allowed them to choose the dose that they wanted to
10 study in the RELAX-AHF. And really, I wouldn't
11 look into it any more than that. That's my point
12 there.

13 So that concludes the clinical presentation,
14 and we're available to take questions.

15 **Clarifying Questions to Presenters**

16 DR. LINCOFF: All right. Thank you to the
17 FDA.

18 We had multiple questions before the break
19 for the sponsor. In order to keep this together,
20 I'm going to ask now for questions to the FDA. I
21 have the list of people who wanted to have
22 questions of sponsors, and we will come back to

1 that after lunch. So now specifically questions to
2 the sponsor. Dr. D'Agostino? I mean, to the FDA.
3 Yes.

4 DR. D'AGOSTINO: Thank you for the
5 presentation. I'd like to go through a few items,
6 and I'll do it quickly.

7 First of all, I don't like the word
8 imputation the way we're using it. It has a
9 negative connotation that it's missing data. Here
10 you're talking about you did the imputation on
11 missing data, but they were doing a scaling for the
12 different outcomes.

13 When I go on to the scaling, they scale to
14 zero. And I started with the FDA back in '74, and
15 we had all of this thing. We had scales, and you
16 take the worst value, and you get a smaller p-
17 value. And then the question becomes, how far can
18 you drive that p-value to nonsignificance by
19 changing different outcomes or different ways of
20 doing the scaling.

21 The sponsor had a whole group of them. And
22 they started off with the .007 or something, and

1 they move to getting closer and closer to .02 and
2 so forth. And you come all the way down to .21.
3 And I think that's very important, that we see that
4 the sponsor was doing the usual scaling. You fuss
5 around with it. You change some of the values.
6 You make them more extreme; the p-value gets
7 smaller. You make them less extreme; the p-value
8 gets bigger. And I think we need to be grappling
9 with how much we think of the .21. And even if we
10 don't think of the .21, those sponsor values,
11 they're getting us closer and closer to
12 nonsignificance by the different rule we have.

13 Then the other thing I want to impose on
14 this is that are we not going to pay any attention
15 to the sponsor's statement about the reason why
16 they attach the worst score was because of rescue
17 medication being needed.

18 So to boil that down, tell me about why
19 don't we need to worry about the sponsor's issue of
20 the rescue medication; then once there is a
21 worsening, then you have to somehow or other not so
22 much look at the following values, but think of

1 the -- you went in and you intervened with that
2 individual, so the remaining scores aren't useful.

3 Then tie into that, if you would, the p-
4 value of .21. And then I'm going to throw it out
5 now because I know the chairman's going to tell me
6 I can't ask two questions -- he should tell
7 me -- but I'm worried about after that.

8 DR. LINCOFF: That's what I'm going to --

9 DR. D'AGOSTINO: Yes. We have two studies
10 here. I don't think we have two studies that you
11 can combine for the information. So I'd like you
12 to reiterate that. But the first comment about the
13 scaling and the wandering p-values, it's not
14 surprising that the p-values keep getting
15 smaller -- I mean, keep getting larger. It's not
16 surprising they don't trip over into
17 nonsignificance with the way the sponsor was saying
18 it.

19 But the way you're saying, with that .21,
20 just reiterate, if you would, what was going on.

21 DR. BLANK: Okay. Well, I'll try to address
22 your questions.

1 It might be reasonable to assign some sort
2 of imputation method, or whatever you want to call
3 it if you don't like that word, to worsening heart
4 failure. And that's why we did those sensitivity
5 analyses, to look and see how -- really mostly
6 looking at the more severe cases and seeing, did
7 that really affect the results?

8 We didn't see that. So that's what made us
9 conclude that it was really more mild to moderate
10 worsening of heart failure that happened in this
11 trial. But the thing was, no one really
12 anticipated that this was going to drive the
13 results of the trial, I don't think. And that's, I
14 think, the thing that I keep on coming back to, is
15 could this be just a chance finding.

16 So then it doesn't really matter what
17 imputation method you use. It's kind of --

18 DR. D'AGOSTINO: That's part of it. It's
19 sort of like there was a small difference to begin
20 with, and it gets perpetuated by --

21 DR. BLANK: Well, that's it.

22 DR. D'AGOSTINO: -- by the imputation.

1 DR. BLANK: Right. So you're amplifying
2 this effect on the worsening heart failure, which
3 in my opinion, I just wasn't convinced that it
4 wasn't chance. Really, the hypothesis was dyspnea,
5 and that's what I was looking for mostly.

6 Then I explored the treatments because of
7 this worsening heart failure thing, and looked and
8 saw that there was not that much of a difference
9 between groups in the treatments. It was a
10 20-milligram average furosemide dose over the
11 5 days, which was a little unimpressive.

12 So I'm sorry, what else?

13 DR. D'AGOSTINO: I hear what you're saying
14 now. Should we ignore this notion that there was
15 rescue medication being given, so somehow or other
16 you can't go back --

17 DR. BLANK: No. I think it's worth
18 considering. That's why we're asking you this
19 question. I think you should consider, do you feel
20 confident that there's a real difference between
21 the groups, that that's real? It wasn't
22 prespecified, in my opinion, as what we were going

1 to decide.

2 If they had prespecified worsening heart
3 failure as their primary endpoint, they would have
4 won, but hopefully they would have defined it a
5 little better. But then you'd be stuck with just
6 one trial. So you have a lot of barriers here and
7 obstacles to hurdle. I think that's the concern.

8 DR. LINCOFF: Okay. As we move forward, if
9 you could, try to keep to one question so we can
10 get as many people who want. Dr. Rich is next,
11 please.

12 DR. RICH: Yes. This is just regarding the
13 FDA review. So I'm clear, with respect to their
14 definition of worsening heart failure, if a patient
15 in a study got one single dose of 20 milligrams of
16 IV Lasix at one time, that patient then qualified
17 as worsening heart failure and, by their ranking,
18 they'd get the imputation score of zero all the way
19 through?

20 DR. BLANK: Well, I was a little perplexed
21 by this, too, so I think the sponsor should answer.
22 But I had the impression that it had to be

1 20 milligrams above 40 milligram IV. But then --

2 DR. RICH: All right. So let's say 60 now.

3 DR. BLANK: Okay, right. Yes. Definitely
4 that. But I did see one -- I went through some of
5 the case report forms of the worsening heart
6 failure, and I did see one case where the subject
7 was designated as worsening heart failure, and all
8 they had was 40 milligram IV use. Because they
9 hadn't gotten any for 24 hours, and so then --

10 DR. RICH: So I'll take the dose away and
11 just say one dose of IV Lasix.

12 DR. BLANK: Yes. Yes.

13 DR. RICH: Making rounds in the morning and
14 seeing a little worse. Give them one dose of
15 IV Lasix.

16 DR. BLANK: Yes.

17 DR. RICH: That now gets worst rank
18 throughout?

19 DR. BLANK: Yes.

20 DR. RICH: By the table that you have, where
21 you show the breakdown and 50 percent were
22 diuretics, there was diuretics only?

1 DR. BLANK: Yes.

2 DR. RICH: So half of the people who got a
3 worst rank could have gotten a single dose of
4 IV diuretic, and then your display curve showed
5 most of the doses of IV diuretic were actually
6 pretty low anyway.

7 DR. BLANK: Right.

8 DR. TEMPLE: But Melanie, they also had to
9 check the box saying there was worsening heart
10 failure.

11 DR. BLANK: Yes.

12 DR. TEMPLE: Yes. So the --

13 DR. RICH: So they could have done it and
14 not checked the box and it wouldn't have counted.
15 Okay.

16 DR. TEMPLE: They checked the box, and all
17 they did was give them an extra 20; then they'd
18 count.

19 DR. LINCOFF: Dr. Sager?

20 DR. SAGER: Let's see. On your
21 slide -- it's hard to know the numbers, but will
22 you explain to us --

1 DR. LINCOFF: They're really tiny in the
2 bottom right.

3 DR. SAGER: Thank you. Twenty-six. You
4 explain to us that the amendment that defined
5 worsening heart failure, to the degree it was
6 defined, happened in amendment 5. But the
7 imputation rule, because that's the word we're
8 using, was that in the protocol from the very
9 beginning, or did that happen at a later time point
10 also? Or was the initially in the very beginning,
11 from the start?

12 DR. BLANK: The imputation rule was in the
13 statistical analysis plan. But it was not in the
14 protocol until the fifth amendment. And it was
15 slightly different.

16 DR. LINCOFF: I'm going to ask a related
17 question, then, from the FDA. Was this subject to
18 review by you and agreed upon, this imputation
19 rule, prospectively?

20 DR. BLANK: We did not review it. It was
21 not discussed.

22 DR. BAI: I wasn't the original reviewer for

1 this SAP either, so --

2 DR. BLANK: Yes. I wasn't, either. But
3 we're not trying to pass the buck.

4 DR. LINCOFF: Well, was it subject to an
5 SPA? Is this --

6 DR. BLANK: No. But it was looked at.

7 DR. TEMPLE: Melanie said it was
8 not -- you're saying it was not specified in the
9 protocol, but only in the SAP. So that sometimes
10 gets a slightly lower level of attention.

11 DR. LINCOFF: All right. In the interest of
12 being fair here, I'll let Dr. Grant and then the
13 sponsor briefly address this.

14 DR. GRANT: I looked over the end of phase 2
15 meetings -- oh, excuse me, this is Steve Grant.
16 I'm the deputy director of the Division of
17 Cardiovascular and Renal Products. Sorry.

18 I looked over the end of phase 2 meeting
19 minutes. There's no mention of the words
20 "worsening of heart failure" or any indication that
21 it was an objective of this program. The
22 indication sought was relief of dyspnea in acute

1 heart failure. There was no mention or discussion
2 of worsening heart failure at all.

3 DR. LINCOFF: Sponsor?

4 DR. NATHWANI: Yes, please. Thank you.

5 Could I have slide C-218? Slide up, please.

6 So just to say that this was in the
7 protocol, this statement here, at the time, and in
8 the statistical analysis plan. So what was stated
9 here is that for subjects who die or have worsening
10 heart failure event either during or index
11 hospitalization or rehospitalization for heart
12 failure at day 5, the worst score observed in any
13 patient at any time point would carry forward for
14 all the time points thereafter. So just as a
15 clarification.

16 DR. LINCOFF: Was this in an amendment or
17 the original protocol?

18 DR. NATHWANI: This was in the original
19 protocol.

20 DR. BLANK: Okay. But there was not a
21 definition of worsening heart failure in that
22 original protocol.

1 DR. LINCOFF: Yes. The question, though,
2 had been was this prespecified.

3 All right. Dr. Proschan?

4 DR. PROSCHAN: In the briefing document,
5 there was a concern about the sample size change
6 that occurred. You did not raise that here. I'm
7 wondering if you're satisfied with that now.

8 DR. BLANK: We're pretty satisfied. There
9 were some other things that came out in the last
10 few weeks that showed that they used some more data
11 that they had looked at, and they hadn't told us
12 about that. But the reality is that there were
13 minutes, and we saw some slides. So we feel pretty
14 confident that they didn't take an interim look at
15 the data.

16 DR. LINCOFF: Dr. Orza?

17 DR. ORZA: I wanted to understand the
18 primary endpoint and your thoughts about the
19 primary endpoint a little better. So if we assumed
20 that this was a statistically robust result and we
21 weren't having any questions at all about that,
22 what is the clinical meaningfulness of the effect

1 size that we saw on the primary endpoint, the
2 dyspnea?

3 It seems to me that that would be an
4 endpoint that's important to patients, that feeling
5 of breathlessness, and then relieving that would be
6 something that would be meaningful for them. But
7 on the Likert scale, it showed no difference, and
8 on the VAS scale, it showed a very, very tiny
9 difference. And I don't know, even if that had
10 been a statistically robust result, does it mean
11 anything in the final analysis to the patient?

12 DR. BLANK: Well, it's very hard to say.
13 But I would tell you that it's a messy scale, and
14 if I felt really confident that it really measured
15 a change in dyspnea, I would be encouraged. I have
16 to say that from my own personal view. I think
17 there are other people in the FDA that don't agree
18 with me.

19 But I also have to say that at the 24-hour
20 time point, there was a difference of 3 millimeters
21 on the VAS and there was a 5 percent difference in
22 the Likert, even though that wasn't statistically

1 significant or anything. But it was numerically
2 5 percent different for the subjects who had
3 moderate to marked improvement, so 63 percent
4 placebo versus 68 serelaxin.

5 So it's a numerical difference. They're
6 trending in the same direction. I don't know
7 really what to say. If we believe those numbers
8 were real, true, you could always repeat it no
9 matter how many people you studied, then I would
10 say there was a difference. But again, that's if
11 this was purely dyspnea.

12 Throwing in the worsening heart failure
13 thing to me makes it so that I can't interpret
14 those results. That's the way I'm seeing it. I'm
15 having a hard time interpreting what those
16 different numbers mean.

17 DR. LINCOFF: Dr. Li?

18 DR. ORZA: The other part of my question, I
19 think, was addressed by your slide number 23. But
20 it was about whether there were any -- for the
21 people who had a really robust response, and there
22 didn't seem to be any difference in these groups in

1 terms of people who really had a big change in
2 their dyspnea.

3 DR. BLANK: Yes. And this was just done for
4 day 5. So perhaps the sponsor has this result for
5 6 hours, 12 hours, 24 hours, and every day after.
6 So we could look and see if there is, at one of
7 those time points, a difference. But at least at
8 day 5, there was not.

9 DR. LINCOFF: Does the sponsor wish to
10 comment on that, since you were invited?

11 DR. NATHWANI: Thank you very much. We have
12 got data on two things, if you'd permit us. One is
13 the time to Likert scale. Can I have Dr. Lefkowitz
14 come up, please? And just a second piece, just to
15 address -- slide up.

16 DR. LEFKOWITZ: This is looking at how
17 quickly patients achieved moderate or marked
18 improvement on the Likert scale. So unlike our
19 primary endpoint, which required an improvement by
20 hour 6 to be a responder, this was a prespecified
21 other efficacy endpoint.

22 You can see that patient achieved moderate

1 or marked improvement about 12 hours, or about
2 10 hours, quicker over the first 1 to 2 days, in
3 which patients are particularly dyspneic. So on
4 the Likert scale, using how quickly they achieved
5 moderate to marked improvement, we were able to
6 demonstrate an effect.

7 DR. NATHWANI: Just to follow-up on the
8 interpretation of the 447 millimeters, just to say
9 that the way that we would look at that is actually
10 represented by a 47 percent reduction in the risk
11 of worsening heart failure because it was part of
12 the integrated endpoint, so the way that we would
13 interpret that in a millimeter change. Thank you.

14 DR. LINCOFF: All right. Dr. Li?

15 DR. LI: I'm just going to change focus
16 here a little bit. We're quibbling over small
17 differences in the first few days of diuretic dose
18 or worsening heart failure or a Likert scale.

19 But one thing which intrigues me is if
20 there's relatively small differences with a 48-hour
21 infusion to the FDA as well as the sponsor, why is
22 there such a significant reduction in death in

1 180 days? Because that just does not make any
2 sense to me. And what is the mechanism for that?

3 DR. LINCOFF: Yes. Go ahead.

4 DR. NATHWANI: For us? Thank you.

5 Dr. Severin, could you -- sorry. You're asking the
6 FDA? Sorry.

7 DR. LINCOFF: Well, is this directed at the
8 FDA?

9 DR. LI: We haven't touched upon that. And
10 I think that's the one compelling finding I'm
11 seeing, and we haven't addressed that. Were there
12 any data collected, and what's the mechanism for
13 that? We were seeing relatively small clinical
14 differences in the 5 days.

15 DR. LINCOFF: I don't know if the FDA has
16 addressed this in their analysis. If not, we'll
17 ask the sponsor.

18 DR. BLANK: Well, we have the same question.
19 So it's a big question.

20 DR. LINCOFF: Does the sponsor have a
21 response to it?

22 DR. BLANK: But perhaps there is something

1 here. We can't say. But it also could be chance.

2 DR. LINCOFF: All right. Let's give the
3 sponsor a chance to answer that.

4 DR. NATHWANI: The basis of our breakthrough
5 therapy status that we were trying to get was based
6 on the mortality findings. And in that, one of the
7 things that we saw some -- and it would be
8 speculating -- some of the biomarker changes that
9 we see quite early, in particular things like
10 troponin and cystatin C and BNP, may be one of the
11 things that happens early on in the disease.

12 But it would be pure speculation, and that's
13 why we did the confirmatory study. And that's one
14 of the reasons why we believe in both trials right
15 now that there's a signal there that deserves
16 further investigation in the mortality study.

17 DR. LINCOFF: Dr. Papademetriou?

18 DR. PAPADEMETRIOU: Yes. I'm a little
19 puzzled, too, about the primary endpoint and the
20 change in the perception of dyspnea, that it was
21 set as the primary endpoint for this study.

22 I have the feeling that this is not a

1 representative population of heart failure patients
2 that we see day in and day out in our practice. It
3 is, rather, a selected patient population. From
4 what I see in the baseline characteristics, about
5 45 percent of them preserved ejection fraction,
6 and I don't still know the average EF of this
7 population. I suspect it was fairly high. It's
8 not the typical patient we see with low blood
9 pressure and low ejection fraction below 10 to
10 20 percent.

11 This population, with a systolic of 140 and
12 preserved ejection fraction mostly, are much easier
13 to treat and get improvement in their symptoms and
14 in their dyspnea perception. And they can improve
15 with any vasodilator, with any medication you can
16 add.

17 I have the feeling that the changes that
18 were seen with the study drug could also be seen
19 with any other vasodilator that could be
20 administered. For me, the component of the
21 endpoint, the secondary endpoint, mortality, is
22 much more meaningful and more important.

1 My question to you is that you reported that
2 during hospitalization, there was increase in
3 mortality with serelaxin as compared to placebo,
4 which was the opposite in the long run. Do we have
5 it by model behavior here of the study drug, early
6 on worsening mortality and later improvement?
7 What's your perception?

8 DR. BLANK: I'm sorry. If I said that
9 serelaxin had increased mortality, I misspoke. I
10 don't think I said that.

11 DR. PAPADEMETRIOU: I thought it was 10
12 versus 4. No?

13 DR. LINCOFF: Can we clarify the mortality
14 data? Either the FDA or the sponsor.

15 DR. NATHWANI: Yes. We'd be very happy to
16 clarify that. Dr. Lefkowitz?

17 DR. LEFKOWITZ: The mortality through day 5,
18 where there were 5 deaths on placebo, 4 deaths on
19 serelaxin, and then through day 14, it was
20 12 deaths on placebo and 6 deaths on serelaxin.

21 DR. BLANK: That's what I recall. So if
22 it's wrong in my review, I'm sorry. But I don't

1 think so.

2 DR. TEMPLE: That's in the people with
3 nominal worsening. It was 5 to 4. That's what you
4 showed.

5 DR. BLANK: What's that?

6 DR. TEMPLE: That's in the people who were
7 identified as worsening, and it was 5 to 4 deaths.

8 DR. BLANK: Yes.

9 DR. TEMPLE: That's what you showed.

10 DR. LINCOFF: Yes. That was one of the
11 worsening -- okay. Dr. Lewis?

12 DR. LEWIS: First --

13 DR. NATHWANI: Can we clarify that?

14 DR. LEFKOWITZ: Just to be clear, our
15 worsening heart failure endpoint contained death,
16 rehospitalization, and the dyspnea component.
17 There was only one rehospitalization in the first
18 5 days on placebo. In the first 5 days, again,
19 there were 5 deaths in the entire population, not
20 just worsening heart failure. There were 5 deaths
21 on placebo, 4 deaths on serelaxin.

22 DR. LINCOFF: Okay. Dr. Lewis?

1 DR. LEWIS: First I want to, as I, I think,
2 said informally to you, to formally say that both
3 you and Dr. Bai deserve kudos for a very well-
4 written briefing document. It was excellent.

5 The one thing, though, I rushed to the end
6 of it assuming that there would be a section from
7 your PRO group. There were some comments in the
8 text about it, but I was actually anticipating a
9 full write-up from them. And I wonder if you could
10 share if they had more to say to you.

11 For example, and I'm not expert in this
12 area, but I noticed on a scale from 1 to 100 there
13 are no anchors in the middle. I tried to think
14 about, in fairness to the sponsor, what else you
15 would do with these people who got treatments, even
16 if, say, it was all horrible worse heart failure,
17 whatever. How would you do it? Would you censor
18 them? Would you do this? Would you do that? All
19 of them seem to have intended consequences.

20 So I'm wondering if your PRO group feels
21 that, going forward for indications for heart
22 failure, this instrument is perhaps the best to

1 use. Do they say more to you than you put in
2 there? Because they said, right, that 21 -- the
3 one paper out there, there didn't seem to be much
4 data.

5 DR. BLANK: Right.

6 DR. LEWIS: You needed a 21-millimeter
7 difference for it to be real. It seems like to
8 indicate a drug for nationwide use, you would need
9 an instrument that would be more robust.

10 DR. BLANK: Well, I think it should be
11 studied more for that purpose and try to get some
12 kind of anchoring. But they did say that it would
13 be okay to use it for dyspnea. They just didn't
14 agree with the other possible indication for it.
15 But they did say that it would be fine.

16 That paper was a little difficult to apply
17 to this situation because it was intra-patient
18 change. You know? So here is more inter-patient,
19 inter-group. It's hard to draw a real comparison
20 and say that you have to have 21 millimeters to
21 show a difference.

22 DR. LEWIS: Other than a historical use of

1 it, by today's standards of evaluations of PROs,
2 has this got the validity behind it that we would
3 now demand for a new PRO?

4 DR. BLANK: Well, probably not. Not for
5 like a qualified one.

6 DR. LINCOFF: If the sponsor wants to make a
7 comment directly related to that?

8 DR. NATHWANI: Yes, we do. May I invite our
9 PRO expert?

10 DR. GWALTNOY: Thank you. I'm Chad
11 Gwaltnoy. I'm a consultant from ERT. The sponsor
12 has compensated me for my time and travel.

13 I believe the question was about evaluation
14 of the visual analog scale against what we would
15 consider the state of the art validation
16 techniques. I would distinguish between
17 qualification, which is a process to have an
18 instrument approved across multiple studies for a
19 target population, and what is typically done,
20 which is validation of an instrument within a
21 particular program.

22 The sponsor has conducted the types of

1 psychometric analyses and looked at things like
2 content validity, which are mentioned in the FDA's
3 PRO guidance, in order to establish the reliability
4 and validity of this instrument. So yes, this is a
5 reliable and valid tool beyond its credibility
6 based on its previous use.

7 DR. BLANK: Yes. I would agree that that
8 has content validity. That's what the PRO consult
9 told us.

10 DR. LINCOFF: Dr. Temple, you have a
11 comment?

12 DR. TEMPLE: Well, in developing our PRO
13 guidance, we talk about this stuff all the time. I
14 don't even know what the concept of content
15 validity means for a VAS. It's a score on how bad
16 your dyspnea is; doesn't that have content
17 validity? You're asking the patient how tough your
18 breathing is.

19 Our guidance, the final version of it,
20 avoids focusing too much on specifying exactly what
21 difference means something because it's very hard
22 to do. And as a practical matter, if we believe

1 the scales reasonable, we generally buy it if you
2 show a difference.

3 Maybe we could do better or maybe there
4 could be more intelligence applied to it. I don't
5 know. But the main question here isn't so much on
6 the size of the difference; it's whether there is a
7 difference, given the way the imputation was done.

8 Just one point. It turns out -- I must say
9 I hadn't fully appreciated this -- there were
10 scores available for most of those people who got
11 the imputation, at least for most of it. And when
12 Dr. Bai showed the results of doing that, the
13 results were considerably reduced.

14 So you've got to talk about whether the
15 imputation makes sense, whether you should give
16 someone a zero for the rest of his life if he needs
17 extra diuretic. But there were actual scores that
18 you could look at in those people. And they did
19 that.

20 DR. LINCOFF: I'd like to clarify your
21 assertion that the issue here really isn't the
22 magnitude of the benefit because the first third of

1 their presentation really did focus on how much
2 difference this actually was, before they dealt
3 with the issue of "and the imputation." So at
4 least it looks, from your presentation, that there
5 is some concern that this is not a clinically
6 meaningful magnitude.

7 DR. TEMPLE: I'm not saying you don't want
8 to discuss that. But it's very hard to do it with
9 precision. And I'm saying as a practical matter,
10 once we buy the scale, if you sort of win, we are
11 usually inclined to say, okay. You won on a scale
12 we consider reasonable.

13 To me, a 100-point scale on the symptom of
14 interest is not a bad way to measure the symptom of
15 interest. I like it best when it doesn't reflect
16 change from where you were before and is an
17 absolute scale, but those are other discussions.

18 DR. LINCOFF: Does the FDA have another
19 comment?

20 DR. THOMPSON: I'm Aliza Thompson. I'm also
21 a medical officer in the Division of Cardiovascular
22 and Renal Products. It sounds like we've moved on

1 to some other issues, and other important aspects
2 of this are being highlighted.

3 But I just want to speak specifically to
4 the SEALD consult and just provide a clarifying
5 comment. This was the consult related to the
6 instrument. And they were actually consulted in
7 part because, as you may be aware, it's not just
8 the indication that's being sought. It's not just
9 related to dyspnea. It's a broader claim related
10 to the symptoms of heart failure. So they were
11 also consulted in that context.

12 But specifically, related to the dyspnea
13 scale, this is what they put in their consult, and
14 I'll just read it to you. Hopefully I can get the
15 microphone and the computer.

16 So a point that they emphasized in their
17 consult was that they were not involved in the
18 discussions related to the end of phase 2 meeting,
19 and that they did not revisit the issues previously
20 agreed upon with the agency, given the prior
21 agreement to accept these endpoints. And so the
22 review focused on outlining any limitations of

1 these measures.

2 So they made that statement up front, that
3 they recognized that these endpoints had been
4 agreed to and so they weren't going to revisit it.
5 I just want to make that clear.

6 DR. LINCOFF: Dr. Sager, you had a question?

7 DR. SAGER: Yes. My question comes back to
8 another issue that was raised in the FDA briefing
9 document, which is, we have this worsening heart
10 failure use in the protocol, which was very vague.
11 It didn't have clearly a prospective, defined
12 characteristics, and it wasn't adjudicated.

13 But then you also raise the question that it
14 would be pretty simple to unblind who got active
15 and placebo therapy, that all one had to do was
16 shake it. And I wanted to see how much of a
17 concern you thought that was and whether the FDA
18 has in some way looked into that.

19 DR. BLANK: Well, I've never run a clinical
20 trial, and I don't really know what it's like to
21 have that kind of temptation. But if they were
22 really tempted, they could shake the vial.

1 DR. LINCOFF: Okay. But there's no data in
2 that regard.

3 DR. BLANK: I didn't want to focus on it too
4 much because I don't want to make an accusation
5 that I really have no data to support.

6 DR. LINCOFF: Dr. DeLemos?

7 DR. DELEMOS: Another related issue about
8 blinding. What's your level of concern about
9 functional unblinding because of the hemodynamic
10 effects of the drug and the importance of -- the
11 endpoint ends up being driven not by the dyspnea
12 scale, but rather, by this worsening heart failure
13 endpoint that includes administration of diuretics
14 and vasoactive medications that may be influenced
15 by the patient's blood pressure.

16 So there may be a differential likelihood
17 for meeting the endpoint that ends up driving the
18 visual analog scale. Your comments on that?

19 DR. BLANK: Yes. That's possible also. But
20 there were quite a few hypotensive episodes in the
21 placebo group as well.

22 DR. LINCOFF: Are there other questions for

1 the FDA?

2 (No response.)

3 DR. LINCOFF: All right. So we've got about
4 10 minutes before lunch. So I think rather than
5 starting lunch early -- because that may screw up
6 schedules -- we'll use that 10 minutes to start to
7 go back to the people who wanted to talk to the
8 sponsor. So that would start with Dr. Rich.

9 DR. RICH: All right. So these are
10 questions to the sponsor. First I want to just
11 talk about the conduct of the trial.

12 I note that it was done over 34 months in
13 96 centers, the majority of which were in Eastern
14 Europe. And so since the primary endpoint was a
15 communication between doctor and patient, I am
16 curious. Was the patient given a written
17 explanation of how to respond? Was it just verbal
18 between a doctor or a nurse and patient? How was
19 the communication to the patient made so that the
20 patient could respond when asked the question?

21 DR. NATHWANI: May I invite Dr. Severin?

22 DR. SEVERIN: Tom Severin from the clinical

1 team. So the study used defined worksheets, and
2 these were handed to the patients. And they had to
3 mark the visual analog scale or circle the number
4 on the Likert scale. And the study personnel had
5 to be trained, and they had to be named on the site
6 log of people qualified to do the study.

7 DR. RICH: Were there instructions on the
8 worksheets that the patients could read to let them
9 understand better what they were supposed to --

10 DR. SEVERIN: Yes. There were instructions,
11 and they were in the specific language of the
12 specific country. And the instructions were also
13 possibly read to the patients if they were not able
14 to read them. So this was a defined process, and
15 we can show you the papers. We have them here.

16 DR. RICH: The next question has to do with
17 the baseline characteristics in your briefing
18 document. So one of them was ejection fraction
19 last determined, whenever that was. But another
20 was functional class. What was the determination
21 of functional class? At the time of entry into the
22 study?

1 DR. NATHWANI: Yes. The functional class
2 was one month before entry.

3 DR. RICH: One month prior to entry?

4 DR. NATHWANI: One month.

5 DR. RICH: Okay. Because I note that only
6 60 percent were functional 3 and 4, which means the
7 majority of these people were minimally symptomatic
8 with their heart failure, which is interesting.

9 DR. NATHWANI: I think, if I can just
10 clarify, because part of the symptomatic at entry
11 point is they would have been given an IV dose of
12 diuretic before they actually were randomized. So
13 they could have well -- the point of admission and
14 the symptoms at the point of randomization may well
15 have differed.

16 DR. RICH: One more time?

17 DR. NATHWANI: You were just talking about
18 they were minimally symptomatic in the trial.

19 DR. RICH: Well, if you're telling me this
20 is a one month prior to determination -- but then
21 how did you get it from one month? You went to the
22 medical charts or records, or how did you know what

1 their functional class was --

2 DR. NATHWANI: I invite Dr. Cotter up.

3 DR. RICH: -- 30 days prior to coming in
4 with acute heart failure? Because I'm assuming
5 that at presentation, you would call them all 4.

6 DR. COTTER: Right. Dr. Cotter, Momentum
7 Research. The sponsor has paid for my travel and
8 my time.

9 That was the solicited medical history by
10 the physicians during the admission notes. So the
11 physicians were asked during the admission notes to
12 ask the patient about their functional status, like
13 they ask about the history of diabetes or CABG, et
14 cetera. How was their functional class? That was
15 approximately one month prior to entry, and
16 documented.

17 DR. RICH: Okay. So that's soft because you
18 didn't have a document at the time. You went back
19 and --

20 DR. NATHWANI: But just to clarify, that was
21 their history. They were admitted for the acute
22 admission.

1 DR. RICH: Okay. Then there's another
2 mention, at least in the briefing document, that
3 these patients represented real world heart failure
4 patients. But I think they really don't. I'm
5 wondering if you would feel that this drug would be
6 contraindicated in anybody whose systemic blood
7 pressure was less than 125 millimeters of mercury
8 on presentation.

9 DR. NATHWANI: I'd like to invite
10 Dr. Greenberg to comment about what these patients
11 actually represent. But certainly in our
12 prescribing information, proposed prescribing
13 information, we would not be proposing to actually
14 have patients with a blood pressure below 125.

15 DR. RICH: I didn't ask the neg. I asked
16 the positive. Would you recommend a
17 contraindication, this drug should not be used in
18 any patient with acute heart failure whose systemic
19 blood pressure was less than 125 systolic?

20 DR. NATHWANI: We don't have data to
21 contraindicate the patient. We don't have data to
22 support the use of the drug in those patients.

1 DR. GREENBERG: I think, Dr. Rich, we simply
2 don't know because that population wasn't studied
3 here.

4 To go back and address your question about
5 whether or not this is a representative population,
6 though, if you look at the admitting blood pressure
7 in this population, it's very similar to what we've
8 seen in large-scale registries.

9 An example would be the ADHERE registry,
10 which looked at over 180,000 patients admitted with
11 decompensated heart failure, and the mean systolic
12 blood pressure in that population, which was
13 considered to be very representative of what we're
14 seeing, is virtually identical to what we saw in
15 this population.

16 DR. RICH: I assume you're also aware of the
17 paper that was published a few weeks ago in
18 Circulation, "Heart Failure Outcomes," which
19 suggested it's about 20 percent in national
20 registries.

21 DR. GREENBERG: Yes. I am aware of that
22 paper. There are some issues with that paper, and

1 we're not saying that the patient population that
2 was included in RELAX-AHF is representative of the
3 entire population. There are groups of patients
4 who were included in our population who would best
5 respond to this drug. It's not the entire
6 population, for sure.

7 DR. RICH: Could you put up your slide
8 number 97 again?

9 DR. NATHWANI: Slide 97, please.

10 DR. RICH: Is that yours or is that FDA's?

11 DR. NATHWANI: That's ours.

12 DR. RICH: That's yours. Hold on a second.
13 Oh, I'm sorry. Can we go ahead to 98 or 99? What
14 I want to get to -- the next one, then.

15 DR. NATHWANI: Next one, 99.

16 DR. RICH: The argument made about worsening
17 heart failure only addresses the visual analog
18 scale, and yet Likert was a primary endpoint. It
19 seems like we're going to call it the L-word
20 because no one ever wants to mention it again other
21 than to state it was a primary endpoint.

22 Did you ever do any other analysis with

1 Likert instead of the VAS?

2 DR. NATHWANI: Yes.

3 DR. RICH: If so, can we see that?

4 DR. NATHWANI: Yes. Certainly can. May I
5 invite Dr. Lefkowitz -- sorry, Dr. Severin -- to
6 talk about these?

7 DR. SEVERIN: Tom Severin from the clinical
8 team. As you have seen in the primary analysis, we
9 used a Likert to 7 points scale only in two
10 categories, the moderate and marked improvement.

11 But if we look at the Likert scale over the
12 entire scale, and not only 24 hours but the
13 5 days -- and if I can have the slide up, please.
14 So basically, if we do the AUC analysis, similar to
15 the VAS analysis now for the Likert scale, then we
16 see here a 15 percent improvement and a --

17 DR. RICH: Yes. We saw this. This is not
18 what I'm asking. I'm asking about trying to fold
19 this into this whole worsening heart failure
20 argument, that when you fold the area under the
21 curve with VAS into the entire spectrum of
22 worsening heart failure, it was supportive.

1 DR. SEVERIN: So the area under the curve
2 analysis, which I just presented --

3 DR. RICH: I saw that.

4 DR. SEVERIN: -- includes the improvement
5 and worsening. But we did also an analysis where
6 we only looked at the worsening at different time
7 points. And we can have slide C-119, please. This
8 slide shows now the dyspnea assessment on the
9 Likert scale by different time points.

10 DR. RICH: I'm sorry. I didn't ask this.
11 That's okay. Thank you.

12 DR. LINCOFF: All right. So I have a list
13 now still of five people who had earlier wanted to
14 talk to the sponsor. We will get to that
15 immediately after -- I mean, after lunch, I think,
16 is the public presentation, and then we will get to
17 these. So I have the list.

18 So now -- oh, Dr. Unger, do you want to take
19 a moment? We have an interlude here for a moment.

20 DR. UNGER: Dr. Papademetriou, on behalf of
21 the people of the United States and the Division of
22 Cardiovascular and Renal Products and the Office of

1 Drug Evaluation I, we would like to present you
2 with this certificate to thank you for your service
3 on the advisory committee for -- five years?

4 DR. PAPADEMETRIOU: Four years.

5 DR. UNGER: We'd like to thank you very much
6 for that.

7 DR. PAPADEMETRIOU: Thank you very much.

8 (Applause.)

9 DR. LINCOFF: Okay. We will now break for
10 lunch. We'll reconvene again in this room in one
11 hour from now at 1:00 p.m. Please take any
12 personal belongings you may want with you at the
13 time.

14 Committee members, please remember there
15 should be no discussion of the meeting during lunch
16 amongst yourselves, with the press, or with any
17 member of the audience. Thank you.

18 (Whereupon, at 12:00 p.m., a luncheon recess
19 was taken.)

20

21

22

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

(1:01 p.m.)

Open Public Hearing

DR. LINCOFF: All right. I think we can get started. We can resume.

All right. We're going to proceed on now. I've been told that the webcast people are having trouble hearing us. So if we could all speak loudly directly into the microphone when we have a chance to speak.

We're first going to do the open public hearing. Then we're going to go back to asking questions. And the sponsor has some responses to the questions asked earlier, and then we'll have the chance for the questioners that didn't have a chance earlier. So starting now with the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA

1 believes that it is important to understand the
2 context of an individual's presentation.

3 For that reason, FDA encourages you, the
4 public hearing speaker, at the beginning of your
5 written or oral statement to advise the committee
6 of any financial relationship that you may have
7 with the sponsor, its product, and if known, its
8 direct competitors. For example, this financial
9 information may include the sponsor's payment of
10 your travel, lodging, or other expenses in
11 connection with your attendance at this meeting.

12 Likewise, FDA encourages you at the
13 beginning of your statement to advise the committee
14 if you do not have any such financial
15 relationships. If you choose not to address this
16 issue of financial relationships at the beginning
17 of your presentation, it will not preclude you from
18 speaking.

19 The FDA and this committee place great
20 importance on the open public hearing process. The
21 insights and comments provided can help the agency
22 and this committee in their consideration of the

1 issues before them.

2 That said, in many instances and for many
3 topics there will be a variety of opinions. One of
4 our goals today is for this open public hearing to
5 be conducted in a fair and open way, where every
6 participant is listened to carefully and treated
7 with dignity, courtesy, and respect.

8 Therefore, please speak only when recognized
9 by the chair. Thank you for your cooperation.

10 Will speaker number 1 step up to the podium
11 and introduce yourself? Please state your name and
12 any organization you are representing for the
13 record.

14 DR. DOAMEKPOR: Good afternoon. My name is
15 Lauren Doamekpor, and I'm a senior fellow at the
16 National Research Center for Women and Families.
17 Our research center, our nonprofit center, assesses
18 scientific and medical data and provides objective
19 health information to patients, providers, and
20 policy-makers. Our organization does not accept
21 funding from drug companies, and therefore I have
22 no conflicts of interest.

1 We have carefully reviewed the data provided
2 to your committee by the sponsor and the FDA, and
3 are here to share our perspective and concerns. As
4 you can see, serelaxin had no benefit in terms of
5 one of the primary endpoints, shortness of breath
6 during three time points in the first 24 hours.

7 It had no benefit in terms of the two
8 secondary endpoints, which are crucial outcome
9 measures, days alive and out of the hospital
10 through day 60, or in terms of cardiovascular death
11 or rehospitalization from heart failure or renal
12 failure through day 60.

13 The so-called success of the RELAX-AHF
14 clinical trial is based on just one primary
15 endpoint. Patients on serelaxin reported more
16 improvement in shortness of breath from baseline
17 through day 5 compared to placebo. This was only
18 statistically significant because of an imputation
19 or scaling protocol that was inappropriate and
20 methodologically unsound.

21 In addition, this measure is a subject
22 measurement that has been found in the research

1 literature to be not very accurate for measuring
2 changes due to treatment, and I can provide
3 citations to the FDA.

4 Those of you who have taken courses in
5 research methods know that a 7-point Likert scale
6 is more accurate because the gradations are greater
7 than for the 100-point VAS. The VAS can provide
8 useful information, but also can have lots of false
9 positives in terms of improvement. Scores can
10 change as patients get used to being short of
11 breath, for example, not because they are getting
12 better.

13 We agree with the FDA scientists that the
14 results of this test, whether statistically
15 significant or not, is unlikely to be clinically
16 meaningful. Given these methodological problems,
17 none of us can have confidence that this drug will
18 actually benefit patients.

19 This may seem harsh, but as many of you
20 know, clinical trials must be designed correctly.
21 Patient outcomes must be measured using very
22 accurate instruments, which the VAS is not. And

1 results must be analyzed correctly to be
2 meaningful.

3 It is always possible to get what seems like
4 statistically significant results if the data are
5 manipulated in particular ways. It doesn't matter
6 if the manipulation of the data is intentional or
7 not. In this study, the only significant finding
8 used the weakest scale and was contaminated by the
9 imputation or scaling protocol. The other three
10 endpoints showed no improvement, and two of these
11 endpoints are the ones that really matter, survival
12 and staying out of the hospital for 60 days.

13 As noted in the FDA's review, the imputation
14 protocol allowed patients with worsening heart
15 failure to be given the VAS score of zero for the
16 remainder of the observation period. As a result,
17 this endpoint did not take into account the
18 severity or the length of each episode of worsening
19 of heart failure.

20 When this was corrected, the sensitivity
21 analyses show that there was no difference in the
22 degree of patient-reported dyspnea. That means

1 that there was no reported benefit to the patients
2 regarding shortness of breath or anything else.

3 The sponsor submitted an addendum last week
4 that includes a series of analyses addressing this
5 methodological problem. This is not how FDA
6 process is supposed to work.

7 All data presented at the meeting should be
8 fully vetted by FDA scientists and statisticians
9 and provided to the advisory committee in advance.
10 The new analyses need to be carefully and
11 cautiously analyzed by unbiased FDA scientists to
12 determine whether or not this drug is effective at
13 all.

14 Let me emphasize that three out of the four
15 endpoints found no improvement compared to the
16 placebo. The sponsor is claiming a very modest
17 benefit in shortness of breath through day 5, a
18 difference that is very subjective and that the FDA
19 believes is not clinically meaningful. And if the
20 data were not analyzed correctly, there's no
21 benefit at all.

22 We can't assume that this last-minute

1 analysis by the sponsor proves that the drug is
2 beneficial. This needs to be carefully vetted by
3 the agency, and since the advisory committee did
4 not have access to this vetting, you should not
5 take this last-minute analysis into consideration
6 when you vote today.

7 Another important concern about this trial
8 is the lack of diversity. An overwhelming majority
9 of the patients in this trial were white, and less
10 than 5 percent were African American. This should
11 not be acceptable in a study for a drug for heart
12 failure, the number one killer in every racial and
13 ethnic minority group in the U.S. In particular,
14 African Americans are more likely to have heart
15 failure, more likely to suffer more severely, and
16 more likely to get worse faster.

17 Even though they used a definition of Latino
18 that is not the one that FDA requires, at most,
19 less than 10 percent of the patients were Latinos.
20 Latinos are at very high risk for heart disease,
21 and as the largest minority group in this country,
22 the sponsor should have included more in the study.

1 Research tells us that some naturally
2 occurring genetic variations may influence the way
3 certain drugs are metabolized and work in women
4 compared to men, older patients compared to
5 younger, and certain racial and ethnic groups. For
6 this reason, subgroup analyses are essential to
7 make sure a drug is safe and effective at
8 particular doses for these major groups.

9 There were not enough African American
10 patients in the study to conduct subgroup analysis
11 to find out if this drug is safe or effective for
12 African Americans. There were perhaps enough
13 Latinos to do a subgroup analysis, but the company
14 didn't do one.

15 The FDA should have required the company to
16 have enough African American and Latino patients to
17 separately analyze safety and efficacy for these
18 two large minority groups, but they didn't do so.
19 So in addition to not knowing if this drug has any
20 meaningful benefits for any patients, we know
21 nothing at all about the benefits or risks for
22 people of color.

1 The FDA has very clear guidelines that urge
2 sponsors to include women and minorities in their
3 clinical trials. When sponsors ignore these
4 guidelines, using one excuse or another, advisory
5 committees like this one should speak up about it.
6 I hope some of you will.

7 It isn't enough to require more diversity in
8 postmarket studies, for the simple reason that
9 companies too often ignore that requirement. They
10 no longer have any incentive to follow FDA
11 guidelines once the drug is on the market. The
12 FDA's own data confirmed this in a report they
13 released last year, the 907 report.

14 I don't think that our country's largest
15 minority groups, African Americans and Latinos,
16 should be paying for drug treatments that have not
17 been adequately studied on them. But in this case,
18 I don't think any patient should pay for treatment
19 that is not conclusively proven to work, either.

20 The company pointed out that the serelaxin
21 patients had lower all-cause mortality. But as you
22 know, with all statistical analyses, this could

1 easily occur by chance. There is no evidence it
2 was the drug that caused this result, given that
3 the 60-day mortality and hospitalization did not
4 differ from placebo.

5 Given the lack of credible evidence that
6 this drug is more effective than the placebo, we
7 urge you to advise the FDA to not approve it at
8 this time, and to require better research as well
9 as subgroup analyses on African Americans and
10 Latinos.

11 This is not a lifesaving drug. Postmarket
12 studies usually take 10 years to be completed.
13 Proof that it works should be required before it
14 is on the market. It would be terribly unfair to
15 patients and providers to approve it without clear
16 evidence and then wait 10 years for postmarket
17 studies to be completed. Thank you.

18 DR. LINCOFF: Will speaker number 2 step up
19 to the podium and introduce yourself? Please state
20 your name and any organization you are representing
21 for the record.

22 DR. ALMASHAT: My name is Sammy Almashat. I

1 am a research physician with Public Citizens Health
2 Research Group, and we have no conflicts of
3 interest.

4 Public Citizen opposes the approval of
5 serelaxin for many of the reasons mentioned today,
6 in addition to a few others. For one, serelaxin
7 has exceedingly marginal, if any, benefits on
8 subjective, transient, patient-reported dyspnea,
9 and no proven benefits on any systemically assessed
10 objective cardiovascular outcomes.

11 In addition, the proposed indication bears
12 little resemblance to what was actually studied in
13 the primary or secondary endpoints. And finally,
14 I'll mention a paper that's recently been published
15 showing the extremely poor generalizability of
16 RELAX-AHF to the broader inpatient acute heart
17 failure population; in fact, only about 20 percent
18 of all heart failure admissions would qualify for
19 RELAX-AHF.

20 So I'll quickly go through the primary
21 endpoints, as this has been discussed extensively
22 this morning. RELAX-AHF had two prespecified

1 endpoints, both subjective measures of dyspnea in
2 the acute setting. One was the responder analysis,
3 the proportion of respondents with moderately to
4 markedly improved dyspnea on a 7-point Likert scale
5 at three time points within 24 hours of the drug
6 administration.

7 The second was this endpoint that has been
8 much studied this morning, the visual analog scale,
9 specifically, the area under the curve over a 5-day
10 period after drug administration.

11 But before I talk about the results, I think
12 it's worth noting what the FDA's stance was prior
13 to the presentation of the results. Specifically,
14 because only one trial was allowed to be conducted
15 rather than the customary two, including one
16 confirmatory trial, the FDA stated that at least
17 one of the two dyspnea co-primary endpoints would
18 have to have a p-value of less than .00125, and
19 importantly, the other endpoint would have to
20 demonstrate a trend consistent with the results on
21 the first endpoint.

22 Primary endpoint number 1, the respondent

1 analysis, was not significant at three time points
2 24 hours after drug administration. And primary
3 endpoint 2 was statistically significant with the
4 imputed analysis, 448 millimeter/hours over a 5-day
5 period at a level of .007; however, I should note
6 this is still above the FDA's required standard for
7 approval based on a single trial.

8 As was discussed this morning, this mean
9 difference was based not only actual VAS values but
10 driven primarily, if not entirely, by the sponsor's
11 chosen imputation method for subjects with
12 worsening heart failure.

13 So the sponsor decided that all subjects
14 with worsening heart failure, what it dubbed
15 worsening heart failure, regardless of severity,
16 were automatically given the worst possible VAS
17 value of zero for all subsequent values through
18 day 5, regardless of what the patient themselves
19 reported during that time.

20 In addition, it's worth noting no criteria
21 were provided for worsening heart failure; a
22 priori, the single criteria mentioned in the

1 protocol was treatment, which is rather a circular
2 definition. The physician will say, it is
3 worsening heart failure because I treated it as
4 such. Well, how do you know it's worsening heart
5 failure? Because it required treatment.

6 But even then it was not subsequently
7 adjudicated by independent, blinded investigators.
8 So given the tremendous variability in physician
9 discretion of treatment of acute heart failure in
10 terms of dosage, in terms of the choice of
11 diuretics, it's extremely concerning that the
12 physician was relied upon to make this
13 determination and not required to provide any
14 justification for their diagnosis.

15 Now, given that vague definition, it is true
16 that twice as many placebo subjects had worsening
17 heart failure as serelaxin subjects. However,
18 returning to the primary endpoint, which is the
19 only relevant endpoint here for approval, that
20 means that replacing the raw VAS values for both
21 groups disproportionately and markedly reduces the
22 VAS-AUC scores in placebo subjects.

1 As was mentioned today, two-thirds of these
2 worsening heart failure patients were adequately
3 treated with additional infusions of IV diuretics
4 or nitrates. After conducting six different
5 sensitivity analyses employing alternative and less
6 extreme imputation protocols, the FDA concluded
7 that only the sponsor's chosen prespecified
8 imputation scheme met the required p-value of .025
9 needed for success of the trial.

10 In addition, the FDA noted that if the raw
11 VAS scores were used instead of the imputed scores,
12 difference in AUC change from baseline in VAS
13 scores over 5 days was 168 millimeter/hours.

14 Therefore, the actual difference between the
15 serelaxin and placebo groups at any one time point
16 during those 5 days was 1.4 millimeters on a
17 100-millimeter scale, subjectively reported by the
18 patient, far below any conceivable threshold for
19 clinical significance.

20 Again, this is the FDA's slide from this
21 morning showing the actual difference in VAS scores
22 over 5 days versus the imputed scores. And I think

1 it's important to note the baseline VAS scores in
2 both groups. These patients didn't start from
3 zero. So both groups had a VAS score of
4 44 millimeters at the beginning, before the study
5 drug intervention.

6 Therefore, even when taking the sponsor's
7 analysis at face value, when looking at the
8 patient-reported dyspnea at any one time over those
9 5 days, you have less than 4 millimeters on a 100-
10 millimeter scale difference between the two groups.

11 Because both groups started at
12 44 millimeters, that means the placebo group
13 improved from 44 to approximately 64 millimeters
14 over the 5 days. The serelaxin group improved from
15 44 to 68 over 5 days. Again, I ask you whether
16 that is clinically significant.

17 In fact, people have studied this. In 2004,
18 Ander et al. conducted a study on acute heart
19 failure in patients, and according to the FDA,
20 patients who experienced about the same difficulty
21 in breathing experienced a mean change of
22 2.7 millimeters on the VAS, with a confidence

1 interval including the 3.7 millimeters found in
2 RELAX-AHF. Patients who experienced a little less
3 difficulty had a mean change of 21.1 millimeters on
4 the VAS, about five times higher than what was seen
5 in RELAX-AHF.

6 The FDA concluded that judging by the study
7 by Ander et al., a 4-millimeter difference on a
8 100-millimeter dyspnea VAS does not appear to
9 represent a clinically significant change. And we
10 agree.

11 The secondary endpoints of days alive and
12 out of the hospital through day 60, no difference
13 between the two groups. The combined endpoint of
14 cardiovascular death or rehospitalization due to
15 heart or renal failure through day 60, again, no
16 significant difference between the two groups.

17 Now, there has been a focus on one of these
18 two components, cardiovascular death and a related
19 endpoint, all-cause mortality, and I'll discuss
20 this briefly.

21 Given that this was a post hoc
22 analysis -- mortality was a post hoc analysis,

1 especially at day 180 -- the burden is therefore on
2 the sponsor to demonstrate a convincing biological
3 mechanism by which a drug, given as a single
4 infusion over 48 hours, can result in a mortality
5 benefit weeks and months into the future.

6 For such one-time therapies, one would
7 expect diverging survival curves in the days
8 immediately following therapy, followed by a
9 leveling off of residual effects and increasingly
10 parallel curves.

11 What was seen, however, was, looking at the
12 cardiovascular mortality component of the secondary
13 endpoint only through 60 days, we notice an
14 increasingly divergent pair of survival curves
15 going out to day 180. This is something one would
16 expect only with chronic therapy administered
17 through day 180 or repeatedly administered acute
18 therapy, which was not the case here.

19 Of course, it could be argued that the
20 initial differences in rates of worsening heart
21 failure would not be reflected in cardiovascular
22 mortality differences until a later time point,

1 even as far out as 180 days for patients who
2 deteriorate in the immediate period and
3 subsequently have lengthy ICU stays and die at a
4 later point.

5 However, for this to happen, for a 60- to
6 180-day cardiovascular mortality difference
7 attributable to serelaxin on the scale seen in
8 RELAX-AHF, would of course require that a
9 substantial number of patients were severely
10 decompensated in the days following therapy, and
11 that this number of patients was substantially
12 different between the two groups.

13 But this was not seen. Two-thirds of all
14 subjects with worsening heart failure through
15 day 14 were successfully treated with IV diuretics
16 or nitrates. Only 16 subjects in the placebo group
17 and 11 in the serelaxin group with worsening heart
18 failure through 14 days required IV pressors,
19 positive inotropes, mechanical ventilation, or
20 ultrafiltration.

21 Furthermore, a cursory look at FDA's post
22 hoc analysis of all-cause mortality rates,

1 stratified by worsening heart failure in the first
2 2 weeks, makes a causal connection even more
3 unlikely. As can be seen, virtually all of the
4 180-day difference in all-cause mortality is driven
5 by the different rates in subjects with no
6 worsening heart failure in the initial 14-day
7 period.

8 Furthermore, the divergence in rates between
9 placebo and serelaxin groups for those bottom two
10 dotted lines starts at around day 60. Before then,
11 they're virtually identical. This makes any claim
12 of a causal link to a treatment administered
13 60 days before extremely unlikely.

14 In fact, I would say that if you look at the
15 baseline demographics of this trial, there were
16 substantially more patients in the placebo group
17 who were New York Heart Association Class III or
18 IV, and I would attribute that divergence in
19 mortality rates at day 60 much more likely due to
20 the chronic heart failure status than any treatment
21 given in the acute setting. Of course, that's
22 speculative.

1 For those subjects with worsening heart
2 failure, so the top two lines, the solid lines,
3 placebo subjects actually appear to have a
4 consistently lower rate of all-cause death
5 throughout the duration of the 180-day follow-up
6 period.

7 Now, this, of course, may also be a chance
8 finding, but it's striking nonetheless when
9 considering the overall differences in rates
10 between placebo and serelaxin, which were presented
11 in the survival curves this morning.

12 This is all just to say that the difference
13 in mortality, in all-cause mortality, is due to
14 patients who actually didn't experience any
15 deterioration during or immediately after the study
16 drug administration.

17 Now, while it is possible that serelaxin was
18 responsible for the mortality differences at 60 and
19 180 days -- for example, through prevention of
20 irreversible cardiac remodeling in the acute
21 phase -- until the confirmatory trial currently
22 underway is concluded, the mortality findings can

1 only be considered hypothesis-generating and should
2 certainly not factor into today's decision on
3 approval.

4 Another point raised by the FDA was the
5 potential for unblinding. The serelaxin solution
6 is frothy when shaken and the placebo solution is
7 not, which may have caused unblinding. This is
8 particularly relevant because both primary
9 endpoints measured were subjective, and the one
10 purportedly significant difference in VAS-AUC
11 scores was exceedingly marginal, which means that
12 even a few unblinded investigators and/or patients
13 may have unintentionally skewed the results in
14 favor of serelaxin.

15 Finally, very quickly, I'll go through the
16 indication for serelaxin that's being proposed
17 today. The sponsor is proposing that serelaxin be
18 approved to improve the symptoms of acute heart
19 failure through reduction of the rate of worsening
20 of heart failure. This is two component
21 indications.

22 The first indication, the improving the

1 symptoms of acute heart failure, the only symptom
2 that was measured in this trial was dyspnea at
3 rest. Of course, acute heart failure symptoms are
4 not restricted to dyspnea at rest, particularly for
5 Class I to III patients, for whom dyspnea on
6 exertion is the defining characteristic.

7 In addition, you have peripheral edema. You
8 have other pulmonary edema, low cardiac output
9 symptoms such as cough, wheezing, fatigue,
10 et cetera. So it's not clear to us how the
11 proposed indication reflects what was studied in
12 the primary endpoints.

13 The second component is a reduction of the
14 rate of worsening of heart failure. Again, as we
15 saw, this was not adjudicated, it was not defined,
16 and it implies an improvement in some objective
17 measure of heart failure severity. No such
18 objective indicators were measured.

19 Finally, the indication is extremely broad
20 given the selective patient population enrolled
21 into RELAX-AHF. This year, Wang et al. published a
22 study comparing the patients qualifying for RELAX-

1 AHF with 196,000 patients enrolled in two
2 registries, one in the U.S., one internationally,
3 of all acute heart failure admissions. The
4 registries enrolled patients from 2001 to 2009.
5 Consecutive enrollment was encouraged.

6 What was found was only 16 percent of acute
7 heart failure patients internationally would have
8 qualified for this trial. Twenty percent of U.S.
9 patients with acute heart failure would have
10 qualified for the trial.

11 Furthermore, RELAX-AHF-eligible patients
12 were significantly more likely to be older, female,
13 have higher systolic blood pressure on
14 presentation -- not surprising, given the inclusion
15 criterion -- more well-preserved ejection fraction,
16 better renal function, in addition to a host of
17 other indicators that point to a markedly healthier
18 population in this trial as opposed to the broader
19 AHF population.

20 Not surprisingly, in-hospital mortality was
21 lower in patients who would have qualified for this
22 trial than it is for all other patients with acute

1 heart failure. And this is just to show that the
2 differences in qualification among different
3 regions were not different.

4 Finally, the EMA rejected serelaxin on
5 identical grounds laid out by the FDA. The
6 committee noted that the study results did not
7 demonstrate a benefit for short-term relief in
8 dyspnea. It was not clear that they were
9 clinically relevant.

10 The committee had concerns about the
11 analyses, as did the FDA. And the EMA concluded
12 that another study would be needed to confirm the
13 effectiveness in serelaxin. Therefore, the
14 benefits did not outweigh the risks, in the EMA's
15 opinion.

16 In conclusion, serelaxin has exceedingly
17 marginal, again, if any, benefits on subjective
18 dyspnea and no proven benefits on cardiovascular
19 outcomes. The mortality outcomes are dubious and
20 should be confirmed with a further trial. And the
21 patients were not generalizable to the broad AHF
22 population.

1 Our hope, as everyone else surely is, is
2 that the confirmatory trial currently underway does
3 show a mortality benefit, it does confirm a
4 mortality benefit. This would be a breakthrough in
5 the treatment of acute heart failure.

6 However, we cannot approve a drug based on
7 exploratory endpoints and marginal clinically
8 significant endpoints. And that is why we should
9 delay approval until we see the results of the
10 confirmatory trial. Thank you.

11 **Clarifying Questions to Presenters (continued)**

12 DR. LINCOFF: The open public hearing
13 portion of this meeting has now concluded, and we
14 will no longer take comments from the audience.
15 The committee will now turn its attention to
16 address the task at hand, the careful consideration
17 of the data before the committee, as well as the
18 public comments.

19 So we take this time now -- first I'll
20 invite the sponsor, who has some responses to some
21 of the questions that were brought up. Then we'll
22 proceed through the questions that the people have

1 already said they wanted, and then anybody else who
2 has questions. So first the sponsor.

3 DR. NATHWANI: Thank you, Mr. Chairman.
4 We'd like to spend five minutes just addressing
5 five issues, which are just clarifications and left
6 over.

7 First Dr. Rolli will talk about the question
8 you left, Dr. Lewis.

9 DR. ROLLI: Yes. Dr. Lewis, thanks again.
10 We were talking about AEs indicative of renal
11 impairment or in context of blood pressure at
12 baseline below 130. And I would like to share the
13 following data with you. Slide up, please.

14 What you here see, all renal and urinary
15 disorder reports in Pre-RELAX and RELAX together
16 in the patient population with a baseline blood
17 pressure below 130. And we highlighted the ones
18 that could be of interest in that
19 context -- azotemia, oliguria, proteinuria, renal
20 failure, acute renal failure and renal
21 impairment -- and see that there is no increased
22 risk for patients receiving serelaxin with a blood

1 pressure below 130 milligrams at baseline.

2 DR. LEWIS: How about the patients who were
3 enrolled with a baseline of 130 but experienced a
4 hypotensive event?

5 DR. ROLLI: Out of those, I cannot --

6 DR. LEWIS: Because there were about 118
7 people, I thought, who had --

8 DR. ROLLI: A hundred and eight.

9 DR. LEWIS: Or something like that. So
10 there's a fair number of them.

11 DR. ROLLI: Yes. I cannot answer this out
12 of this patient population at this point.

13 DR. NATHWANI: Thank you.

14 The second clarification point we'd like is
15 to a point raised by Dr. Temple. You asked the
16 question whether or not we actually had any data at
17 the time of the worsening heart failure event. And
18 I'm just going to have the slide up on the patient
19 journey, just to point out that the worsening heart
20 failure events occurred between visits. And can I
21 have slide up, please?

22 So if I just take the middle box just to

1 illustrate the point, this is the worsening heart
2 failures. The curved line represents the VAS
3 journey in most patients. Those dips are the just
4 diagrammatic worsening heart failures. We had the
5 green circles represent the visits. Those dips
6 that we had represent the worsening heart failure.

7 In all of our worsening heart failure, we
8 have no data at the time of worsening heart failure
9 event, per se. We have data before, and I think we
10 represented some data thereafter.

11 I'd like to invite Dr. Greenberg to just
12 talk about a particular case.

13 DR. GREENBERG: Thank you. I'd like to make
14 a comment about the use of the VAS. We were
15 greatly informed by the data from Pre-RELAX in
16 which VAS was one of the endpoints that was looked
17 at. And worsening heart failure was given a
18 similar assignment in Pre-RELAX.

19 We were aware of the fact that the VAS score
20 was driven by worsening heart failure in Pre-RELAX,
21 and we wanted to include this in the RELAX study
22 and RELAX-AHF, in the trial that we've been talking

1 about today, because we felt that it really
2 captured the patient journey during the hospital,
3 so that it was one of the co-primary endpoints
4 defined exactly the way it was in Pre-RELAX. There
5 was no difference there.

6 One of the issues that came up is whether or
7 not worsening heart failure is a trivial issue to
8 these patients. And I would argue that it clearly
9 is not. This represents a failure of therapy in
10 these patients. It represents the fact that they
11 are entering a period of instability. And it
12 changes the trajectory of their clinical course.

13 The way that it's already been presented to
14 you is the prolongation of hospitalization, which
15 is substantial in these individuals who experience
16 a worsening of heart failure event during the
17 clinical trial.

18 I'd like to call your attention to a study,
19 to one patient who was included in the study.
20 Slide up, please. This is a patient on placebo,
21 and in fact, it is the very same patient that was
22 pointed out in the FDA review earlier.

1 It's a 75-year-old man who had preserved
2 ejection fraction. I also should point out that
3 about half of the people who come in with
4 decompensated worsening heart failure in the United
5 States now have worsening heart failure. Blood
6 pressure was 155/80 at the time the patient was
7 enrolled, again characteristic of the patients, and
8 we've seen that from the registry data.

9 This patient had been felt to be NYHA
10 Class III a month prior. However, he was dyspneic
11 at rest and was Class IV when he was admitted. At
12 that time, his N-terminal-proBNP was greater than
13 3000. He received 80 milligrams of IV furosemide
14 prior to the initiation of study drug infusion.

15 Thereafter, he developed a worsening event
16 on day 1, and the arrow showing that first
17 worsening event is really misplaced. It's between
18 the first and second closed circles on that slide,
19 so that what we're seeing here are the VAS scores,
20 not at the time of the event, but before and after.

21 However, it's clear that this patient
22 suffered an event, was treated at that time with

1 increase in IV diuretic, and his VAS score went up
2 to almost 80 and continued there through day 4. At
3 that time he experienced then a second worsening
4 heart failure event. This required treatment with
5 IV furosemide and nitroglycerin.

6 The patient was subsequently hospitalized
7 for a totality of 14 days. He was discharged at
8 that time, and then rehospitalized on day 16. This
9 was an important clinical event for this patient,
10 and I think that the worsening heart failure events
11 that we recorded in this study, which we recognized
12 were going to be part of the VAS score, are very
13 important to the patients and their families.

14 DR. LINCOFF: Leave that slide up because we
15 have two questions related to that slide. First
16 Dr. Lewis.

17 DR. LEWIS: Yes. So again, I did try to
18 think hard about what to do with the VAS scores on
19 patients who had worse heart failure. But in a
20 sense, doesn't this show us that standard of care
21 therapy, Lasix, which is pretty cheap, returns this
22 patient to feeling very well, and that serelaxin,

1 if you let them get better, doesn't do any better
2 than Lasix?

3 DR. GREENBERG: Well, I think we saw very
4 clearly that there is a markedly prolonged
5 hospitalization stay in those patients that develop
6 worsening heart failure. And if you can prevent
7 that by almost 50 percent, you can greatly reduce
8 the time in the hospital for this patient
9 population.

10 DR. LEWIS: But not rehospitalization.

11 DR. GREENBERG: That's correct.

12 DR. LINCOFF: Dr. DeLemos?

13 DR. DELEMOS: Can you leave that slide up,
14 please? Yes. The issue goes to the question of
15 anchoring for that. In terms of content validity
16 of the instrument, how can this patient who is
17 serving as an example have a score of 100 at the
18 time of enrollment and be used as -- how does this
19 instrument then reflect his disease state?

20 DR. NATHWANI: I'd just like to point
21 out -- I'm sorry. Go ahead.

22 DR. GREENBERG: Yes. This score was taken

1 after the patient received the initial dose of
2 IV furosemide. That was required for entry into
3 the study. And the patient obviously reported that
4 score at that time and then subsequently
5 deteriorated.

6 DR. NATHWANI: Just to remind, at the point
7 of entry, when they were admitted into hospital,
8 they had to have evidence of acute heart failure,
9 elevated BNP, chest X-ray. And then the furosemide
10 could well have got them to that score.

11 This just illustrates the point that I think
12 was raised of the clinical instability and the
13 inability to predict their course based on their
14 baseline VAS scores. But their prognosis is still
15 poor in the sense that when they deteriorate, we
16 don't have the VAS scores at that time, but they've
17 actually had a poor course.

18 They had IV nitrates and diuretics. Then
19 they had a subsequent worsening heart failure.
20 They stayed in hospital longer. They went out and
21 then they came back again in hospital despite
22 having a baseline VAS score of 98.

1 DR. LINCOFF: All right. Well, I'll ask the
2 sponsor to put that slide back up. You showed it;
3 now you opened a can of worms. Now you've got
4 questions.

5 DR. NATHWANI: Yes. Sure. Please, slide
6 back up.

7 DR. LINCOFF: So please leave it up until I
8 ask you to take it off.

9 Dr. Rich?

10 DR. RICH: Yes. But to be clear to
11 everybody, the driver here is not dyspnea. The
12 driver here is worsening heart failure, an
13 arbitrary decision made by a physician making
14 rounds, who might walk in the room and see that
15 even though the patient had a great physiologic
16 response, was still edematous, told the nurse to
17 give 40 milligrams of IV Lasix, and the nurse then
18 checks the box saying worsening heart failure.

19 So I think this is totally misleading. This
20 is not helpful. This to me is more misleading and
21 almost reinforces the charade here that we don't
22 know what worsening heart failure was, nor do you,

1 because no one captured that.

2 You're trying to sell us that the dyspnea
3 score linked to the worsening heart failure was a
4 driver, and it was not. It was something that you
5 recorded before and then way after, and then
6 imputed in the beginning.

7 So this doesn't clarify a thing. And an
8 example of one out of the whole trial is even
9 worse.

10 DR. PACKER: Still, let me just say one
11 thing. The events were recorded. The time of the
12 onset of the event was recorded in the case report
13 form. And that did not correspond to the daily
14 assessment, just so we know.

15 I'm really glad this slide is up. Thank
16 you. Can I just ask the committee to engage in a
17 thought experiment, and imagine that the Y axis
18 here is not VAS but it's blood pressure. And you
19 are developing a new drug to maintain blood
20 pressure because you're a nephrologist and you
21 think that maintaining blood pressure to the kidney
22 is important.

1 The patient goes into a condition. You give
2 the drug, placebo or this new drug that maintains
3 blood pressure. And during the course of the study
4 period, the blood pressure plummets, and you start
5 Levophed or dopamine or whatever you would like to
6 increase the blood pressure back up to where you're
7 comfortable.

8 Is that a treatment failure? My thought is,
9 yes, it is, and those blood pressures on the
10 alternative pressor is not a reflection of the
11 effect of randomized therapy. That is a treatment
12 failure.

13 Now, the question is, one, you may or may
14 not believe that was well enough documented in this
15 trial. That's fine. But if you believe it was
16 well documented, then the minute that treatment
17 failure occurs, that patient has already failed
18 prescribed therapy. The question is, how do you
19 handle that in the analysis?

20 My personal view is, to take the scores on
21 the alternative pressor is not the right approach.
22 So you may not like zero. You may think there's

1 another number. I happen to like rank. Whatever
2 it is, it's a failure on therapy.

3 Dr. Lewis, you're shaking your head.

4 DR. RICH: Wait. I'm going to grab it
5 because I was last up here. But come on, Milton.
6 Look. You go from 100 to 15 here, a plummet, a
7 person with worsening heart failure, again. And
8 then the score was not the driver here. This was
9 clinical situation.

10 They get a treatment, they get better, and
11 they have another event, the exact same event.
12 They have IV furosemide, nitroglycerin, pulmonary
13 edema. They're on death's door. And the score
14 falls from 80 to 70.

15 So how does that score have anything to do
16 with the clinical situation?

17 DR. PACKER: You do not know what the score
18 was during the event here. And you cannot --

19 DR. RICH: Nor do you. All we have is what
20 you're reporting in your data. That's all we have
21 to look at.

22 DR. PACKER: I'm not saying that, and

1 Dr. Lewis questioned the documentation of the
2 events. And I take your point very seriously. But
3 if you believe that those were worsening heart
4 failure events, then the question is, should they
5 or should they not override the subsequent VAS
6 scores, just like in a trial of a drug to maintain
7 blood pressure?

8 DR. LEWIS: So since we're going to have a
9 discussion about this particular patient and you
10 called on me, why wouldn't this be a case where
11 they gave him 80 of Lasix, he vasodilated a little
12 bit, had an acute effect, but maybe his renal
13 function, he didn't really have a natriuresis with
14 the 80, so he needed the 120, and he sure did well
15 on it?

16 DR. PACKER: The patients are randomized to
17 therapy. The physician is treating the patient
18 according to his or her standards. Okay? If a
19 patient doesn't do well and that happens twice as
20 often on placebo or the active drug, that's
21 indicative of the drug effect.

22 DR. LEWIS: So we're confusing two issues,

1 or I am, maybe. One issue is which VAS score
2 should be used. I think this patient is an example
3 of the subsequent VAS scores, as opposed to zero,
4 being valid, showing that standard of care therapy
5 made their subsequent VAS scores just as good as
6 serelaxin did.

7 Now, there's a separate issue of whether
8 there were more worst heart failure episodes in the
9 placebo group, and we have an issue about how well
10 those were adjudicated and documented.

11 DR. PACKER: But let me ask a question --

12 DR. LEWIS: But the question of what scores
13 to use, whether to make them all zeros, I think
14 this would say maybe not.

15 DR. PACKER: Again, I don't want to debate
16 this. I just want to establish the principle. If
17 you believe that Lasix IV and nitroglycerin IV
18 work -- okay, I happen to think they do -- but if
19 you think they work, and if you think that
20 intensification of IV Lasix and IV nitroglycerin
21 can replicate the response to serelaxin, then
22 serelaxin works.

1 DR. LINCOFF: Okay. Are there others who
2 want to respond direct to this slide? Because we
3 still have a list of people who want to talk
4 about -- in general.

5 All right. Dr. Sager?

6 DR. SAGER: Just very quickly, again, doing
7 this slide, when it went down, let's say the person
8 just got a single shot of Lasix, because there are
9 people like that, and then went back up for 3 or
10 4 days, and then had another deterioration.

11 Is that dissimilar to someone who has a
12 hypotensive episode with a blood pressure-lowering
13 drug, gets a bolus of saline, blood pressure goes
14 up? We continue to measure their blood pressure.
15 We don't give them, in a trial, a blood pressure of
16 zero.

17 So I think this actually does speak to maybe
18 the acute event. Maybe that's a zero -- I don't
19 know what that is at the acute event -- but then
20 after that, using the actual recorded data. And
21 again, I think, just to rely on the points that
22 have been made, this does call into question how

1 they can have pulmonary edema at one point, and
2 their breathing at -- they got a VAS score of 75.

3 But I think, actually, the slide illustrates
4 some of concerns we're having about the imputation
5 method and does that really reflect physiology.
6 And I do appreciate the worsening heart failure
7 concept and its potential clinical significance.
8 And I find all the elegant work you've done here
9 really thoughtful for investigating in future
10 trials, again using, I think you've heard, a more
11 prospective defined definition.

12 DR. NATHWANI: I'm going to take that as a
13 two-part piece because it's so important to get
14 clear. I'd like to invite Dr. Koch just to talk
15 about how you would assign this particular case.
16 And then I'm going to ask Dr. Lefkowitz to actually
17 answer some of the clinical interpretations, so
18 what happened to the patient, what did the
19 clinicians do, what were they instructed to do, and
20 how did that carry forward. So Dr. Koch?

21 DR. KOCH: Gary Koch, University of North
22 Carolina at Chapel Hill. My only financial

1 relationship with the sponsor is through a
2 cooperative agreement with my university.

3 I think one of the things that needs to be
4 taken into consideration in the discussion is what
5 regimens are being compared. If one regards the
6 study as comparing placebo, plus rescue treatment
7 as needed for WHF or whatever, to serelaxin, plus
8 rescue treatment as needed for WHF, then you would
9 use the values that were observed after WHF, and
10 you would see little difference between the
11 regimens, as has been recognized.

12 If you regard the study as comparing
13 initially randomized patients to serelaxin to
14 initially randomized patients to placebo,
15 recognizing that the WHF events represent treatment
16 failure -- aside of the limitations in their
17 documentation, which I am not able to speak
18 to -- then you would consider the values after the
19 WHF event to in some sense be confounded with the
20 rescue treatment and then be uninterpretable with
21 respect to the originally randomized regimens.

22 Now, when you adopt that particular view,

1 that they are treatment failures, how well they do
2 after failing doesn't make them less of a failure.
3 They are still treatment failures. So then it
4 comes down to how you manage them in the analysis.
5 And at this point we could bring up slide 97
6 temporarily.

7 The sponsor took the view of assigning a
8 worst value and using a t-test. When they did
9 that, they actually took a risk. That risk was
10 that if there had been more worsening heart failure
11 and death, even just a little bit more, in the
12 serelaxin group than substantial differences on the
13 good side, making the dyspnea better, it would not
14 have been detected by the t-test. Their t-test
15 would only detect a treatment difference if
16 serelaxin reduced the extent of deaths and
17 worsening heart failure.

18 Now, whether or not the zero assignment was
19 excessive was a consideration that all reviewers
20 who have looked at these trials have always raised
21 that question. And the rank-based type of analysis
22 was one way of trying to address it, and that was

1 what was put into the addendum, because that
2 doesn't specifically assign a value. So in that
3 case, the deaths get ranked worse, the worsening
4 heart failure patients get ranked next worse, and
5 then all the others.

6 A log rank test is used because it is
7 particularly sensitive to the treatment group that
8 has relatively more of the biggest ranks. It's the
9 standard method for survival data. In survival
10 data, you're interested in which group has more
11 long-term survivors. Long-term survivors have the
12 biggest ranks.

13 Here the biggest ranks went to the patients
14 who actually had the worst outcome, the deaths and
15 the worsening heart failure patients. And the
16 different paradigms for ordering them is identified
17 in the slide.

18 But when you use a log rank test, a method
19 that does not assign an explicit score numerically
20 but does emphasize which group has more patients
21 that died or had worsening heart failure, you do
22 detect a difference between the groups.

1 DR. LINCOFF: Actually, Dr. Scott, you had a
2 question related to this slide?

3 DR. SCOTT: Yes. I heard earlier that you'd
4 used the same imputation method during phase 2.
5 And I wondered whether, during the Pre-RELAX study,
6 whether that data had been shared with the FDA
7 because then people would have been pretty clear as
8 to what the imputation method is.

9 I'm a little troubled by people choosing a
10 method prospectively and then having that replaced
11 by post hoc methods that come out with a different
12 outcome.

13 DR. NATHWANI: Yes. Slide down, by the way.

14 So for Pre-RELAX -- and that was one of the
15 other clarifications -- the same method for VAS was
16 used in Pre-RELAX as in RELAX. So the findings of
17 Pre-RELAX and the VAS score that were illustrated
18 earlier today are driven by exactly the same
19 drivers, worsening heart failure.

20 The statistical analysis plan was submitted
21 and reviewed by the FDA at the end of phase 2
22 meeting on three occasions. So the methodology

1 between Pre-RELAX and RELAX are the same, and
2 there's a concordance in the way that the VAS data
3 were analyzed and behaved.

4 So, as Dr. Greenberg actually mentioned,
5 this was not a surprise. And it was mentioned
6 earlier today that this was an unexpected finding.
7 It's a different way to describe. So we're now
8 describing this because we're trying to find a
9 clearer way to describe the clinical impact of
10 serelaxin.

11 But just to be clear, when the VAS was
12 chosen as a primary endpoint, it was very apparent
13 at the time, and the executive committee knew, that
14 it was driven in the same way that it was driven
15 here. And worsening heart failure was still in
16 both of those analyses.

17 DR. LINCOFF: Dr. Temple?

18 DR. TEMPLE: There's a disconnect here that
19 I'm interested in, and I think that's what many of
20 the comments are reflecting. This was a trial to
21 look for an effect on dyspnea. As Milton said in
22 his very first talk, a really good thing to do with

1 a drug for heart failure would be to characterize
2 the effect on heart failure worsening.

3 I would submit that if you were to do that
4 with some kind of combined endpoint, you could do
5 need for treatment. You could do dyspnea worsening
6 by 20 percent. You could have a series of things,
7 all of which you'd characterize. But you wouldn't
8 describe it as a dyspnea trial. You'd describe it
9 at a worsening trial, which is not what you did.

10 What you're now saying if I understand you
11 is, even though we were just doing a dyspnea trial,
12 we think worsening is really bad, so we're going to
13 give people a really bad score on dyspnea if they
14 worsen. And not only that, it's going to be a bad
15 score that persists not just for the two moments
16 when you saw the person deteriorate, but for the
17 entire thing. Once you worsen, your dyspnea is
18 terrible.

19 The logic of that somewhat escapes me. I
20 think Milton's initial idea of a combined endpoint
21 that looked at various measures of worsening would
22 be a very good thing to be able to show.

1 Typically, you wouldn't do that if your primary
2 endpoint was dyspnea, though. You can't go nosing
3 around for finding stuff; you're not allowed to do
4 that.

5 So I'm still interested in what evidence
6 there is that you were actually testing worsening,
7 which is the only good excuse that sounds
8 reasonable to me for giving people a terrible
9 dyspnea score. You're sort of saying, oh, we
10 weren't really measuring dyspnea at all; we were
11 measuring worsening. Am I missing something?

12 DR. NATHWANI: I'd like to invite
13 Dr. Greenberg back up to the microphone. And while
14 he does so, I think there were two endpoints, just
15 to be clear. The intent of the study was to look
16 at the first 24 hours from dyspnea as well as the
17 VAS.

18 DR. GREENBERG: So just to reiterate, we
19 were trying to capture the entirety of the patient
20 experience during this dynamic 5-day period of the
21 hospitalization.

22 The Likert scale was used to look at the

1 acute response, favorable response, to the drug.
2 The VAS looked at for the entirety of the 5 days
3 and allowed us to incorporate what we recognized
4 was going to be an important component of that, and
5 that was the worsening of heart failure during that
6 time. But we felt that it was important to capture
7 all of these things in evaluating the effect of the
8 drugs in these patients.

9 DR. TEMPLE: But didn't you think that the
10 VAS score would capture the effect on dyspnea of
11 worsening heart failure? So why wouldn't you
12 measure dyspnea as often as you could? And you
13 already showed that if you actually -- or Dr. Bai
14 showed -- if you look at the actual dyspnea score
15 in these people who had a period of worsening, it
16 didn't matter. It's only if you count them as zero
17 forever that it matters. Why is that reasonable?

18 DR. GREENBERG: The recognition was that
19 these patients were going to develop the episodes
20 of worsening heart failure at times, which we were
21 not going to be able to capture the VAS or the
22 Likert scale.

1 DR. TEMPLE: But you got them the next day.

2 DR. GREENBERG: We did, and I believe that
3 analysis was shown on what the --

4 DR. TEMPLE: Yes. But when you do that,
5 when you use their actual dyspnea scores after they
6 recover, after they're treated with diuretics or
7 whatever it does, then there isn't any effect on
8 the VAS. Right?

9 DR. NATHWANI: But, Dr. Temple, that does
10 break the principle that they've been intervened
11 with something that actually changes fundamentally
12 the score immediately after, and thereafter,
13 subsequently. And as you can see, as we showed
14 before, the worsening heart failure patient, even
15 in that case, had a recurrent event, stayed in
16 hospital longer, and is captured by a number of
17 other events.

18 DR. TEMPLE: Right. So if you had counted
19 those events, those worsening events, as the study
20 endpoint and won, everybody would be cheering, I
21 would say. But that's not exactly what you did.
22 You allowed those events to alter your dyspnea

1 score. And I think that's what's bothering
2 everybody.

3 DR. NATHWANI: I'm going to invite Dr. Koch
4 just to comment on that.

5 DR. KOCH: Gary Koch. I think your
6 assessment is on target. I think the reason why
7 the assignment of this worst value was built into
8 the VAS was so that the VAS would not only be
9 somewhat sensitive to whether there was a treatment
10 difference on the good end, but would also be
11 sensitive to a treatment difference on the
12 worsening.

13 Furthermore, it had the property that you
14 could only detect a treatment difference on the
15 good end if you actually showed a favorable
16 difference or no difference on the worse end.

17 Now, the notion of when the zero applies and
18 how long it applies is partly alleviated by using
19 the rank method that's been put into the addendum
20 because with that method, one can say all the
21 worsening heart failures are the same, or you can
22 order them in different ways, and you give them

1 worst ranks. And so it's not as heavy in terms of
2 how it manages the worsening heart failure
3 patients.

4 But I think originally, the reason why it
5 was built into the VAS was so that if a favorable
6 treatment difference was detected for the VAS, it
7 would at least partly have corresponded to fewer
8 bad events in the serelaxin group.

9 DR. LINCOFF: Dr. DeLemos?

10 DR. DELEMOS: Yes. Can the sponsor pull up
11 slide 111, please? So as that's coming up, I agree
12 with the FDA reviewers. It seems pretty clear --

13 DR. NATHWANI: What number?

14 DR. DELEMOS: 111, yes, of the sponsor
15 presentation. So it seems pretty clear that the
16 drug, despite the hypothesis going in, doesn't
17 actually make people feel better faster, and that
18 it may alter rescue therapies, but we have problems
19 with the way that was defined and the way that was
20 adjudicated.

21 But here's a piece of objective evidence
22 that the drug has a biological effect that may be

1 clinically meaningful that supports the mortality
2 findings.

3 My question here is, have these data been
4 stratified by presence or absence of worsening
5 heart failure? I.e., is there an effect on length
6 of stay in patients that do not have worsening
7 heart failure? Or does the drug only prevent
8 rescue therapies, or does it also hasten recovery?

9 DR. NATHWANI: That's a great question. Can
10 I invite Dr. Lefkowitz to comment.

11 DR. LEFKOWITZ: The answer is that it does
12 have an effect in the overall population. If you
13 look at the patients without worsening heart
14 failure, the effect on the hospitalization is
15 0.6 days, which is significant.

16 So worsening heart failure accounts for some
17 of it, but there is an effect in the overall
18 population. That was with the patients without
19 worsening heart failure, .6 days.

20 DR. LINCOFF: Dr. Orza, do you still have a
21 question? You had raised your hand a while back.

22 DR. ORZA: I had a couple that I didn't get

1 to ask in the round with the sponsor that the
2 public commenters reminded me about. Sorry.

3 One, I wanted to ask the sponsor why the
4 patient population was not as representative of the
5 epidemiology of heart failure as it perhaps should
6 have been, and whether that has been remedied in
7 the second trial that's ongoing.

8 I also had a question about the nature of
9 the drug being a hormone that I think, if I
10 understood the background materials correctly,
11 occurs naturally but only in women, and in terms of
12 how often and for how long the typical heart
13 failure patient who would be getting this would be
14 exposed to it.

15 Is there anything to think about the effects
16 of that on women, in which the hormone does other
17 things, and in men, in whom it doesn't occur
18 naturally at all?

19 DR. NATHWANI: Okay. There are two parts to
20 that question. If I can invite Dr. Severin just to
21 comment on the applicability of the population;
22 then I'll take the second question.

1 DR. SEVERIN: Thanks. Tom Severin. So
2 RELAX-AHF as well as the serelaxin program targeted
3 a targeted patient population -- not the entirety
4 of the acute heart failure patients, but a large
5 population representative to patients who typically
6 present as elderly patients with dyspnea, with
7 congestion, with several comorbidities.

8 Can we have slide 155 up, please? We
9 compare in this slide the baseline characteristics
10 in RELAX-AHF with baseline characteristics in the
11 large acute heart failure register ADHERE and in
12 OPTIMIZE. We see a similar age. We see a similar
13 range of blood pressure. We see similar
14 comorbidities. Dr. Greenberg may add, or already
15 explained, about the applicability of the patient
16 population. If we look at the primary endpoint --

17 DR. ORZA: Specifically, though, race is not
18 on there. Do you have that?

19 DR. SEVERIN: Yes. We did analysis for the
20 primary endpoint as well as for worsening heart
21 failure for mortality for several endpoints across
22 several subgroups. And if I can have slide 353,

1 please.

2 This shows now a subgroup analysis, a forest
3 plot, for the primary endpoint. Slide up, please.

4 And here we did several subgroup analyses. Only
5 some of them are shown on this slide. And here you
6 see the point estimates for the regions, including
7 North America, which in our trial was on the U.S.

8 So the treatment effect here favors the
9 region of North America similarly to the treatment
10 effect in other regions and to the overall study.

11 DR. ORZA: Yes. I saw this slide and this
12 data in the background materials. But go back to
13 the previous slide.

14 DR. SEVERIN: Yes. Can we go back, please?

15 DR. ORZA: Because that's a very small group
16 when it comes to the race comparison.

17 DR. NATHWANI: Did you mean the slide on the
18 registries? Is that right?

19 DR. ORZA: Yes. The one you just -- just
20 before this.

21 DR. SEVERIN: Yes. Can we go back to the
22 comparison, baseline characteristics with ADHERE

1 and with OPTIMIZE? Slide up, please.

2 DR. ORZA: What does the row for race look
3 like? Why isn't it up there?

4 DR. SEVERIN: Sorry. So your question, just
5 to clarify, it's about race?

6 DR. ORZA: Yes.

7 DR. SEVERIN: Okay. I can clarify that.
8 No, it's not on this slide. But the study which
9 was conducted in 11 countries, several European
10 countries, in Argentina, Israel, and North America,
11 enrolled the majority of patients of Caucasians.
12 These were around 94 percent.

13 Then, of the remaining patient population,
14 most of them were African Americans, around
15 4.5 percent of the study. And we looked at the
16 treatment effect particularly in that group, and we
17 can go back to slide 353, where we see also
18 subgroup analysis here. Can we have 353 and slide
19 up, please?

20 So above the area of region, we see race.
21 We see the treatment effect in white and
22 Caucasians. And then we see on this slide only one

1 group, which is called "Other Race," which
2 predominately included the African Americans. And
3 here the treatment effect is also positive in favor
4 of serelaxin, and the magnitude of the effect is
5 even much more pronounced.

6 DR. NATHWANI: If I may just address the
7 second question that you raised very quickly about
8 the effect in women. So relaxin is found,
9 obviously, in women. It goes up during pregnancy.
10 It's at very low levels in men, and it's at higher
11 concentrations in the prostate.

12 We have not studied, clearly, pregnant women
13 or women who got pregnant with this drug in our
14 proposed label. We would suggest that the
15 benefit/risk could be under the evaluation of the
16 treating clinician. We have no theoretical reasons
17 to believe it will be an issue, but we have not
18 studied that in any way right now.

19 DR. LINCOFF: Dr. D'Agostino, you had
20 questions?

21 DR. ORZA: But could I just understand what
22 would be the expected exposure to this drug of the

1 typical patient?

2 DR. NATHWANI: Yes.

3 DR. ORZA: If it were approved, how often
4 and for how long would the typical heart patient
5 get it?

6 DR. NATHWANI: Yes. For every incident
7 right now, we're looking at a 48-hour infusion. On
8 average, these patients present back between one
9 and a half to three times a year, and it depends on
10 their recurrences. So it would be between one and
11 a half to three times a year.

12 DR. LINCOFF: All right. Do we have direct
13 follow-up? Dr. Li?

14 DR. NATHWANI: We have not studied
15 repeat -- just to be clear, we have a repeat dose
16 study ongoing, but it's just starting now. But we
17 have not studied repeat dose.

18 DR. LI: Just a direct follow-up. If you
19 expect people to get repeat dosing, it's a fairly
20 complex molecule, and I would expect that a protein
21 like this, there would be some antibody response.
22 So do you have any animal data whether people would

1 develop antibodies or anaphylaxis or have any
2 problems with it with repeat dosing?

3 DR. NATHWANI: Certainly, yes. In the RELAX
4 study, we had one patient who actually developed
5 very low levels of antibodies, and they were not
6 neutralizing. Just one patient. And given the
7 route of administration, we would not expect it to
8 actually have that.

9 We obviously are doing the repeat dose study
10 to actually investigate whether there is further
11 antibody formation. We don't expect to have high
12 levels. This is a natural hormone, and actually,
13 we don't think that that's going to be -- but it's
14 a key issue. We have not seen a hypersensitivity
15 reaction in our studies as a consequence.

16 DR. LINCOFF: Dr. D'Agostino?

17 DR. D'AGOSTINO: My comment goes back to
18 Dr. Temple's and Dr. Koch's presentation. If I'm
19 reading it correctly, we had a dyspnea study that
20 was driven by worsening of heart failure, and then
21 we have the scaling issue.

22 If I hear things correctly, Dr. Koch was

1 saying once you go into this worsening of heart
2 failure, then it's like a trial where a rescue
3 medication counts you as a failure, and you're a
4 failure forever. And you could vary a bit on how
5 they call it a failure forever in terms of the
6 ranking and so forth, but you're always low.

7 But our dilemma, I think, is that we don't
8 consider this worsening heart failure necessarily
9 to be tied to dyspnea, and we don't necessarily
10 think that it's a forever activity. And many of us
11 are saying, or many of the comments were, that you
12 can go back to looking at the actual value they
13 get. If we do that, then you go from a .02, with
14 all the sensitivity analysis of the sponsor, to a
15 .2, with not restoring to your level.

16 What I'd like is, from a sponsor, am I
17 reading this correctly that it all hinges on this
18 idea of once you hit this worsening, you're in the
19 rescue medication, and then you're penalized for
20 that, and if we say we don't believe that, that you
21 can be restored, then your significance goes away?

22 DR. NATHWANI: Can I have slide C-338, and

1 slide up. The fundamental principle, I think,
2 we're trying to illustrate again -- you've seen
3 this many times -- is that the way that this was
4 prespecified by the design from both Pre-RELAX and
5 in RELAX was that this is a multi-component
6 endpoint which has death, in-hospital worsening,
7 and change in dyspnea. This is prespecified.

8 If we go back to this and we say, well,
9 okay, are the events in the middle group, which are
10 at the moment assigned a zero within the
11 prespecified rules, driving everything? So yes,
12 most of this was driven by the middle component.

13 Then the question that I think we tried to
14 address today is, if you rank the middle component
15 using a different methodology of sensitivity, and
16 that's where the clinical ranking came in, and
17 apply the log rank principle, is the data still
18 robust? Because it doesn't just reflect that this
19 is driven by minor events, which are regarded as
20 clinically trivial.

21 DR. D'AGOSTINO: But that still penalizes
22 you, what the alternative is, that once you're

1 restored, then whatever your actual score is,
2 that's what gets counted, not this penalizing from
3 having this worsening of heart failure.

4 DR. NATHWANI: I'm just going to invite
5 Dr. Lefkowitz to comment.

6 DR. LEFKOWITZ: Thank you. Martin
7 Lefkowitz. If I could just add a few comments,
8 also going back to Dr. Temple's question.

9 Worsening heart failure has been an
10 endpoint, and a primary endpoint, in fact, in most
11 of the recent acute heart failure studies. It's
12 been a component of the primary endpoint. So this
13 is nothing new. And in fact, Dr. Packer showed the
14 slide 387, and slide up.

15 So worsening heart failure has been
16 recognized, I think, as an important goal of
17 treatment. What's different here is that not all,
18 but most, used a clinical composite. The rationale
19 for not doing that in this study disease that the
20 Likert was used to measure one of the primary
21 endpoints, to look at the early dyspnea relief.

22 Then, as Dr. Greenberg explained, we used

1 the VAS because there was some concerns on the
2 recall bias with the Likert. So the VAS was used
3 to look at the dyspnea, but the worsening heart
4 failure was an integral component, as was death.
5 And that was the rationale as to how this endpoint
6 was constructed.

7 The assignment of worst score is consistent
8 with previous studies, and these are not trivial
9 events. Recall, the patients were in the hospital
10 8 days longer, and this is what's been seen in
11 other studies.

12 So I do want to point out this consistent
13 with other studies. Worsening heart failure has
14 been recognized as an important endpoint.

15 DR. TEMPLE: But nobody disputes that
16 worsening heart failure might be a great endpoint.
17 The question is how you would create that endpoint.
18 And it would be multi-component, you'd say. It
19 could be need for diuretic or it could be this or
20 it could be that. Or it could be a deterioration
21 of dyspnea of a certain amount.

22 But to incorporate it into a VAS, that's

1 novel, and I don't think we've seen that. And
2 we've all talked about what the result of that is.

3 DR. LINCOFF: Well, yes. In regard to that,
4 I'd like to ask a follow-on question about this
5 directly.

6 So you list here several trials that used
7 heart failure, used worsening heart failure.
8 There's been a lot of talk here about the fact that
9 this was not adjudicated. So I'd like to ask
10 Dr. Packer, or others, have there been trials where
11 in-hospital worsening heart failure -- not
12 recurrent heart failure, which there are clear,
13 standardized definitions -- but in-hospital heart
14 failure, have they been adjudicated?

15 DR. PACKER: No.

16 DR. LINCOFF: Does the FDA agree with that
17 or disagree? Because we've talked about this a
18 lot, but we run a clinical events committee.

19 DR. PACKER: You're asking a question -- to
20 date, to date, has worsening heart failure -- can
21 we put up the slide with the trials? It's coming
22 up. Slide up. I feel like a magician or

1 something. I don't know.

2 So if you look there, the last five trials
3 are the ones that used worst rank or score for
4 worsening heart failure or death for the primary
5 endpoint, in VERITAS, REVIVE, PROTECT, and RELAX.
6 And those are the trials that have been completed
7 to date. There has been no adjudication.

8 The ongoing trial, TRUE, does use
9 adjudication, okay, upon the insistence of FDA.
10 The investigators took the position that these
11 events are very hard to adjudicate. The FDA wanted
12 them adjudicated, and there is an adjudication
13 process in TRUE. But if you ask the question, of
14 the trials that have been completed to date, has
15 worsening heart failure been adjudicated, the
16 answer is no.

17 DR. LINCOFF: So setting aside the issue of
18 whether or not this should have been incorporated
19 into dyspnea score, there's been a lot of criticism
20 here that this wasn't adjudicated. And unless the
21 FDA knows of other trials, there is not precedent
22 for having a completed trial showing that you can

1 accurately adjudicate, or that you have
2 adjudicated, in-hospital heart failure?

3 DR. TEMPLE: Let me just make one
4 observation about adjudication. Not everybody in
5 the world thinks that adjudication is always better
6 than local determination. And I don't think we
7 have a position on that.

8 People do a lot of adjudication. It's
9 routinely incorporated into a great many trials.
10 But there are publications that say it doesn't
11 necessarily help, and I don't think we have a fixed
12 and final view on that.

13 So my problem with this wouldn't be the
14 question of adjudication primarily, although other
15 people might feel it. It's the things that
16 everybody's been talking about, was this the
17 endpoint, and all that. But we could accept trials
18 that didn't adjudicate. We'd have to think about
19 it. And apparently we have.

20 DR. LINCOFF: Dr. Papademetriou, you're
21 next.

22 DR. LEFKOWITZ: Could I address the

1 adjudication issue also?

2 DR. LINCOFF: All right. And then --

3 DR. LEFKOWITZ: On part B --

4 DR. LEWIS: Can I just say it's not just an
5 adjudication issue. There was also no information
6 about what the principal investigator -- what
7 symptoms and signs made him decide, or she, that it
8 was heart failure worsening?

9 It's not just that it wasn't adjudicated.
10 There was nothing like, chest X-ray looks worse.
11 Patients can't breathe. Code was called. There
12 was nothing. There is just a check box. So it's
13 more than no adjudication.

14 DR. PAPADEMETRIOU: A lot of the questions
15 I had have already been asked and discussed
16 extensively. But I'll go ahead and ask some of
17 them anyway.

18 One of them was whether there is any measure
19 in your records assessing the patients' fluid
20 status. Did you know if the patients a lot of
21 edema, if they had a lot of congestion in their
22 X-rays, if they had any clinical evidence of heart

1 failure, and if there were any differences between
2 the two groups? That's one.

3 The second is that you report here that the
4 percent of patients with the ejection fraction less
5 than 45, it was about the same. It was 55 percent.
6 But do we know that a severely reduced ejection
7 fraction, if it was equally distributed? Do we
8 have patients with the numbers below 20 percent?
9 If they were equally between the two groups?

10 It was already suggested by one of the
11 speakers before that Class III and IV New York
12 Heart Association failure was more frequent in the
13 placebo group. Was that true also for the absolute
14 ejection fraction? Was the average ejection
15 fraction between the two groups?

16 DR. NATHWANI: You've asked a number of
17 questions. I'll come back straight to them. If I
18 could just ask a request for one thing. I just
19 want to complete the response to Dr. Lewis, and
20 Dr. Greenberg wants to do that. And I'll come back
21 to all of your points in a minute, if that's okay.

22 DR. GREENBERG: So going back to the

1 adjudication issue, this is something that we dealt
2 with in depth at our executive committee meetings
3 when we were coming up with this study. And the
4 feeling was at that time not to do adjudication.

5 Some argued for it, and we recognized that
6 it would be exceptionally uncommon for a CEC to
7 overturn the investigator's determination that this
8 was worsening heart failure event.

9 It was spelled out in the protocol. It was
10 taught to the investigators during the investigator
11 meetings that they needed to define worsening heart
12 failure, and it had to be an actionable event. And
13 both of those needed to be present.

14 It's a lot different than from a chronic
15 heart failure, where I'm a strong advocate of
16 adjudication of those events. For somebody in the
17 hospital with decompensated heart failure, the end,
18 the bandwidth for the differential diagnosis, is
19 very narrow. And almost certainly, these are going
20 to be more heart failure events on top of their
21 initial heart failure.

22 Even in the outpatient studies, adjudication

1 reverses very few of these. For an inpatient
2 population that's already defined as having heart
3 failure, we would not expect this to be overturned
4 almost at all.

5 DR. LINCOFF: All right. So Dr. Proschan?
6 Because I know you had been waiting.

7 DR. NATHWANI: Can I just come back to your
8 question?

9 Dr. Severin, can you just talk about the
10 signs and symptoms that we did collect and the
11 other information you asked? And if we are missing
12 any information, please let us know. We'll clarify
13 it for you. Dr. Severin?

14 DR. SEVERIN: The signs and symptoms of
15 heart failure were assessed at baseline and then at
16 every visit. And here I would like to show
17 you -- slide up, please -- the signs and symptoms
18 of congestion at day 2, at 48 hours at the end of
19 the infusion period. And the assessments were done
20 for dyspnea on exertion, for orthopnea, for edema,
21 rales, and for ejacular venous pressure.

22 It's a very busy slide. The different

1 colors, they represent different categories of
2 severity. For example, for orthopnea, the second
3 column from the left, the different categories,
4 they show whether the patient needs one or two
5 kilos or above a 30 degree position to feel
6 comfortable.

7 So what we see here in summary is a
8 significant reduction of dyspnea on exertion,
9 orthopnea, edema, and rales, and a trend for
10 improvement for GVP at day 2.

11 DR. PAPADEMETRIOU: Do you have that at
12 baseline, though? This is on day 2.

13 DR. SEVERIN: Yes. These are the signs and
14 symptoms at day 2. And we also have these signs
15 and symptoms at baseline, if we can bring up that
16 slide. Slide up, please.

17 So here we see the signs and symptoms of
18 heart failure at baseline. And we see here much
19 more of the bars shaded in red, which is the most
20 severe category for each of these signs and
21 symptoms of heart failure.

22 DR. PAPADEMETRIOU: One more thing. Do you

1 have any information on comorbidities that could
2 affect shortness of breath such as emphysema,
3 history of emphysema or COPD?

4 DR. SEVERIN: Among the baseline
5 characteristics, we collected a number of
6 comorbidities which are similar to the acute heart
7 failure population, which typically has a number of
8 comorbidities.

9 If we can bring up the baseline
10 characteristics, I can point out different
11 comorbidities, which were balanced by treatment
12 group.

13 Can we have baseline characteristics? The
14 next one, the comorbidities, please.

15 While we're looking for it, I can just
16 address the question which also was raised on the
17 average ejection fraction. So the most recent
18 ejection fraction captured in the study was around
19 38 for the placebo group and 39 for the serelaxin
20 group.

21 But this was the most recent ejection
22 fraction, which was not necessarily captured

1 directly at the time of randomization in the study.
2 And around 55 percent of patients had an ejection
3 fraction below 40 percent in RELAX-AHF.

4 Slide up, please. This slide now shows the
5 baseline medical history of the patients. In the
6 study, we see a majority has hypertension, and
7 there are more than 50 percent with a history of
8 ischemic heart disease. You asked specifically on
9 COPD, which is listed with asthma and bronchitis in
10 the lower row of this table.

11 DR. NATHWANI: If I may just beg indulgence.
12 Thirty seconds, if I may? Could I have slide 610
13 up, please?

14 You've seen this data before. I just wanted
15 to make sure that people understand worsening heart
16 failure was regarded by the executive committee as
17 not a trivial event. You've seen these data that
18 it tends to result in an increased length of stay.

19 Can I have 614? Slide up. This is a meta-
20 analysis that has just been completed taking RELAX,
21 the entire RELAX data set, and PROTECT, which is a
22 much larger data set in acute heart failure.

1 Just to walk you through the slide, this is
2 looking at death through day 180. And you see the
3 hazard ratios there, which are unadjusted for the
4 relative increase in the hazard. When you look at
5 the combined data set -- so it's not just in RELAX,
6 but also in the combined data set -- that worsening
7 heart failure events are regarded as having a worst
8 outcome. Thank you.

9 DR. LINCOFF: But this doesn't show that
10 preventing them prevents the death. It's just
11 association. So that's --

12 DR. NATHWANI: Yes. I totally appreciate
13 it.

14 DR. LINCOFF: Okay. Dr. Proschan?

15 DR. PROSCHAN: So I actually really do have
16 a clarifying question.

17 (Laughter.)

18 DR. LINCOFF: You've been very patient.

19 DR. PROSCHAN: That involves the log rank
20 that was done. So as I understand it, then, this
21 would be like the worst event that a patient had.
22 So for example, if a patient had worsening heart

1 failure and then later had a death, but that death
2 was the earliest among all deaths, then that
3 patient would be the first time point in the log
4 rank analysis. That would be like the first death
5 in our usual kind of log rank. Is that correct?

6 DR. KOCH: That would be -- Gary Koch.

7 DR. PROSCHAN: No. I knew that.

8 (Laughter.)

9 DR. KOCH: That would be my understanding.
10 There were different conventions. Under some
11 conventions, all of the deaths would have gotten
12 the same log rank score, and all of the worsening
13 heart failure patients would have been shared the
14 same next worst score.

15 DR. PROSCHAN: Right. But I guess what I'm
16 getting at, though, is that that death, even though
17 it came later, would be counted as like a more
18 serious -- it would still be counted even though it
19 wasn't the first event for that patient.

20 DR. KOCH: Yes. Yes. The deaths were
21 ranked worse.

22 DR. PROSCHAN: Okay. And could I just ask

1 one other thing, then? On slide 128, I'm just
2 wondering whether you have an explanation for why
3 things get worse with the higher dose. Was it a
4 matter of people not being able to tolerate it and
5 going off of it, or what's your explanation for
6 that on the rightmost plot?

7 DR. NATHWANI: Certainly. I invite
8 Dr. Severin.

9 DR. SEVERIN: Thomas Severin, clinical. So
10 we see a consistent effect here on the visual
11 analog scale on the left across four doses. But
12 the effect on the Likert scale is really
13 inconsistent. And the study was designed not to
14 compare single doses versus placebo, looking at the
15 p-values, but to look at dose-response across
16 doses.

17 So the result on the visual analog scale
18 seems to me more robust and more comparable to what
19 we have seen in the RELAX-AHF study. And it was
20 pointed out that it used to say methodology for
21 assigning worst score for patients with worsening
22 of heart failure.

1 Now, your question also goes to the
2 different doses and how they applied in terms of a
3 U-shaped curve. And if I can have slide C-15,
4 please. This is a very important topic
5 because -- slide up, please -- this is the way how
6 also the dose selection in the study was done, that
7 the favorable effects were seen across several
8 endpoints, including the Likert scale for the
9 30 microgram per kilo per day dose, which compared
10 favorably to other doses here, up to 250 tested.

11 We saw, at the dose of 250 microgram per
12 kilo per day, unfavorable renal results, so that
13 dose was then not selected. And the most
14 consistent effects were seen for the 30 dose.

15 DR. PROSCHAN: But with all due respect,
16 that doesn't answer the question I had, which is,
17 why is it that, for example, the 100-milligram dose
18 is doing worse on the Likert scale? Why would that
19 be? I understand maybe at 250 it's --

20 DR. NATHWANI: So I think it's very clear
21 from the Pre-RELAX. We didn't see a consistent
22 dose-response on Likert. The only dose that

1 actually seemed to apparently have an effect was at
2 the 30, and that's one of the reasons why it was
3 still pulled across in the RELAX study. So there
4 is no clear dose-response on the Likert.

5 DR. PROSCHAN: Yes. I understand that. I'm
6 asking your --

7 DR. NATHWANI: We have no explanation.

8 DR. PROSCHAN: Okay. That's all you had to
9 say at the very beginning. Just, I don't know,
10 would have been fine.

11 DR. NATHWANI: Thank you.

12 DR. LINCOFF: Dr. DeLemos?

13 DR. DELEMOS: Question about, are there
14 subgroup data based on any validated risk
15 instrument for either the VAS or the worsening
16 heart failure across patient risk categories to
17 demonstrate whether or not the treatment effect is
18 consistent across patient risk status?

19 There's a number of models that have been
20 developed to predict in in-hospital heart failure,
21 and I'm wondering if those were evaluated as
22 subgroups.

1 DR. NATHWANI: I don't think we did. No.

2 DR. LINCOFF: Dr. Sager?

3 DR. SAGER: If we think about a 3 to 4 mean
4 difference in the VAS scores, is there data that
5 could help us think of this in a clinical context?
6 The paper that the FDA had supplied by Ander, and
7 also another one in that paper by Koros, both speak
8 to around a 20, 21 millimeter. But I don't know if
9 there was other data that would be good for the
10 committee to know about.

11 DR. NATHWANI: I'd like to invite
12 Dr. Gwaltnoy up to comment.

13 DR. GWALTNOY: Chad Gwaltnoy, ERT. Let me
14 speak to the Ander paper.

15 The Ander paper, the estimate of clinically
16 relevant change is not appropriate to apply to the
17 serelaxin program. These sorts of clinical
18 relevance estimates are very specific to the trial
19 context in which they're developed.

20 There are significant methodological
21 differences between the Ander trial and the
22 serelaxin program that make it impossible to use

1 that Ander estimate. For example, even the nature
2 of the scale, the visual analog scale, that was
3 used in Ander is different from what was used in
4 serelaxin.

5 More importantly, the sponsor is correctly
6 interpreting the effect of serelaxin on worsening
7 heart failure. And it's the magnitude --

8 DR. SAGER: I'm sorry. I have to interrupt.
9 That's really not one of the endpoints, primary
10 endpoints, of the study. The endpoint of the study
11 was the Likert scale and the VAS scale. So is
12 there data that exists that would help us put into
13 context a 3- to 4-millimeter mean change between
14 the two groups? And if there isn't, we understand.

15 DR. NATHWANI: No. We don't have that data.

16 DR. SAGER: Then the other question has to
17 do with the long-term prognosis of having worsening
18 heart failure. Can you show us the data separated
19 out for serelaxin and the data for placebo on
20 long-term prognosis if you develop worsening heart
21 failure? Obviously, the data is more robust in the
22 placebo group.

1 DR. NATHWANI: Let me get Dr. Lefkowitz. Do
2 you want to talk about this?

3 Are you asking about -- just trying to
4 clarify this. You're looking for worsening heart
5 failure and its long-term outcome. Is that
6 correct?

7 DR. SAGER: Yes. It was stated earlier that
8 developing worsening heart failure is associated
9 with a long-term bad prognosis.

10 DR. NATHWANI: Sure. Certainly. So can I
11 have slide C-342?

12 DR. SAGER: You showed us the data for both
13 groups combined. But we wanted also to see them
14 separately.

15 DR. NATHWANI: But the groups are, by
16 definition, then, losing their randomization post-
17 worsening heart failure. We do have that data if
18 you'd like to see it, but it's no longer randomized
19 data.

20 DR. SAGER: Okay. Thank you.

21 DR. NATHWANI: Would you like to see it?
22 Yes?

1 DR. SAGER: Yes, please.

2 DR. LEFKOWITZ: Again, I just do want to
3 point out that this is a post-randomization event.
4 There may well be selection bias. And in fact, the
5 baselines of the two groups are different. It may
6 well be that the most refractory patients are going
7 to stay in both groups. So with that in mind, if I
8 could go to slide 446, please. And slide up.

9 So this is all-cause mortality, first on the
10 right side in RELAX, and then we did a pooled
11 analysis. So you can see that the number of -- we
12 used day 5 as our day 5 worsening heart failure,
13 which was the primary endpoint.

14 So you could see that the number of deaths
15 in both groups is relatively low, 9 versus 6.
16 However, it is elevated in both groups in terms of
17 the hazard ratio. You could see the 17.7 versus
18 13.9 percent.

19 However, when you looked at the pooled
20 analysis, now we're adding more patients from both
21 studies. You could see that the overall mortality
22 rate is quite similar, although the hazard ratio,

1 of course, is higher in serelaxin because the
2 placebo group has less deaths in the non-worsening
3 heart failure group. So those are the results.

4 DR. SAGER: So in the RELAX heart failure,
5 the placebo group, the point estimate was
6 increased, but it's nonsignificant despite having
7 twice as many events?

8 DR. LEFKOWITZ: That's true. But again, I
9 really think if one's talking mortality here, one
10 needs to look at the randomized population, and
11 there the results are quite clear in this study.

12 DR. SAGER: Thank you.

13 DR. NATHWANI: Dr. Koch had a comment to
14 your previous question.

15 Dr. Koch?

16 DR. KOCH: Yes. Please bring up C-227.
17 It's going to be a cumulative distribution display
18 so that one has another way to interpret the
19 sponsor's original -- slide up, please -- primary
20 endpoint rather than a difference in means.

21 So this is showing patients whose outcome
22 was .6000 or less, or .5400 or less. So it's

1 showing proportions of people whose outcome on the
2 originally specified VAS with the sponsor's
3 conventions of using a zero value for patients with
4 worsening heart failure or death, and the main
5 observation here that you can see is that if you
6 look at negative 1200, there's about a 5 percent
7 difference between the groups.

8 Five percent more placebo patients were
9 minus 1200 or worse, which on average is a minus
10 10-millimeter change or worse. If you go to minus
11 2400, you'll see that it's about 4 percent more
12 patients had a minus 2400 or worse, or a minus
13 20 milligram.

14 These differences of 4 to 5 percent are
15 largely driven by the difference in worsening heart
16 failure proportions, as you heard before. And
17 they're consistent with the number needed to treat,
18 in the vicinity of 20, as you also heard before.

19 But this information directly comes out of a
20 cumulative distribution display of what the t-test
21 was applied to. And this is the information that
22 underlies why the t-test provided a positive

1 result, basically a 5 percent or so difference in
2 the more severe outcomes.

3 DR. LINCOFF: Dr. D'Agostino, you had a
4 question?

5 DR. D'AGOSTINO: It's been so long since I
6 had my questions, they're probably not relevant any
7 more.

8 But I wanted to make a point that the issue
9 I was raising is not addressed by adjudication of
10 the heart failure. What I think all of this hinges
11 on is, do we believe that once you get a worsening
12 heart failure and you get a rescue medication, then
13 you're stigmatized forever in the study? And then
14 also, do we believe that the worsening heart
15 failure is really telling us about dyspnea?

16 We can take it that the heart failure is
17 completely correct, as given. That's not the
18 question. The question is, how do we incorporate
19 that information into our understanding and
20 interpretation of the study?

21 DR. NATHWANI: That seems to be central. Is
22 the concern that you're articulating, and I think

1 Dr. Temple articulated as well, that we're calling
2 it dyspnea or worsening heart failure, is that some
3 of the issue?

4 DR. D'AGOSTINO: Well, does it correspond to
5 what the study is claiming it's about?

6 DR. PACKER: This is really important.
7 Ralph and Bob have brought this to bear, but let me
8 try to see if I can synthesize this.

9 Dr. Lewis, your concern primarily is not
10 adjudication or non-adjudication. It's
11 documentation, if I understand it correctly.

12 DR. LEWIS: Okay. I have multiple concerns,
13 and they're separate. One concern is that we don't
14 know anything about it. And in chronic renal
15 failure patients, you could have been giving
16 totally inadequate doses of Lasix. And giving a
17 little more is really a whole different story.

18 But my other consideration is, I can't even
19 figure out how you wouldn't -- even if you chose to
20 censor the scores after the heart failure event or
21 you chose to use the regular scores, depending on
22 what happened, you could be criticized for how

1 those scores were then interpreted.

2 So in a disease where you're going to have
3 worse heart failure events, I think it is going to
4 confound, and you will be criticized no matter how
5 you choose to do the scores afterwards. What if
6 serelaxin gave more worse heart failure, and you
7 censored the scores after they got that? Well,
8 you'd be criticized. I mean, you can't win.

9 DR. PACKER: I have a great solution to
10 being criticized.

11 (Laughter.)

12 DR. LEWIS: No. I mean being criticizable.

13 DR. PACKER: Or at least I like to think so.
14 Can we put up slide 338? Because this addresses
15 the concern of multiple members of the committee,
16 and I just want to make sure that I understand this
17 because this may essentially crystallize what a lot
18 of people have brought up.

19 This is the way that the primary endpoint,
20 visual analog scale-area under the curve, was
21 constructed and predefined in terms of analysis.
22 As I understand it, what really bothers the

1 committee is that this is described as a dyspnea
2 score. And if it's described as a dyspnea
3 score --

4 DR. D'AGOSTINO: But also that you're
5 penalized forever.

6 DR. PACKER: Yes. I totally understand.
7 And if it's called dyspnea and one wonders how one
8 should be penalized and how long someone should be
9 penalized for, if one didn't call this a dyspnea
10 score, if one called this a clinical course
11 assessment, with death being really bad and
12 clinical instability being bad, then that is what
13 this score is. Is that not true?

14 DR. LEWIS: I'm sorry. Your primary outcome
15 was patient-reported change in dyspnea using the
16 VAS and Likert scales.

17 DR. PACKER: I hear you loud and clear. I
18 just want to make sure that I understand. If this
19 were called a clinical course assessment, it sounds
20 like people would be more comfortable. It's called
21 a dyspnea score, so people are uncomfortable. No?

22 DR. LINCOFF: I don't know that I disagree

1 with that. I think that's kind of what I'm
2 hearing. If we just set aside what they
3 prespecified that they were calling this score and
4 just call it something else, is it a valid endpoint
5 if it doesn't --

6 (Crosstalk.)

7 DR. PACKER: No. I don't want to
8 suggest --

9 DR. D'AGOSTINO: It's an invalid endpoint.

10 DR. LEWIS: The instrument you used as your
11 measure of your primary outcome, which is stated as
12 dyspnea, is an instrument for asking patients if
13 they feel more or less short of breath. It is not
14 a composite outcome of the VAS score and worse
15 heart failure, which I would surely hope, if that
16 was part of a composite outcome, we'd have a little
17 more information about or whatever.

18 It is a dyspnea score. That was your
19 primary outcome. I don't think you can re-call it
20 something else. I think it is confounded by heart
21 failure worsening, and I'm sorry that it was. I
22 can't even figure out how it wouldn't be.

1 DR. PACKER: No, no.

2 DR. SCOTT: It doesn't matter what they
3 called it. It is what it is in the protocol. So
4 if you just take the name away, this is what it is.
5 So it doesn't matter whether you called it a
6 dyspnea.

7 DR. LINCOFF: All right. So why don't we
8 let Dr. Packer finish his response, and then we'll
9 go on to another question.

10 DR. PACKER: No, no, no. Please, there is
11 no intent here to perform revisionist history and
12 change what this was called. There is no intent.
13 The sponsor called this a dyspnea assessment, and
14 that's what it's called in the protocol. But --

15 DR. LEWIS: They ask the patient if they're
16 short of breath.

17 DR. PACKER: Yes.

18 DR. LEWIS: That's what it asks.

19 DR. PACKER: Yes.

20 DR. LEWIS: That is the two questions, the
21 two anchors, at 100 and zero.

22 DR. PACKER: Yes. I don't disagree. But

1 as constructed, this is an assessment of clinical
2 course. Okay? It's not called that. It's not
3 called that. People who die get a bad score.
4 People who are clinically unstable over 5 days get
5 a bad score. People who get more dyspnea
6 improvement get the best score.

7 A clinical course name is different than a
8 dyspnea name. I don't want to say it's not. But
9 understand that as constructed, although it is
10 called a dyspnea score and relied on a visual
11 analog scale assessment of dyspnea, it is
12 constructed as a clinical course score. I just
13 wanted --

14 DR. TEMPLE: Can I --

15 DR. LINCOFF: Dr. Rich is next. Oh,
16 Dr. Temple, go ahead. He takes precedence.

17 (Laughter.)

18 DR. TEMPLE: No. Milton, I'm curious. If
19 you really wanted to do that, you could have death.
20 You could have in-hospital worsening. And then
21 you'd have some defined dollop of change in dyspnea
22 score that would be added to your composite

1 endpoint. And then everybody would say, that's
2 wonderful.

3 But here the in-hospital worsening heart
4 failure score has a profound affect on the dyspnea
5 score. Isn't that a problem?

6 DR. PACKER: If you call it dyspnea, it is.

7 (Laughter.)

8 DR. TEMPLE: Even if you don't, it's sort of
9 double-counting.

10 DR. PACKER: No, no. I don't think there's
11 double. Every patient just contributes once.
12 Right?

13 DR. SAGER: No. They can have multiple time
14 points they contribute, so it actually is
15 quadruple-counting in some cases.

16 DR. PACKER: It's okay. I think that the
17 clarification is in place. I just wanted to make
18 it.

19 DR. GRANT: Norm isn't here.

20 DR. LINCOFF: Go ahead.

21 DR. GRANT: So I'm going to take the
22 privilege of asking on the part of the division,

1 and I [indiscernible - audio static] this on the
2 panel. The prespecified hypothesis here, what was
3 discussed at end of phase 2, had none of that
4 flavor. It was all about dyspnea. We're going to
5 get a claim for reduction of dyspnea in acute heart
6 failure.

7 Had we known prospectively what the effect
8 that the sponsor or the applicant actually wanted
9 [indiscernible - audio static] was some measure of
10 these three components, what would have been a
11 better-constructed scale?

12 How would you do this if you now were
13 sitting -- if tomorrow we have someone walk in and
14 they say, we saw this AC yesterday and we
15 understand your concerns about a scale that's
16 really meant to measure dyspnea but captures some
17 other things, maybe imperfectly, how would you have
18 designed this prospectively?

19 DR. LINCOFF: Who are you asking? Anyone?

20 DR. LEWIS: He said the statisticians on the
21 advisory panel.

22 DR. GRANT: I'm happy to hear from anybody

1 on the panel. But this is a question --

2 DR. RICH: Well, I'll be happy to give a
3 quick answer because I have another question for
4 the FDA.

5 DR. LINCOFF: All right. Dr. Rich. You're
6 actually next up anyhow, so go ahead.

7 DR. RICH: Thank you. I think this is a
8 wonderful hypothesis-generating study, really, and
9 I think it's getting us much closer to defining a
10 clinical scenario that we can say represents
11 worsening heart failure.

12 But if it's going to be worsening heart
13 failure, then there has to be some explanation of
14 how the investigator made a decision to call it
15 worsening heart failure and why they chose the
16 intervention they did, so at least we can say,
17 okay, we're all speaking the same language.

18 I have to tell you that I can't imagine many
19 of these patients in the United States being
20 hospitalized based on the baseline characteristics
21 of these people. I think, depending on countries
22 and the quickness to hospitalize people, many

1 people we would see in the clinic. We would give
2 them some diuretic and have them come back 48 hours
3 later, whereas this great drug, lifesaving and all
4 these kinds of things, only got tested because in
5 other countries they put them in the hospital and
6 treat them with one dose of Lasix.

7 So that I find very, very problematic. And
8 I think that the next study of a worsening heart
9 failure study should define all of these things,
10 but it wasn't done in this study. So I don't think
11 we can come any closer than to say, hypothesis-
12 generating. Very interesting. There seems to be
13 some biologic effect. And that's as close as we
14 can get.

15 DR. LINCOFF: All right. We've got about
16 15 minutes before the break, and I want to finish
17 up the questions because when we come back from the
18 break, we're going to be discussing questions only,
19 clarifying questions.

20 DR. RICH: I do have one question for
21 Melanie.

22 DR. RICH: Wait. Let him answer.

1 DR. LINCOFF: All right. I'll defer.

2 DR. LINCOFF: Okay. One answer.

3 DR. D'AGOSTINO: You could do something like
4 they did. And Bob was describing that you could
5 develop a scale where each of those components gets
6 points and so forth. Mortality is terrible.

7 The issue we're having here is that the
8 second and third are confounded by the second, that
9 once you get the heart failure and what's the trap
10 here, the worsening heart failure here, the trap
11 here is that that penalizes you for the rest of the
12 study. And it also impacts greatly on the third
13 component. It just wipes out the third component.
14 You're no longer measuring dyspnea. But you could
15 do those things very carefully in a composite
16 score.

17 DR. LINCOFF: All right. Clarifying
18 questions for the next 15 minutes. Dr. Rich?

19 DR. RICH: Okay. And this is to the FDA
20 reviewer, Melanie. You didn't talk about it in
21 your presentation today, but it was in your
22 briefing document on pages 19 and 20. So I'll just

1 briefly mention that you looked at outliers with
2 respect to -- actually, it started out by looking
3 at financial commitments.

4 But you make a statement here that if one
5 site was removed from the efficacy analysis, the
6 p-value for RELAX goes from .008 to .02, and that
7 this site had a large role in the statistical
8 strength of the outcome of the trial because many
9 cases of worsening heart failure came from this
10 site.

11 So you didn't bring it up today, and I'm
12 just curious. Do you still feel that way? Do you
13 think this is an issue or is this a non-issue?

14 DR. BLANK: It's an issue. I'm not sure how
15 big an issue as again, it goes to the possibility
16 that this investigator might have been biased.
17 It's there. I didn't want to make it a big issue.
18 Most of you have read the package. I figure you
19 can judge by yourselves how important an issue that
20 is.

21 DR. NATHWANI: May I respond to that? This
22 is clarifying.

1 DR. LINCOFF: Okay.

2 DR. NATHWANI: Can we have Dr. Severin?

3 DR. SEVERIN: Thomas Severin, clinical.

4 Regarding this particular site to which you just
5 referred, Dr. Blank, this is a site of one of our
6 investigators who's also a member of the executive
7 committee.

8 If we look at the patients he enrolled, yes,
9 this was a very large number. But if we look at
10 the treatment effect at his site, for example, for
11 worsening heart failure, which had a hazard ratio
12 of .54, that's exactly how it was in the overall
13 study.

14 We see no indication at all that there was
15 any bias at that site. And as you know, this study
16 site was also inspected by the FDA.

17 DR. LINCOFF: Ms. Leighton, you had a
18 question?

19 MS. LEIGHTON: My question is this. We like
20 to see patient-reported outcomes in clinical
21 trials, obviously. The patient community likes
22 that. But you're looking at an elderly population

1 here. And my question is this. If you're
2 depending on them for their reported
3 outcome -- hey, how's your breathing today -- you
4 may not always get an accurate answer.

5 Did you ask caregivers? Did you rely on
6 some objective data to back that up to assign that
7 dyspnea score?

8 DR. NATHWANI: Thank you. Dr. Severin?

9 DR. SEVERIN: Thank you. This is a very
10 good question related to this patient population.
11 So we had patient-reported measures, as we
12 discussed a lot about visual analog scale and the
13 Likert scale. And then the physician assessed
14 signs and symptoms, so dyspnea on exertion, edema,
15 rales.

16 So we have subjective measures from the
17 patients and also objective measures recorded by
18 the treating physicians. And the physicians were
19 trained how to assess the different severity
20 categories for each of these signs and symptoms,
21 and they also had in writing how the different
22 levels of severity were defined. So we had as well

1 subjective and objective components to describe the
2 patient's state at the time when the visit
3 occurred.

4 DR. LINCOFF: Dr. DeLemos?

5 DR. ORZA: Do you have anything that shows
6 how those line up?

7 DR. NATHWANI: Sorry? Dr. Severin?

8 DR. ORZA: The patient reported on the --

9 DR. NATHWANI: Could you just show how these
10 line up, the concordance between them?

11 DR. SEVERIN: Can we have the slide on signs
12 and symptoms again on the 48 hours, please?

13 So at the time where we had the dyspnea
14 assessments when the signs and symptoms were
15 carried out -- slide up, please -- we see here, for
16 example, at the end of the 48-hour infusion
17 significant improvements on dyspnea on exertion,
18 orthopnea, and edema and rales. And we carried out
19 these measurements at various time points according
20 to the visit schedule in the study. And where we
21 see improvements on the VAS and Likert scale and
22 most pronounced in the early time frame when the

1 infusion was running, we see significant
2 improvements on signs and symptoms.

3 DR. NATHWANI: To your specific question of
4 lining up, I'm going to invite Dr. Gwaltnoy, who
5 has done a correlation.

6 DR. GWALTNOY: Chad Gwaltnoy, ERT. Just to
7 add to that, there were correlations that were
8 calculated between the patient-reported dyspnea and
9 the clinician-reported measures that you just saw.
10 And as we would expect, there are relationships
11 that are between .2 and .5, which suggest overlap
12 but definitely not redundancy. We wouldn't expect
13 there to be redundancy in this case.

14 DR. LINCOFF: Dr. DeLemos? You're done?
15 Okay.

16 Dr. Sager, any more questions? You had had
17 your -- no?

18 Dr. Proschan, did you have any more? Go
19 ahead. We've gone through so many times.

20 DR. PROSCHAN: Yes. No, I don't think I had
21 anything other than what I've already said.

22 DR. LINCOFF: All right. Dr. D'Agostino,

1 did you have any others? I have your name here.

2 All right. Are there any other

3 than -- okay. Dr. Li?

4 DR. LI: One thing that I find a little bit
5 discrepant is that the serelaxin patients weighed
6 more, or didn't lose as much weight as the placebo.
7 And part of that may be because of the increased
8 diuretic use.

9 But if you think that they didn't lose as
10 much weight because they're more fluid-overloaded,
11 that's a little bit concerning. Can you talk about
12 that?

13 DR. NATHWANI: Certainly. Can I have slide
14 C-295 up? Slide up.

15 Just to say that the weight loss was
16 actually very similar between the two groups
17 despite the fact that there was much less diuretic
18 use in the serelaxin group. So we believe that is
19 the difference. Even in Pre-RELAX, the differences
20 were very, very similar between placebo and older
21 doses.

22 DR. LI: But at day 14, wasn't there a

1 statistically significant weight difference?

2 DR. NATHWANI: Dr. Lefkowitz will address
3 that.

4 DR. LEFKOWITZ: So at day 14, the difference
5 was 3.6 versus 3.0 kilograms in weight out to
6 day 14. Whether that may have been related to a
7 less diuretic dose that patients may have left on,
8 we can't really speculate. But that was the
9 observation.

10 DR. LINCOFF: Dr. Papademetriou?

11 DR. PAPADEMETRIOU: The mortality curves
12 divert after day 60, which is a little too late to
13 tie in to the treatment that happened 2 months
14 earlier. Do you have any good explanation why that
15 happened and why the sub-divergence in the curves
16 occurred? Any rational explanation from you?

17 DR. NATHWANI: Certainly. I'm going to
18 invite Dr. Severin to talk you through the curve.
19 But in our view, the hazard is pretty constant
20 throughout. It's a kind of illusion that it
21 diverged. Can I have slide 122 up? Slide up.

22 The difference appears very early and is

1 continuous. And the hazard at each of the time
2 points is fairly similar throughout the time frame.
3 So there doesn't appear to be a secondary or late
4 divergence in this particular curve, if that's what
5 your question was. Does that answer the question?

6 DR. PAPADEMETRIOU: I thought it became
7 statistically significant after 60 days.

8 DR. NATHWANI: I think that was more just an
9 accumulation of events as opposed to actually the
10 hazard at each of the time points. So we don't
11 believe that the curve is diverging as much as the
12 numbers became significant because of the
13 accumulation of events.

14 DR. SEVERIN: Just to add, the hazard ratio
15 at day 60 was already .7. But there were not
16 enough events for statistical significance at the
17 time point at day 60.

18 DR. LINCOFF: Other questions?

19 DR. NATHWANI: I have just one clarifying to
20 Dr. Rich, just a very quick --

21 DR. LINCOFF: Okay.

22 DR. NATHWANI: I just wanted to disagree

1 with the fact that you said that these are very
2 mild patients who are recruited into the hospital.
3 I think that in this study right now, these are
4 acute heart failure patients. They represent, as
5 Dr. Greenberg said, a proportion of patients that
6 were specifically targeted to study in the RELAX
7 program.

8 Many acute heart failure programs have
9 targeted blood pressures which are lower than this,
10 and these are the ones that most cardiologists are
11 probably more concerned about, more familiar with.

12 But this group of people was targeted
13 specifically because we have a mechanism here which
14 is vasoactive. We have seen drugs in the past fail
15 in acute heart failure because they have not been
16 targeted in the types of patients they're trying to
17 address.

18 That's why we had a higher proportion of
19 patients with HFPEF. That's why their in-hospital
20 mortality and out-of-hospital mortality is lower
21 than a follow-up acute heart failure spectrum that
22 may have lower blood pressures.

1 It's also why we try to protect the kidney
2 and to make sure that the lessons from other trials
3 didn't include lower blood pressures because there
4 was a risk that blood pressures would drop and that
5 could have adverse outcomes.

6 So we regard this as a targeted study in a
7 targeted group of people with an unmet need.
8 Clearly, these people are still sick. They still
9 die. They have in-hospital worsening. And so I
10 just wanted to just comment on the fact that we
11 don't believe that these are mild patients.

12 DR. RICH: Well, fair. I wasn't trying to
13 imply that they didn't warrant treatment. And I
14 wasn't trying to imply that none of them were in
15 hospitalization.

16 But I will tell you, the single physiologic
17 descriptor of this group that had the greatest
18 impact on me was not their blood pressure. It was
19 their resting heart rate of 82. And maybe I'm not
20 very experienced. I have not done this too long.
21 But when I take care of patients in our intensive
22 care unit in acute heart failure, the first

1 question I ask the resident is, what's the resting
2 heart rate? And when he says, 82, then I say, this
3 patient's going to do just fine.

4 So that is an outlier. Either these people
5 were not as sick as you're trying to sell, or
6 something about the reporting of the resting heart
7 rate was inaccurate because a resting heart rate of
8 82 in someone in acute pulmonary edema is
9 distinctly uncommon.

10 DR. NATHWANI: But again, just to point out
11 that there was a time difference between the time
12 of admission and the time of randomization. So
13 again, we should be careful about the fact that
14 they had elevated BNPs. They had radiographic
15 evidence that they were acutely unwell.

16 DR. RICH: Then I have to tell you, I just
17 don't know what we're talking about, honestly,
18 because every time we ask a question, the answer
19 changes a definition.

20 So maybe you have three baseline
21 demographics. Maybe you have a baseline
22 demographic of 30 days before, at randomization, at

1 Lasix, after the first 6 hours -- I don't know
2 because the data you give us changes every time we
3 ask the question.

4 So all I know is that I was told that the
5 baseline characteristic of this group was a resting
6 heart rate of 82. Now if you're going to say,
7 well, I didn't mean to say that, then fine. But I
8 have to tell you, that is a powerful physiologic
9 signal, and that speaks of wellness, not of
10 sickness, to me.

11 DR. LINCOFF: Are you finished with your
12 response, then?

13 DR. NATHWANI: We do have a response to
14 that.

15 DR. LEFKOWITZ: Can I just add one thing?
16 As Dr. Unger said, these patients were stabilized
17 before being randomized. And these patients had
18 11 percent mortality, all-cause mortality to
19 6 months; maybe not as high as all heart failure
20 patients, but that's quite a high risk.

21 DR. LINCOFF: Yes. In fairness, the sponsor
22 did point out that they had to have received a dose

1 of diuretics before they were randomized. And
2 baseline is always at the time of randomization.

3 All right. We are done with questions,
4 except now we're going to address the questions
5 when we come back.

6 So we'll now take a short 15-minute break.
7 Committee members, please remember there should be
8 no discussion of the meeting topic during the break
9 amongst yourselves or with any member of the
10 audience. We will resume at 3:15 p.m. to address
11 the questions.

12 (Whereupon, a recess was taken.)

13 **Questions to the Committee and Discussion**

14 DR. LINCOFF: So staying on time, let's get
15 started. We're going to now proceed with the
16 questions.

17 Now, it's been pointed out that a lot of
18 these questions we've already discussed. So we may
19 have relatively short answers to ones if there's no
20 dissension that we've answered them.

21 The advisory committee is asked to opine on
22 the approvability of serelaxin, a recombinant form

1 of relaxin-2 hormone, to improve the symptoms of
2 acute heart failure through reduction of the rate
3 of worsening of heart failure.

4 In support of the proposed indication, the
5 applicant submitted the results of a randomized,
6 double-blind, placebo-controlled combined phase 2/3
7 trial. The phase 2 component of the trial,
8 Pre-RELAX-AHF, was a dose-ranging trial and was
9 used to guide dose and endpoint selection for the
10 second stage of the trial.

11 The phase 3 component of the trial,
12 RELAX-AHF, was conducted in 1161 patients with
13 acute heart failure, systolic blood pressure above
14 125 millimeters of mercury at the time of
15 screening, and an estimated glomerular filtration
16 rate of 30 to 75 milliliters per minute per
17 1.73 meters squared.

18 RELAX-AHF had two primary endpoints, both of
19 which were intended to assess serelaxin's effect on
20 dyspnea: one, the area under the curve, AUC,
21 representative the change in patient-reported
22 dyspnea from baseline through day 5, as measured by

1 a 100-millimeter visual analog scale, VAS; and two,
2 moderately or markedly better dyspnea relative to
3 the start of the study drug at 6, 12, and 24 hours,
4 all three time points, as assessed using a 7-point
5 Likert scale.

6 The type I error was controlled at the two-
7 sided .05 level using the Hochberg approach.

8 Statistical significance would be declared if the
9 test of either endpoint was statistically
10 significant at the two-sided 0.025 level or if both
11 tests were significant at the two-sided 0.05 level.

12 Secondary endpoints included days alive
13 and out of the hospital through day 60 and
14 cardiovascular death or rehospitalization from
15 heart failure or renal failure through day 60.

16 The primary endpoint results are shown in
17 the table there below. I'm not going to read them.

18 According to the prespecified analytic
19 approach, a two-sample t-test, the trial won on the
20 VAS-AUC primary dyspnea endpoint.

21 So question a. "This endpoint incorporated
22 an imputation rule that assigned subjects with

1 worsening heart failure the worst observed VAS
2 score, zero, for the remainder of the 5-day
3 observation period. Was this imputation rule
4 reasonable?"

5 Now, we've had a lot of discussion on this,
6 so maybe we could just try to focus on, is the
7 consensus yes? Is the consensus no, as it seems
8 most of the discussion? SO who'd like to start?
9 Dr. Rich?

10 DR. RICH: I say no. I don't want to beat
11 the dead horse here, but to give the same zero rank
12 to someone who got 40 milligrams of Lasix one time
13 early in the hospitalization as to someone who died
14 just is too inequitable.

15 DR. LINCOFF: Dr. Scott?

16 DR. SCOTT: So I say yes because if you
17 don't give it zero, whatever score comes
18 afterwards -- and I think people seem to want to
19 give it just the score for the
20 worsening -- whatever score you give afterwards is
21 confounded by the rescue medication you gave. And
22 you don't know whether the new score is as a result

1 of the rescue medication or not.

2 DR. LINCOFF: Other opinions? Dr. Proschan?

3 DR. PROSCHAN: I think there's no doubt that
4 for death, that's the appropriate thing to do.
5 They would have been out of breath if you had
6 measured them again anyway.

7 (Laughter.)

8 DR. PROSCHAN: It's difficult. As you say,
9 it is confounded by the rescue medication, whatever
10 happens after that. But it does seem to have had a
11 big effect, and I think that was not anticipated to
12 have as big an effect. So I think it is reasonable
13 in that situation to look at these sensitivity
14 analyses.

15 Now, I do like the idea that using the worst
16 rank avoids the problem of assigning an arbitrary
17 score. But nonetheless, it did have a big effect,
18 and I think we have to try and take that into
19 consideration, which is going to have to be in a
20 subjective way, I think.

21 DR. LINCOFF: So does that mean you think
22 this imputation rule, not the sensitivity analyses

1 or the log rank -- do you think this imputation
2 rule was reasonable to be used?

3 DR. PROSCHAN: I think it's one of many ones
4 that I would try. So yes, I would say it's not
5 completely unreasonable. It turned out to be
6 highly influential.

7 DR. LINCOFF: Dr. DeLemos?

8 DR. PROSCHAN: By the way, that answer was
9 at least as succinct as the ones I was hearing from
10 the company today.

11 (Laughter.)

12 DR. PROSCHAN: I'd like to agree with
13 Dr. Packer when he said that he felt like a
14 magician. I felt also like he was a magician, and
15 some of the other presentations were magical.

16 DR. LINCOFF: All right. Wait.
17 Dr. DeLemos?

18 DR. DELEMONS: I think it's problematic. The
19 bigger problem is forcing the hard components into
20 the softest component of the endpoint, to me,
21 rather than the other way around. And I think it
22 ends up being a mistake for this trial. What it

1 means going forward is more complicated, but I
2 think had they gone with something more
3 straightforward, it would have been a positive
4 study, not a neutral study.

5 DR. LINCOFF: Dr. D'Agostino?

6 DR. D'AGOSTINO: If you force me for a
7 yes/no, I would say no. And the reason is because
8 I think it had a tremendous impact on it, and I
9 don't think it ties clearly into the endpoint it is
10 supposed to be measuring, the dyspnea and so forth.
11 So I think we have a situation where we end up with
12 a score that we aren't really clear what it is in
13 fact measuring.

14 Just let me throw out, in terms of the
15 sensitivity analysis, I've done a lot of work with
16 visual analog scales and things of this nature.
17 You usually don't see them changing drastically as
18 you try different possibilities. And the thing
19 that's most striking is when you see the FDA
20 presentation, where you didn't have this
21 penalizing, you suddenly lose all your
22 significance.

1 DR. LINCOFF: Dr. Sager?

2 DR. SAGER: I also would say no. I think
3 it's non-physiologic the way it was done, and was
4 too big a penalty for having a heart failure
5 worsening.

6 Then separately, I think the way the heart
7 failure worsening was done was too subjective and a
8 future study, hopefully, because I think that there
9 are results that are promising, will do it in a
10 more specific and defined manner.

11 DR. LINCOFF: From my standpoint, I'm
12 sympathetic with the idea that you couldn't just
13 have a dyspnea score because obviously that would
14 be affected, as we've said, by rescue therapies.

15 I actually am not as bothered by the
16 decision of whether or not a patient had worsening
17 heart failure. I think the effect was so
18 substantial, the treatment effect, that even if
19 there was some noise in that, that it was probably
20 real.

21 But I think that this construction of an
22 endpoint with its drastic imputation rule ended up

1 overwhelming everything else with this one
2 variable. So I think as a combined endpoint,
3 trying to address the entire issue, I don't think
4 it was a reasonable rule.

5 Dr. Lewis?

6 DR. LEWIS: I just want to comment, too,
7 that we have to put this in the context that this
8 is a single trial that didn't achieve the
9 prespecified p-value for a single trial. And there
10 are ways around that, but this contributes to you
11 being less willing to accept the ways around it.

12 Then the disconnect with the
13 rehospitalization makes the 180 day mortality not
14 persuade you that that's something that would make
15 you not want the rule to stand for the appropriate
16 p-value for a single trial.

17 DR. LINCOFF: All right. I think I'll
18 summarize this as most, the majority, felt that
19 this was not a reasonable imputation rule, although
20 there is some need for taking into account the
21 effect of the heart failure events on dyspnea.

22 Next. "Was the observed effect really an

1 effect on dyspnea or more indicative of an effect
2 on worsening heart failure?" Well, as you answer
3 that, also answer these other two.

4 "If you think that this is an effect on
5 dyspnea, the effect might be described as a mean
6 treatment effect of 3.7 millimeters on a 100-
7 millimeter scale maintained over 5 days. Is this a
8 reasonable description of the treatment effect?
9 For example, is the effect uniform over 5 days?

10 "If you think this finding related to
11 worsening heart failure, what was that effect?"

12 So as you answer, first tell me what you
13 think it was, and then answer the relevant part of
14 the question. Who wants to go first?

15 Dr. Papademetriou?

16 DR. PAPADEMETRIOU: I take this as meaning
17 an effect on worsening heart failure. And by the
18 way we know that the medication works, it makes
19 sense to be that way. As a vasodilator, it has an
20 increased release of nitric oxide. It improves
21 peripheral resistance. It improves cell wet
22 pressures. So it improves all the expressions of

1 worsening heart failure. That's the way I see it.

2 DR. LINCOFF: So I think the question is
3 meant, what do you think the magnitude? What was
4 that effect, rather than the mechanism. Do you
5 want to speculate on that or speak to that?

6 DR. PAPADEMETRIOU: Well, the magnitude is
7 certainly small and it cannot be -- on the scale
8 used, it's fairly small. It's 3.7.

9 DR. LINCOFF: Okay. Who else? Dr. Rich?

10 DR. RICH: No. So I do not think this was
11 an effect on dyspnea. I think the best measure of
12 the effect on dyspnea was the Likert scale. I
13 think it's simple. It really describes, are you
14 better or are you worse. The answer was, neither.
15 And so I don't think it had an effect on dyspnea.

16 I think what they did observe was an effect
17 on worsening heart failure, probably real, hard to
18 define simply because it was defined so many
19 different ways, and there's so many arbitrary
20 components to it. But I think there was a real
21 effect. And if they can, in a subsequent trial,
22 better design it so we know the magnitude of that

1 treatment effect, that would be very, very helpful.

2 DR. LINCOFF: Dr. Sager?

3 DR. SAGER: Yes. I would say that the
4 effect that was observed here with the AUC or the
5 mean difference was an effect largely on some
6 measure of heart failure. And I believe the drug
7 likely does have a positive effect on heart failure
8 recurrence, as well as we also saw some objective
9 data on hospital stays.

10 I have no idea how to interpret the
11 3.7-millimeter change. Look at the --

12 DR. LINCOFF: Well, if you don't know it's
13 dyspnea, you don't have to. You just have to talk
14 to the effect on worsening heart failure.

15 DR. SAGER: No. But the next
16 question -- we're getting there anyway -- what was
17 the effect? Because it is part II, so I thought
18 I'd just jump ahead. I just don't know how to
19 integrate that in, and I couldn't find things in
20 the literature, and I just don't know there's
21 enough data out there to really understand what
22 that means.

1 But I really look forward to a future trial
2 that's really concentrated more on what Dr. Packer
3 said in the beginning, which is heart failure
4 worsening.

5 DR. LINCOFF: Given the data from this
6 trial, what do you think was the effect on heart
7 failure, the magnitude of the treatment effect?
8 There was heart failure data as a piece of this, or
9 worsening heart failure.

10 DR. SAGER: It's hard to evaluate because of
11 how the data was collected. But I think there's a
12 small effect.

13 DR. LINCOFF: Others? Dr. Proschan?

14 (Dr. Papademetriou speaks.)

15 DR. PAPADEMETRIOU: We don't have any
16 measures of how to quantitate the effect on
17 worsening heart failure. We don't have wedge
18 pressures. We know from previous studies that this
19 improved, and we don't have measures of peripheral
20 resistance other than the objective improvement of
21 dyspnea.

22 DR. LINCOFF: Dr. Proschan?

1 DR. PROSCHAN: One of the intriguing things,
2 I think, that I thought merited a separate question
3 by itself was the cardiovascular mortality, which
4 could reflect the effect on heart failure, if it's
5 real.

6 I still find that intriguing because when
7 they presented the survival plot, even though it
8 was sort of a second thought, really, it did look
9 suggestive. And I thought it was interesting that
10 when they looked at the -- what was it
11 called -- the pretrial, earlier, the phase 2 trial,
12 when they combined all of those arms versus
13 placebo, it also was a significant p-value in the
14 same direction.

15 So I don't think it can be just easily
16 dismissed. And I don't know how to evaluate
17 whether that is a reasonable outcome for 48 hours
18 of treatment. But I don't think you can completely
19 dismiss it.

20 DR. LINCOFF: Dr. D'Agostino?

21 DR. D'AGOSTINO: I'm not sure I've got a
22 good handle on this. But the sponsor did present

1 two slides, on page 63 and page 81. In 63, they
2 actually plotted the 5-day scores and one could
3 look at the difference on that, and should you be
4 dividing that difference by some kind of standard
5 deviation to get the effect, it's a standard way of
6 doing it, but it's not a very strikingly big
7 difference in terms of the scale that you're
8 dealing with.

9 Then on the slide 81 where they did the
10 time-to-event analysis and they get a hazard ratio
11 of .53, if we want to identify places where effect
12 was attempted by the sponsor, these are, I think,
13 two of the places.

14 DR. LINCOFF: So you're talking regarding
15 the worsening heart failure?

16 DR. D'AGOSTINO: Yes. Exactly. I'm sorry,
17 it's the worsening heart failure I'm addressing.

18 DR. LINCOFF: Who else? Dr. DeLemos?

19 DR. DELEMOS: Yes. I agree. I think that
20 there's no effect at all on dyspnea, but a
21 potentially substantial effect on worsening heart
22 failure that is hard to tell because the endpoint

1 has had some challenges. But I'm encouraged that
2 the effect, the relative effect, seems to be
3 consistent whether you look at small or large
4 diuretic doses, escalation of vasodilators, or even
5 pressors or ventilation.

6 Then rehospitalization data and the
7 biomarker data are very favorable as well. You've
8 got reduction in injury markers and neurohormonal
9 markers. And I think most encouraging is the renal
10 markers. You've got shortened hospital stay, yet
11 renal markers look better.

12 So I think that there's potentially a
13 substantial effect on worsening heart failure.
14 It's just hard to say.

15 DR. LINCOFF: Who else? Dr. Orza?

16 DR. ORZA: I think they set out to measure
17 dyspnea, and they did measure dyspnea. They had
18 two different scales. They also had the
19 confirmation from the physician, and they said
20 there was good concordance between those.

21 So I think they did successfully measure the
22 effect on dyspnea, and there isn't much of one.

1 There's none on the Likert scale, and what we've
2 got on the VAS is something that amounts to the
3 difference between 65 and 68 or 65 and 69. And I
4 don't know that the patient experience of that
5 would be a big difference in their breathlessness.

6 It doesn't tell us anything about any of the
7 other symptoms of heart failure because they were
8 just focused on dyspnea. And I don't know what to
9 think about worsening heart failure because I don't
10 think there was a very clear operational definition
11 of what that was or very clear ascertainment of
12 whether or not it was in fact worsening.

13 DR. LINCOFF: Dr. Lewis?

14 DR. LEWIS: So actually, and I might have
15 misunderstood when I read the briefing document,
16 but they didn't use the bottom part of the Likert
17 scale. I like the Likert scale and thought it
18 actually was better; a patient would be better able
19 to quantitate how they felt. So I agreed with Dr.
20 Rich on that.

21 If you use the bottom half where they could
22 say they got worse, they actually won on the Likert

1 scale. It was just because it was designed to only
2 look at it going one direction. So I actually
3 think it's conceivable the drug does make patients
4 less dyspneic.

5 DR. DELEMOS: They imputed that as well. In
6 that analysis, I believe they imputed worsening
7 heart failure to the worst score you can get on the
8 Likert. So that analysis has the same flaw.

9 DR. SAGER: That's correct.

10 DR. LEWIS: Good pickup. Okay. But anyhow,
11 even it was, 3.7 on a 100 scale in any patient with
12 all kinds of different math literacies, unanchored,
13 and the confounding effects, I don't know what to
14 make of 3.7.

15 DR. LINCOFF: Dr. Unger?

16 DR. UNGER: Yes. But I might add that the
17 imputation is more reasonable there because you're
18 just taking all those patients and putting them in
19 the bottom category, whatever was markedly worse.

20 DR. LEWIS: Yes. It wasn't as big a
21 mathematical --

22 DR. UNGER: Right. It didn't have as much

1 of an effect.

2 DR. TEMPLE: But does it give them the worst
3 case? I mean, the imputation gives them the worst
4 possible score. Right?

5 DR. LINCOFF: Yes. Well, but deterioration
6 doesn't have to be they were falling apart in
7 pulmonary edema. It just had --

8 DR. TEMPLE: Well, it gives them the worst
9 score for the whole rest of the whole thing.

10 DR. LINCOFF: The whole rest, yes.

11 DR. TEMPLE: So if they get sick at day 1,
12 this gives them a zero or worst case all the way to
13 day 5, no matter how they feel.

14 DR. LINCOFF: Well, the Likert was only
15 done --

16 DR. LEWIS: But it's a smaller range.

17 DR. LINCOFF: A shorter range over the first
18 day. All right. The Likert was over the first
19 day.

20 DR. TEMPLE: No, no. The Likert, where they
21 won by looking at the worsening, that's a 5-day
22 analysis.

1 DR. LEWIS: Yes.

2 DR. LINCOFF: You're right. You're right.

3 DR. TEMPLE: I think it is.

4 DR. LEWIS: Do you want to clarify?

5 DR. LINCOFF: Yes. Tell us only about the
6 Likert.

7 DR. NATHWANI: Yes. The Likert was a
8 24-hour. We did measure it out to 5 days. But on
9 the worsening, we did have an effect at the 24-hour
10 time point. But it's also a 5-day analysis. Slide
11 up, C-119.

12 If you look at the day 1 analysis, this is
13 the bottom half of the scale. The white bar is
14 placebo, green bar is serelaxin. Okay. So yes,
15 this whole graph was 5 days, but it was actually a
16 24-hour scale. Thank you.

17 DR. LINCOFF: Other comments about this
18 question?

19 (No response.)

20 DR. LINCOFF: All right. I'll make mine
21 before I summarize. I agree that I think this
22 is -- the findings relate to worsening heart

1 failure. The effect of dyspnea is overwhelmed by
2 the effect on heart failure.

3 I'm actually not as bothered -- I don't
4 think it was rigorous to have collected that
5 endpoint as they did, but I think the magnitude of
6 the treatment effect, which looks to be about a
7 50 percent risk reduction, is so high that there
8 certainly is an effect.

9 Most of those effects, though, we can't
10 assess whether or not they were clinically major
11 events that were prevented. Most, I think, were
12 not; they could have been treated relatively
13 simply.

14 That doesn't change the fact, I think, that
15 the drug does reduce worsening heart failure. It
16 is biologically active, and in some proportion of
17 patients it will prevent a serious event that has
18 consequences.

19 I think that most here -- it can be
20 summarized -- felt that the effect seen in the
21 primary endpoint is an effect of preventing
22 worsening heart failure, the magnitude of which

1 there's some heterogeneity of how comfortable we
2 are talking about whether it's a large magnitude or
3 a small magnitude within the group.

4 I think c is pretty much -- unless somebody
5 has any other -- item c, "How do you interpret the
6 clinical significance of this treatment effect," I
7 think we've had in our answers. But if anyone else
8 wants to address this specifically before we move
9 on?

10 DR. DELEMOS: Can I ask a question? If
11 somebody came to the FDA with a drug for acute
12 decompensated heart failure, that their indication
13 was to reduce the length of hospitalization, and
14 they did that with a safe signal with regard to
15 renal function and 180-day mortality, are we done?

16 Because to me, that's the goal, is forget
17 all this objective stuff that we can't measure.
18 You've got a blinded drug that shortens a hospital
19 stay.

20 DR. TEMPLE: Yes. We would look to see
21 whether that was the primary endpoint or whether
22 the primary endpoint was something else. And this

1 is one of five or six interesting things. You
2 know, all that. Right.

3 DR. DELEMOS: Is a reasonable --

4 DR. TEMPLE: A good endpoint. Yes. Turn
5 your mike on.

6 DR. DELEMOS: Is a good endpoint reasonable
7 from your standpoint?

8 DR. TEMPLE: Yes. I think we would think
9 decreased duration of -- there's a whole variety of
10 endpoints that we would think, along with help from
11 people like you guys, might be considered benefits.
12 Sure.

13 DR. LINCOFF: For the transcript, that was
14 Dr. DeLemos.

15 Any other comments? Dr. Proschan?

16 DR. PROSCHAN: But length of hospital stay,
17 to me that seems like -- what determines that? Is
18 that really a hard and fast criteria? That seems
19 kind of soft to me.

20 DR. LINCOFF: In a blinded trial? It's as
21 relevant as any other endpoint.

22 DR. UNGER: Yes. We'd be very concerned

1 about being able to build it. That would be the
2 thing.

3 DR. LINCOFF: Dr. Lewis?

4 DR. LEWIS: I will say that I also want to
5 echo that I do think the fact that they do not
6 appear to have a worsening renal function signal,
7 again hypothesis-generating, but it's very
8 interesting with this drug since most of the time
9 when we diurese these patients, we end up getting
10 in trouble with that.

11 I would argue, however, that I don't think
12 there's any evidence that cystatin C is better than
13 creatinine or eGFR or anything else. The sponsor
14 had commented on that. But I don't think it's bad;
15 I just don't think it's better.

16 DR. LINCOFF: Anyone else want to comment?

17 (No response.)

18 DR. LINCOFF: Okay. Next question.

19 "Please discuss any confirmatory evidence
20 for the effect you identified in question 1." Now,
21 there's several parts to this, so a, "The other
22 primary endpoint assessed dyspnea by a respond

1 analysis over the first day, assessments at
2 hours 6, 12, and 24. Why are its results to
3 discrepant with the AUC for the VAS?"

4 He who's laughing loudest must answer first.
5 Dr. Rich?

6 DR. RICH: Again, I don't know that we have
7 the answer other than a lot of opinions. And I can
8 just speak for myself. I think Likert represents
9 the real dyspnea, and it said there was no
10 different. And the area under the curve I think
11 was massaged so much that it didn't tell me what I
12 was really after.

13 So that's why I'm laughing. I don't know if
14 we can answer that.

15 DR. LINCOFF: I'll offer a theory. This
16 only took into effect the people who improved.
17 They had already received diuretics, so they were
18 improved to some extent. It was completely
19 insensitive to the people who deteriorated.

20 Since we believe, based upon the other
21 question, that most of the effect was on prevention
22 of deterioration, that is, recurrent heart failure,

1 you could argue that there was no way that these
2 components of that endpoint would have detected
3 what was actually the only effect.

4 Dr. Sager?

5 DR. SAGER: Yes, I agree. And we've seen
6 the data with worsening on the Likert scale. So if
7 this was all combined into one scale, I suspect it
8 actually would have been positive.

9 DR. LINCOFF: Anyone else want to comment?
10 No? All right. That was easy. Oh, yes,
11 Dr. D'Agostino?

12 DR. D'AGOSTINO: I don't know where to come
13 in, but I feel embarrassed that we don't have
14 something that talks about the mortality finding.

15 DR. LINCOFF: We'll do that in c. How about
16 that?

17 DR. D'AGOSTINO: "Are there
18 supportive" -- well, it's from -- "or elsewhere."
19 Is that it?

20 DR. LINCOFF: All right. So we will
21 prospectively plan to talk about that under c.

22 All right, b. Oh, do I want to summarize?

1 I think most people agree that this endpoint was
2 not able to detect because it only was responsive
3 to improvements and didn't deal with the
4 deteriorations.

5 Dr. Temple?

6 DR. TEMPLE: What about the possibility that
7 there was no imputation in that scale and there was
8 in the other? That's related to deterioration, of
9 course. But it also was the raw scores, which were
10 unchanged in both scales.

11 DR. LINCOFF: Dr. Orza?

12 DR. ORZA: I would just add that I feel like
13 we can't rule out the possibility that this test
14 actually was better than the other one. I don't
15 think we can tell which one did a better job for
16 us.

17 DR. LINCOFF: You know, it's almost as if,
18 with these two endpoints, one endpoint was designed
19 to look at improvement and one endpoint was
20 designed to look at deterioration. I know the
21 second endpoint wasn't designed that way, but
22 that's in effect what it did because it was

1 absolutely overwhelmed by the deteriorations
2 because of the imputation rule. So we can say
3 there's no improvement, but we can't say that
4 there's not less deterioration.

5 All right, 2.b. "Having rejected the null
6 hypothesis for one of its two primary endpoints at
7 p less than 0.025, the study overall was
8 'successful.' Please discuss whether RELAX-AHF has
9 other reliable findings for --

10 "i. The prespecified analytic plan's two
11 secondary endpoints, days alive and out of the
12 hospital through day 60 and CV death or
13 rehospitalization for heart failure or renal
14 failure through day 60.

15 "ii. Other observations from the study."
16 And I guess this is where we could bring in
17 mortality.

18 So what do we think about these other
19 endpoints? Who wants to start? Dr. Sager?

20 DR. SAGER: Well, I think there is real
21 potential for this drug to improve worsening of
22 heart failure, potentially shorten hospital stay,

1 potentially favorably improve both renal and
2 troponin biomarkers.

3 I think this is a lot of things here that
4 are hypothesis-generating. I hope it will be
5 investigated in the future because I think this has
6 real potential promise. But I don't think any of
7 them go beyond hypothesis-generating.

8 I'm not sure what to make of the 180-day
9 difference in mortality. Those curves do
10 look -- they even continue to separate somewhat
11 over time. It's hard for me to think on a
12 mechanistic level about how that could potentially
13 happen. Obviously, an interesting finding.

14 DR. LINCOFF: Dr. Rich?

15 DR. RICH: I'm troubled because I look at
16 these secondary endpoints as being supportive of
17 the primary endpoint, and everything should be
18 consistent. And if the primary endpoints and when
19 the secondary are not, I will forgive it. But if
20 the primary endpoints will win, the secondary are
21 mp, I forgive it. But if primary doesn't win and
22 the secondary doesn't win, then I think it's

1 telling me the truth.

2 So when I look at two primary
3 endpoints -- one worked and one didn't -- and
4 you're trying to say which was telling me the
5 truth, and I look at the secondary endpoints and I
6 see no difference, I tend to believe that there was
7 no difference and that the other one just wasn't
8 really representative. And that's still what I'm
9 coming away with here.

10 We can talk about 180. But come on, we talk
11 about 30-day readmission rate and 60-day
12 readmission rate. And I've never heard before that
13 there's this honeymoon period where you're admitted
14 to the hospital for heart failure and treated and
15 then sent home. And then you do great, and then
16 all of a sudden you fall apart 6 months later.

17 So that's a different issue which we can
18 talk about and what the company can decide about in
19 terms of investigating. But in terms of
20 consistency here, I think the consistent message
21 I'm getting is that whatever treatment effect there
22 was, it wasn't very strong. And that's why these

1 other endpoints don't show it.

2 DR. LINCOFF: Dr. Proschan first? I think
3 you had --

4 DR. PROSCHAN: It says, "Please discuss
5 whether RELAX-AHF has other reliable findings."
6 One thing that I do not find reliable is having
7 that analysis where you combine the p-values from
8 the Pre-RELAX with the RELAX.

9 To me, that's just crazy. That's just
10 insane because if you had seen a p-value of .5,
11 there's no way you would have combined them. You
12 combined them because you saw, oh, if we combine
13 them, that'll work here.

14 So I think that does not make any sense.
15 But as I say, I do think it's intriguing, that 180-
16 day mortality result. With cardiovascular
17 mortality, I do think that that's intriguing. And
18 I don't think it's by itself sufficient, but I do
19 think that that is supportive.

20 I've looked at a lot of survival curves, and
21 you can somewhat look -- in some cases you can tell
22 why it came out statistically significant. That

1 does look like the kind of curves that there really
2 is a difference. And the fact that when they went
3 back to the Pre-RELAX, they saw a similar kind of
4 thing, to me makes it more than just a passing
5 thought.

6 DR. LINCOFF: Dr. Papademetriou?

7 DR. PAPADEMETRIOU: Yes. Treatment with
8 serelaxin almost fulfilled the two reasons why we
9 treat patients: to make them feel better and to
10 make them live longer -- but not quite.

11 I'm a little uncomfortable with the fact
12 that it only met one of the two primary endpoints,
13 and that that effect on dyspnea was marginal, was
14 small. And the effect on -- probably the other
15 fact, the worsening heart failure, is not
16 quantifiable. We cannot quantitate it and give
17 you the number and say, this is how much it
18 improved it.

19 What is intriguing to me and of interest,
20 and I think of a lot of significance to our
21 patients, is the improvement in survival. However,
22 that occurred late and is not easy to tie it to the

1 treatment that occurred during hospitalization.

2 And that's what I have difficulty with.

3 DR. LINCOFF: Dr. D'Agostino?

4 DR. D'AGOSTINO: Yes. I have similar
5 feelings. I don't think that the 60 days adds a
6 tremendous amount. And I really am bothered by the
7 180 days, just how to interpret that. I'd be very
8 hard put to say that it's somehow rather logical
9 from this short treatment period.

10 So in answer to your questions, I don't find
11 internal evidence with the 60 days, and that
12 doesn't convince me that they have an
13 overwhelmingly positive study. But I am bothered
14 by this 180 days mortality.

15 DR. LINCOFF: From my standpoint, I'm not
16 bothered by the lack of benefit at 60 days. I
17 think this drug works during the hospitalization
18 period, and I don't think that degrades the
19 evidence supporting the prevention of worsening
20 heart failure.

21 I don't actually buy the mortality at
22 180 days. I think that this is an example of like

1 ISIS-2 with no benefit of aspirin in patients born
2 under the astrologic signs of Libra and Gemini.
3 And if another study shows it, then that's wrong.
4 But I think until and unless another study shows
5 it, it's neither here nor there and it doesn't
6 support or detract from the results.

7 I think other observations from the study,
8 we can point to the things like hospital stay and
9 ICU stay and some of the biomarkers that I think
10 are supportive of the idea that the drug reduces
11 the incidence of worsening heart failure. So I
12 think that it's consistent, and these other
13 endpoints don't detract from that.

14 Are there any other comments? Dr. Orza?

15 DR. ORZA: I think the potential here to
16 really address things that patients care
17 about -- so to reduce their symptoms, to reduce
18 their time in the hospital, to improve their
19 experience in the hospital, to prevent them from
20 being rehospitalized for a longer period of
21 time -- all of those would be wonderful things.

22 I think we have massaged the data so many

1 different ways and we've done so many different
2 tests without adjusting that, it's just too hard to
3 figure out whether these are spurious kinds of
4 findings. So I agree with the notion that this is
5 very good for hypothesis generation, but not much
6 more than that.

7 I don't completely understand -- because
8 this was compared to placebo, I don't understand
9 how well it would stack up against the other things
10 we could do for people in this situation to prevent
11 their worsening of heart failure, whether this is
12 really a novel thing.

13 DR. LINCOFF: Dr. D'Agostino?

14 DR. D'AGOSTINO: Just to clarify, when I was
15 saying about the 60-day results, I wasn't trying to
16 ponder deeply into -- I was looking more at the
17 p-values that corresponded. There wasn't
18 supportive evidence in the usual statistics
19 evaluation.

20 DR. LINCOFF: Dr. DeLemos?

21 DR. DELEMOS: Yes. I would only say I agree
22 with the comments about mortality, but do think

1 that it's plausible, given that this drug seems to
2 be different from a safety standpoint, particularly
3 for renal safety, and the cardiac injury signal
4 also potentially could have legacy effects that
5 last beyond the infusion period.

6 I think it would be important in continued
7 development to take a look at these biomarkers
8 remote from the infusion, and if that's not been
9 done already, to see whether there are legacy
10 effects on these markers that might associate with
11 a mortality benefit.

12 DR. LINCOFF: Okay. Then to summarize, I'd
13 say that the 60-day isn't supportive or detracting
14 from the findings at 30 days, and that the longer-
15 term mortality, some people are willing to give it
16 the benefit of the doubt and others -- nobody
17 considers it conclusive. And it's hypothesis-
18 generating.

19 Then c, "Are there supportive findings from
20 Pre-RELAX-AHF or elsewhere?"

21 Yes, Dr. Papademetriou?

22 DR. PAPADEMETRIOU: I think the supportive

1 evidence from Pre-RELAX-AHF are pretty good. From
2 what I recall from reading the document, it
3 resulted in improvement in wedge pressures in the
4 peripheral resistance and an increase in cardiac
5 output. And these are all good things.

6 The problems, they don't always correlate
7 with improvement in symptoms or mortality.
8 However, I think this got good supportive evidence
9 and should bear it in mind as we consider this drug
10 for further development.

11 Along with the other evidence, we have seen
12 from the RELAX trial, the preservation of renal
13 function and decrease in the biomarkers, I think
14 that these are good signals and give the medication
15 more credibility to be studied further.

16 DR. LINCOFF: Anyone else? Dr. D'Agostino?

17 DR. D'AGOSTINO: I do think that Pre-RELAX
18 is in a positive direction and so forth. But when
19 you're saying supportive evidence, supportive
20 findings, I don't think, and I believe it was
21 already mentioned, that somehow or other you can
22 tie the two studies together and come up with

1 something that hits you with significance. And
2 this I think is the appropriate place in the
3 meeting to say that.

4 DR. LINCOFF: Who else?

5 (No response.)

6 DR. LINCOFF: Okay. Then I guess the
7 summary is that it doesn't add much. It's
8 consistent but doesn't add much to the findings of
9 RELAX.

10 All right. So this is it. For the voting
11 question, we will be using an electronic voting
12 system for this meeting. Once we begin the vote,
13 the buttons will start flashing and will continue
14 to flash even after you have entered your vote.

15 Please press the button firmly that
16 corresponds to your vote. If you are unsure of
17 your vote or you wish to change your vote, you may
18 press the corresponding button until the vote is
19 closed.

20 After everyone has completed their vote, the
21 vote will be locked in. The vote will then be
22 displayed on the screen. The DFO will read the

1 vote from the screen into the record.

2 Next, we will go around the room, and each
3 individual who voted will state their name and
4 their vote into the record. You can also state the
5 reason why you voted as you did. We will continue
6 in the same manner until all questions have been
7 answered or discussed.

8 Are there any other questions or discussion
9 points before we actually go to the vote?

10 (No response.)

11 DR. LINCOFF: Okay. If there's no further
12 discussion on this question, we will now begin the
13 voting process. Please press the button on your
14 microphone that corresponds to your vote. You will
15 have approximately 20 seconds to vote.

16 Please press the button firmly. After you
17 have made your selection, the light may continue to
18 flash. If you are unsure of your vote or you wish
19 to change your vote, please press the corresponding
20 button again. The question is, should serelaxin be
21 approved for the treatment of acute heart failure?

22 (Vote taken.)

1 MS. TOLIVER: The vote is as follows: zero
2 yes votes, 11 no votes, zero abstentions, zero
3 no votes.

4 DR. LINCOFF: Okay. We'll go around the
5 table, and I think we'll start on the left.

6 Dr. D'Agostino?

7 DR. D'AGOSTINO: I voted no. Ralph
8 D'Agostino. I'm going to mention the name. Ralph
9 D'Agostino. I voted no, I think on two counts.
10 One is the confusion in terms of what was being
11 measured in the study.

12 Even given that, and all the discussion
13 around the appropriate endpoint, and the over-
14 weighting of the worsening of heart failure, and
15 trying to interpret it -- but even if you grant all
16 of that, the level of significance that was
17 attained still doesn't make the usual mark in terms
18 of a single study. And just to put in the record,
19 it's .00125, I guess.

20 DR. PROSCHAN: Michael Proshan. I also
21 voted no for similar reasons, really. I think you
22 have to have really strong evidence to approve it

1 based on one trial, and I just don't buy this
2 combining the two trials, when you see things you
3 like, combining those p-values under that scenario.

4 I think there have been enough questions
5 raised about the worsening heart failure
6 influencing the dyspnea and so forth. But for me,
7 the main consideration is that there's no way that
8 it meets that level of evidence.

9 It reminds me of no matter who's president,
10 the opposing party can always find statistics that
11 support the fact that the economy is doing poorly
12 because there's so many indicators that you can
13 pick some that are doing poorly.

14 Likewise here. If you're allowed to rummage
15 through all the different possibilities, you can
16 come up with things that make it look like
17 everything's going great. So I was not convinced.

18 DR. LEWIS: Hi. This is Julia Lewis. I do
19 think the economy is doing poorly; I just want to
20 say that.

21 (Laughter.)

22 DR. LEWIS: So I think it's a very

1 interesting compound. I actually share a lot of
2 the enthusiasm that's been expressed for the
3 hypothesis-generating data we've seen, especially
4 if we can make these patients with acute heart
5 failure feel and do better in the absence of
6 injuring their kidney or things of that sort.

7 I think, unfortunately -- and I think this
8 was a really hard study to design, and I hope we've
9 given them some better information about it -- but
10 I think this is very difficult to not confound it.

11 I don't want the people who -- I don't know
12 who wrote the original protocol. I know there were
13 two companies involved. But I think it was a good
14 stab at a protocol. I think that it is a very
15 complex thing to measure.

16 However, I do not think they have compelling
17 evidence that would warrant its use in the American
18 public at this time. And I also actually do still
19 have some safety concerns, so I think it's also
20 very good that we do see it in a larger population
21 of patients.

22 I remain worried about the lower end of that

1 blood pressure group having those big drops in
2 blood pressure, what the impact of that will be on
3 their outcomes.

4 DR. PAPADEMETRIOU: Actually, I think the
5 economy is doing better, at least here in
6 Washington.

7 (Laughter.)

8 DR. PAPADEMETRIOU: But that being said, I
9 wish I had enough data, as much as we have for the
10 economy, to vote yes for this serelaxin. But the
11 evidence is not there. I think the primary
12 endpoint chosen showed a very small change in
13 improvement even if we accept and reject all the
14 confounders.

15 I wish we had more evidence that the
16 mortality difference we've seen can be attributed
17 to the medication. And that direction, I think,
18 should be one that should be investigated in the
19 future.

20 I think this drug indeed has potential
21 because we don't have any signals of doing worse or
22 of hurting the patients. And the signals we have

1 are on the positive side, but they are not enough
2 for approval, at least in my opinion, at this
3 point. The improvements we have seen are very
4 small and to endpoints that are not the most
5 important ones for the patient.

6 DR. DELEMOS: James DeLemos. I also voted
7 no for the same reason, that I don't think it meets
8 the evidentiary standard. It's interesting. I
9 think that the drug may do better than the
10 investigators thought it would.

11 They went out to find a drug that only
12 improved symptoms. It didn't really do that, but
13 it affects harder outcomes in a more meaningful
14 way, and they weren't really designed to test that
15 adequately with rigorous endpoints in sufficient
16 numbers. But it's possible, actually, that the
17 drug does more than was intended in the original
18 trial with regard to measurable hard outcomes.

19 DR. LINCOFF: This is Michael Lincoff. I
20 voted no. My feelings on this have been well
21 expressed. I just want to emphasize that I think
22 it's clear the drug does have an effect on

1 worsening heart failure, but that given the
2 limitations on how that was not rigorously defined,
3 that we don't know how much of the effect is on
4 minor heart failure changes versus major. And
5 where this would fit in, particularly in a world
6 where we need to be able to understand the cost-
7 effectiveness, I think that we need better data on
8 understanding the magnitude of benefit in a
9 rigorous fashion. And the data that we have here
10 doesn't stand alone as a single trial for approval.

11 DR. LI: Jennifer Li. I voted no. I
12 struggled somewhat with this decision because I do
13 feel like there were some positive clinical effects
14 to this drug. But I think ultimately it was the
15 way the primary endpoint was weighted that tipped
16 me in the "no" direction.

17 I would like to see further studies of this,
18 including more rigorous definitions of worsening
19 heart failure with some clinical correlations that
20 are a little bit more well-defined, and of course
21 would be very interested in looking at the effects
22 of the long-term mortality and effects of repeat

1 dosing.

2 DR. SAGER: Philip Sager. I voted no, for
3 the reasons that have already been so eloquently
4 stated. I do want to applaud the sponsor for
5 working to develop this drug in acute heart
6 failure. This is a difficult area to develop drugs
7 in. There is an unmet medical need.

8 I think the data that we've looked at today
9 shows that there's real potential for helping
10 patients with harder endpoints such as reducing
11 worsening of congestive heart failure, reducing
12 time in the hospital, time in the ICU, and
13 potentially improving biomarkers, both cardiac as
14 well as renal biomarkers.

15 So I hope that this disappointing vote and
16 meeting today won't preclude the sponsor from
17 continuing to develop the drug.

18 DR. RICH: I'm Stuart Rich. I voted no, for
19 all the reasons stated. I think this was more of a
20 failure of trial design than it was of the drug
21 itself. It was designed to measure dyspnea, and I
22 think Dr. Temple summarized it best of anyone in

1 terms of how they tried to refashion this to some
2 way to measure worsening heart failure.

3 I share the sponsor's enthusiasm, and their
4 consultants', that a drug that will reduce
5 morbidity and mortality, length of stay, intensity
6 of care, for acute heart failure is really needed.
7 And hopefully this would be a learning study where
8 these hypotheses would be better thought out,
9 tested, and then proven in a subsequent trial.

10 MS. LEIGHTON: Susan Leighton, and I voted
11 no. I certainly appreciate the fact that the drug
12 addresses a number of issues that are important to
13 patients. However, I really just could not get
14 past the confusion over the endpoints.

15 DR. ORZA: Michele Orza. I voted no, for
16 all of the reasons that have been well stated. And
17 in looking further into this drug, I would
18 encourage the sponsor not to abandon the patient-
19 focused or the patient-reported outcomes.

20 Just try to get better ones -- I think those
21 are important things to be looking at, as well as
22 the "harder" endpoints, and also to look at a

1 population that is more reflective of heart failure
2 patients in the U.S.

3 DR. LINCOFF: Dr. Scott, I know you're
4 nonvoting. But do you want to make a comment?

5 DR. SCOTT: I guess one of the advantages of
6 my position is that I don't have to say. I didn't
7 think that there were a lot of things in the data
8 set that gave me confidence that the drug worked.
9 And I was a little less confused by the 180-day
10 mortality; I thought that was a very powerful
11 outcome.

12 DR. LINCOFF: Well, I want to thank the
13 sponsor for what actually I think was a very good
14 presentation of a very difficult data set, and the
15 FDA. Are there any final comments from the FDA?

16 DR. UNGER: Yes. I would also like to thank
17 the sponsor. I thought they gave an excellent
18 presentation. It was balanced. I'd like to thank
19 the committee. I'd like to thank the participants
20 from the public; I thought they did an excellent
21 job. And I thought your deliberations were very
22 thoughtful, meaningful, useful, and we've written

1 everything down. So thank you very much. Thanks
2 for coming.

3 **Adjournment**

4 DR. LINCOFF: Well, then, this meeting is
5 adjourned.

6 (Whereupon, at 4:06 p.m., the committee was
7 adjourned.)

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