MEETING OF THE CARDIOVASCULAR AND
RENAL DRUGS ADVISORY COMMITTEE
(CRDAC)

Tuesday, September 9, 2014
12:01 p.m. to 4:13 p.m.

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

DESIGNATED FEDERAL OFFICER (Non-Voting)

Kristina A. Toliver, PharmD

Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

MEMBERS (Voting)

James DeLemos, MD

Cardiology Service Chief
Parkland Memorial Hospital
Sweetheart Ball-Kern Wildenthal, MD, PhD
Distinguished Chair in Cardiology
Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, Texas
Linda F. Fried, MD, MPH
Chief Peritoneal Dialysis
VA Pittsburgh Healthcare System
Professor of Medicine, Epidemiology and Clinical & Translational Science
University of Pittsburgh
Pittsburgh, Pennsylvania

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
A. Michael Lincoff, MD

(Chairperson)

Vice Chairman
Department of Cardiovascular Medicine
Director, C5Research (Cleveland Clinic
Coordinating Center for Clinical Research)
Professor of Medicine
Cleveland Clinic
Cleveland, Ohio

Stuart Rich, MD

Professor of Medicine
University of Chicago Pritzker School of Medicine
Attending Physician
Center for Pulmonary Hypertension
Section of Cardiology
University of Chicago Hospitals
Chicago, Illinois
Philip Sager, MD

Consulting Professor of Medicine
Stanford University School of Medicine
Chair, Scientific Programs Committee
Cardiac Safety Research Consortium
San Francisco, California

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

MEMBER (Non-Voting)

Rob Scott, MD

(Industry Representative)
Vice President Global Clinical Development
Cardiovascular Therapeutic Area Head
Amgen
Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Bonnie Arkus, RN

(Acting Consumer Representative)
Hamilton Township, New Jersey
TEMPORARY MEMBERS (Voting)

Ralph B. D’Agostino, Sr., PhD
Professor of Mathematics and Statistics
Biostatistics and Epidemiology
Executive Director MA/PhD Program in Biostatistics
Director, Statistics and Consulting Unit
Boston University
Boston, Massachusetts

Susan Leighton
(Patient Representative)
Huntsville, Alabama

FDA PARTICIPANTS (Non-Voting)

Robert Temple, MD
Deputy Director for Clinical Science
CDER, FDA

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
ODE I, OND, CDER, FDA
FDA PARTICIPANTS (Non-Voting)

Ellis Unger, MD

Director

Office of Drug Evaluation I (ODE I)

Office of New Drugs (OND), CDER, FDA
## CONTENTS

<table>
<thead>
<tr>
<th>AGENDA ITEM</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Call to Order and Introduction of Committee</td>
<td></td>
</tr>
<tr>
<td>A. Michael Lincoff, MD</td>
<td>10</td>
</tr>
<tr>
<td>Conflict of Interest Statement</td>
<td></td>
</tr>
<tr>
<td>Kristina Toliver, PharmD</td>
<td>13</td>
</tr>
<tr>
<td>FDA Introductory Remarks</td>
<td></td>
</tr>
<tr>
<td>Norman Stockbridge, MD, PhD</td>
<td>17</td>
</tr>
<tr>
<td><strong>Speaker Presentations – Forest Laboratories</strong></td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
</tr>
<tr>
<td>Kathleen Waldron, MBA</td>
<td>24</td>
</tr>
<tr>
<td>Background and Treatment Considerations</td>
<td></td>
</tr>
<tr>
<td>Michael Weber, MD, FACP, FACC, FAHA</td>
<td>29</td>
</tr>
<tr>
<td>Efficacy Results</td>
<td></td>
</tr>
<tr>
<td>David Bharucha, MD, PhD</td>
<td>39</td>
</tr>
<tr>
<td>Safety Results</td>
<td></td>
</tr>
<tr>
<td>Philip Hornick, MD, PhD</td>
<td>52</td>
</tr>
<tr>
<td>Benefits and Risks</td>
<td></td>
</tr>
<tr>
<td>William White, MD</td>
<td>64</td>
</tr>
<tr>
<td>Clarifying Questions to the Presenters</td>
<td>76</td>
</tr>
</tbody>
</table>
## CONTENTS (continued)

<table>
<thead>
<tr>
<th>AGENDA ITEM</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Presentations</td>
<td></td>
</tr>
<tr>
<td>Nebivolol/Valsartan for the Treatment of Hypertension</td>
<td></td>
</tr>
<tr>
<td>George Kordzakhia, PhD</td>
<td>103</td>
</tr>
<tr>
<td>Rajanikanth Madabushi, PhD</td>
<td>108</td>
</tr>
<tr>
<td>Clarifying Questions to the Presenters</td>
<td>120</td>
</tr>
<tr>
<td>Open Public Hearing</td>
<td>137</td>
</tr>
<tr>
<td>Questions to the Committee and Discussion</td>
<td>144</td>
</tr>
<tr>
<td>Adjournment</td>
<td>222</td>
</tr>
</tbody>
</table>
Call to Order

Introduction of Committee

DR. LINCOFF: Good morning, everyone. If everyone could please take their seats, we can get started.

I'd like to remind everyone present to please silence your cell phones, BlackBerrys, and other devices if you've not already done so.

I would also like to identify the FDA press contact for this meeting, Mr. Christopher Baumgartner, if you're here, present.

My name is Michael Lincoff. I'm the chairperson for the Cardiovascular and Renal Drugs Advisory Committee. I will now call this meeting of the Cardiovascular and Renal Drugs Advisory Committee to order.

We'll start by going around the table and introducing ourselves. Let's start down on our right.

DR. SCOTT: Good morning, everyone. My name
is Rob Scott. I'm the head of cardiovascular
development at Amgen, and I'm also the nonvoting
industry representative on the committee.

MS. LEIGHTON: Good morning. I'm Susan
Leighton, and I'm the patient representative from
Huntsville, Alabama.

MS. ARKUS: Good morning. I'm Bonnie Arkus,
and I'm the consumer representative, and I'm from
Trenton, New Jersey.

DR. DELEMOS: I'm James DeLemos, a
cardiologist at UT Southwestern in Dallas.

DR. LI: I'm Jennifer Li. I'm a pediatric
cardiologist at Duke University.

DR. SAGER: Philip Sager. I'm a
cardiologist at Stanford University.

DR. LINCOFF: Michael Lincoff, a
cardiologist at the Cleveland Clinic.

DR. TOLIVER: Kristina Toliver, designated
federal officer, CRDAC.

DR. FRIED: Linda Fried. I'm a nephrologist
at the Pittsburgh VA and University of Pittsburgh.

DR. RICH: Stuart Rich, cardiologist,
University of Chicago.

DR. LEWIS: Julia Lewis, nephrologist, Vanderbilt.

DR. D'AGOSTINO: Ralph D'Agostino, statistician at Boston University in the Framingham study.

DR. STOCKBRIDGE: I'm Norman Stockbridge. I'm the director of the Division of Cardiovascular and Renal Products here in CDER.

DR. UNGER: I'm Ellis Unger. I'm director of Office of Drug Evaluation I and Office of New Drugs in CDER.

DR. TEMPLE: Bob Temple, deputy director, Office of Drug Evaluation I.

DR. LINCOFF: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus as a gentle reminder, individuals will
be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

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

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

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I have the conflict of interest statement.

Conflict of Interest Statement

DR. TOLIVER: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee
under authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. The FDA has determined that members and temporary voting members of the committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for particular individual services outweighs his or her potential
financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.


This is a particular matters meeting during which specific matters related to Forest
Laboratories NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

With respect to FDA's invited industry representative, we would like to disclose the Dr. Rob Scott is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Scott's role at this meeting is to represent industry in general and not any particular company. Dr. Scott is currently employed by Amgen.

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

FDA encourages all other participants to
advise the committee of any financial relationships
that they may have with firms that could be
affected by the committee's discussions. Thank
you.

DR. LINCOFF: We will now proceed with the
FDA opening remarks from Dr. Norman Stockbridge. I
would like to remind public observers at this
meeting that while this meeting is open for public
observation, public attendees may not participate
except at the specific request of the panel.

Dr. Stockbridge.

**FDA Introductory Remarks**

DR. STOCKBRIDGE: Good afternoon. My thanks
to the committee for meeting with us today on what
I think will be an interesting topic.

The division has by my count approved 46
different two-drug combinations for hypertension
and five three-drug combinations. So why are we here?

The answer is I think this one raises some questions about the basis for approval that we've more or less quietly been evolving over the last 10 years. I'll focus mostly on what the algorithm is for two-drug development, and it's basically that one needs to show the effect of a combination on top of the monotherapies.

That has traditionally been done, almost all the time been done, with a factorial design trial with individual components being studied over a dose range that's at least as wide as the individually approved dose ranges.

For a while, the basis for approval was the demonstration that the response surface had a tilt with respect to both axes. In more recent years, we've adopted a -- I think it's the only place in cardiovascular medicine where we have a true co-primary endpoint. We ask that some dose of the combination be shown to beat each of the high dose monotherapy components.
We've never had an explicit test that established a minimum-sized treatment effect. The test is not did you beat the comparator by a certain amount. It's just did you beat it. But the issue how big of a treatment effect matters hasn't really come up because most combinations have a more or less an additive effect.

So we are here mostly today because of the question about whether the effect size matters. And historically, it hasn't mattered very much. You can find funny things in drug labels like diltiazem is approved at doses of 120, 180, 240, 300, 360 and 420 milligrams. Verapamil is approved with doses of 120, 180 and 240 milligrams with scored tablets. That gives you five combinations there, five distinct doses there.

After all, there's a continuous monotonic relationship between blood pressure and the risk of cardiovascular death and stroke. So how much does the effect size matter?

However, we use these drugs to treat patients to goals, and it's clear that most
hypertensive patients require more than one drug to get to goal. Thus, we have more or less adopted a principle that said that small steps would delay or possibly interfere with a patient getting to goal.

We've been sort of implementing this policy even at the level of what doses of monotherapies we've approved. In recent years, we've approved one renin inhibitor, aliskiren at only two dose levels. And the last of the ARBs, the angiotensin receptor blockers, azilsartan, which was quite well tolerated, it only has one approved dose level despite the fact that its effect is larger than that of at least most of the other sartans.

The only place, however, where we've sort of been forced to name a number of what constitutes an important clinical effect size is in the context of a pediatric written request. Pediatric written request is a contract between the FDA and a sponsor where in exchange for the sponsor conducting a study -- not for showing effectiveness, but just for doing the study -- they get rewarded with six months of exclusivity.
So in writing the contracts with sponsors for pediatric antihypertensive development programs, we specify a minimally clinically important treatment effect and require that the study be powered to rule out that effect if the true effect had been zero.

So the attempt is to make sure that if the study fails to show a treatment effect, that failure is meaningful. And the effect size that we have named in those written requests has been 3 millimeters of mercury systolic or diastolic.

So now we've got a case before us where the combination contributes something like 3 millimeters systolic and 1 millimeter diastolic compared to the highest dose of one of the components, nebivolol 40 milligrams.

The sponsor brilliantly, I would say, anticipated this magnitude of treatment effect, having enrolled 500 subjects per arm in their factorial trial and managing to rule out, again compared with nebivolol 40, .1 millimeters of mercury diastolic.
So one question you have before you is whether this demonstration of effectiveness was enough or whether this product, this combination, represents really a nuisance to patients getting to treatment goals.

An alternative basis for approval is improvement in safety or tolerability with more or less preservation or perhaps a small effect on blood pressure. And the closest example of a claim in that regard we have is Ziac, the combination of bisoprolol and hydrochlorothiazide, where it's clear that the combination gives you less bradycardia than the bisoprolol alone, less hypokalemia than hydrochlorothiazide alone. But there in contrast to the current case, the two components gave pretty much additive effects on blood pressure.

For the combination of valsartan plus nebivolol, the improvement in blood pressure is about 2 millimeters of mercury diastolic compared to nebivolol 20 milligrams. And the improvement in tolerability compared to 40 milligrams relates
principally to -- is manifest in reduced withdrawals for bradycardia on the combination compared to nebivolol. But as you will see, it's not clear whose tolerability has been improved, that of subjects, that of investigators, or that of the protocol authors. So with that, I'll stop here.

DR. LINCOFF: We will now proceed with the sponsor presentation.

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 advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters to advise the committee of any financial relationships they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including
equity interest and those based upon the outcome of
the meeting. Likewise, FDA encourages you at the
beginning of your presentation to advise the
committee if you do not have any such financial
relationships.

If you choose not to address this issue of
financial relationships at the beginning of your
presentation, it will not preclude you from
speaking.

I invite the sponsor to start.

**Sponsor Presentation – Kathleen Waldron**

MS. WALDRON: Good afternoon. Mr. Chairman,
members of the advisory committee, FDA staff,
ladies and gentlemen, Forest is pleased to be here
today to present to you an overview of our NDA for
the nebivolol fixed-dose combination with
valsartan.

I am Kathleen Waldron, senior director of
regulatory affairs at Forest, and after a short
introduction, I will be introducing this morning's
speakers.

The nebivolol/valsartan fixed-dose
combination would be the first FDC of a beta blocker and ARB. Each reduces blood pressure through a different mechanism of action with nebivolol as a cardio-selective beta adrenergic blocker with vasodilatory effects and valsartan as an angiotensin receptor blocker.

Both drugs have an established efficacy profile with a low incidence of adverse events. Nebivolol has been approved in the United States since 2007 for the treatment of hypertension at doses of 2.5, 5, 10, 20 and 40 milligrams with an approximately worldwide exposure of 40 million patient-years. Valsartan has been approved in the United States since 1996 for the treatment of hypertension at 80, 160 and 320 milligrams with an approximately worldwide exposure of 180 million patient-years.

In seeking approval of the nebivolol/valsartan fixed-dose combination, a 505(b)(2) application was filed in which we are relying on the agency's previous findings of safety and effectiveness for both valsartan and nebivolol.
This approach is justified by the demonstration of bioequivalence in Study NAC-PK-05, which serves as the bridge between the FDC and the free tablet combination.

The establishment of bioequivalence in NAC-PK-05 also permitted the conduct of our long-term safety study NAC-MD-02 with free tablet combination as agreed upon with the agency. This long-term exposure data collected in this study met and exceeded the required ICH exposure guidelines.

As agreed upon with the agency, Forest conducted a single pivotal efficacy trial utilizing a factorial study design, which consisted of eight treatment arms and allowed for the evaluation of five FDC doses. This study was designed to fulfill the requirements of the combination rule in which each component must demonstrate its contributions to the effect of the FDC.

It was agreed upon with the agency during the pre-IND meeting that some dose of the FDC had to be compared with the highest approved monotherapy doses. Thus an FDC comprised of
20 milligrams nebivolol and 320 milligrams valsartan was compared to the highest approved monotherapy dose of nebivolol at 40 milligrams and valsartan at 320 milligrams.

We are seeking the approval of five FDC doses of nebivolol/valsartan FDC, recognizing that the utility of these doses will vary by indication and allow for tailoring the dosing to the needs of individual patients. We are seeking approval of the nebivolol/valsartan fixed-dose combination for the following indications:

First, as initial therapy, the nebivolol/valsartan fixed-dose combination may be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. Our pivotal efficacy trial NAC-MD-01 was designed to support the use of this FDC as initial therapy.

Second, as replacement therapy, the nebivolol/valsartan FDC may be substituted for the titrated components. And last, as add-on therapy, the nebivolol/valsartan fixed-dose combination may
be used in patients whose blood pressure is not adequately controlled with nebivolol alone or valsartan alone. These patients may be switched to the FDC.

We will now continue with the remainder of our presentation, and I would like to introduce this morning's speakers. Shortly, I will turn over the presentation to Dr. Michael Weber, professor of medicine at the State University of New York and past president of the American Society of Hypertension, for a discussion on background and additional treatment considerations in hypertension; followed by a presentation of our efficacy results by Dr. David Bharucha, senior director of clinical development at Forest.

Dr. Philip Hornick, vice president of clinical development at Forest, will provide an overview of our safety results. And finally, Dr. William White, professor of medicine at the University of Connecticut and immediate past president of the American Society of Hypertension, will provide a summary and evaluation of the
benefits and risks of the nebivolol/valsartan FDC.

In addition to the individuals who we will be presenting to you today, we have Dr. Gary Koch, professor of biostatistics at the University of North Carolina, as well as several subject matter experts from the sponsor that are available to address your questions.

I would now like to introduce Dr. Weber for a presentation on additional background and treatment considerations in hypertension.

**Sponsor Presentation – Michael Weber**

DR. WEBER: Thank you, Kathleen.

Mr. Chairman, ladies and gentlemen, I'm Michael Weber. I'm at the Downstate Medical Center in Brooklyn, and I should disclose that I have been compensated for assisting Forest in preparing for these meetings and for presenting here today.

I'm going to be talking a little bit and obviously very quickly about some of the background to hypertension and some of the considerations that we believe are important in understanding the data. And here's just the checklist of the things that we
believe are relevant, the epidemiology of hypertension and how it pertains to the importance of treatment, the strong relationship that we already heard about from Dr. Stockbridge between blood pressure and cardiovascular outcomes.

I'm going to stress the importance of systolic blood pressure. I'm going to talk about the importance of even small changes in blood pressure. I will briefly introduce the two drugs that are part of this fixed-drug combination. I will talk about why these sorts of combinations are useful practically in the clinical practice of medicine, the importance of tolerability, and finally, why we believe that nebivolol and valsartan is a logical and useful tool for managing hypertension.

We know that about a third of all adults in the United States have hypertension, and we know very, very well, from a variety of sources, that high blood pressure is a major risk factor for stroke, for heart attacks, for heart failure, for chronic kidney disease. And it's even believed
that it may contribute to cognitive decline,

obviously, a major public health issue as well, and

no question that high blood pressure shortens life

expectancy.

These are data from the clinical trialists

collaboration, an article written by Sara

Lewington, already about 10 years ago, still

regarded as explaining why high blood pressure is

such a major cause for concern.

We see regardless of age, the increases in

blood pressure that we see here are associated with

dramatic impacts on mortality and other major

outcomes in people with coronary artery disease,

and it's exactly the same story for stroke. Every

20 millimeters of mercury higher systolic blood

pressure is associated with a doubling of risk.

I should emphasize, and it's very important
to do so, that epidemiology is not always

predictive of treatment outcomes. And lowering

blood pressure by 20 over 10 may not have the same
good effect that raising blood pressure by 20 over

10 would have as a bad effect, but nevertheless,
this does give us a major rationale for treatment.

Systolic blood pressure has become very much a standard now, the leading index of blood pressure in medical practice, and it's of note that the last few drugs that have been considered by the agency for hypertension have indeed focused on systolic rather than diastolic outcomes. It is a stronger predictor of cardiovascular risk.

Here we're looking at data put together by Jeremiah and Rose Stamler and Dr. Neaton a number of years ago. And if we divide their database into deciles of systolic blood pressure -- these are the data of course from the multiple risk factor intervention trial -- we see that once we get to the area of interest with the systolic pressure, in other words, roughly around 130 and on up, we see that systolic rather than diastolic pressure becomes more important. And I'd remind you that this was a relatively young cohort of men.

The people of interest mainly in hypertension would be people older than this. And even though I don't have a slide, the work by
Stanley Franklin based on the Framingham data emphasizes that once we pass the age of 50, diastolic pressure, which had been a pretty good predictor of outcomes, becomes far less so, and it's the systolic blood pressure that becomes the principal determinant of prognosis.

These are data that emphasize that small reductions in blood pressure during treatment can multiply into useful cardiovascular benefits. These are data that come predominantly again from Dr. Stamler.

Just by way of disclosure, this is a slide that is an approved slide used in educational programs based in support of a recently approved angiotensin receptor blocker, azilsartan, to demonstrate that its superiority of 2 or 3 millimeters of mercury over one of its major competitors, in fact, has established a formal claim for superiority. And I would agree, based on these data, that the action of the agency in granting azilsartan that superiority was worthwhile.
I think we're also very aware of the fact, discussed here at previous meetings of this committee, that in a couple of recent pivotal hypertension trials, the VALUE trial and particularly the ALLHAT study, differences of 2 to 3 millimeters of mercury in systolic blood pressure were associated with major differences between treatment groups in cardiovascular outcomes, stroke in particular but other outcomes such as heart failure as well.

What about the angiotensin receptor blockers? Again, from the clinical trialists collaboration, an article by Fiona Turner [sic], and we're looking at angiotensin receptor blockers as a class. This, of course, is a mega meta-analysis being compared with anything that is not an ARB or an ACE inhibitor.

We see that compared with all the other drug classes, the ARBs do well for every outcome, and particularly so for stroke and for heart failure. And you might notice next to the data that the differences in blood pressure that were associated
with these benefits were quite small, 2 over 1.

    Now, let me emphasize, I don't think it's
the 2 over 1 that's the full explanation for why
ARBs have had these kinds of good results.
Nevertheless, it does suggest that small levels of
blood pressure or small changes in blood pressure
can be of importance.

    Just one other quick note about valsartan,
here it is being compared with amlodipine. This is
from the VALUE study. And these are data where
patients receiving either one of the two drugs were
matched for baseline and on treatment blood
pressure, for gender, for previous histories of
cardiovascular outcomes; in other words, very, very
tightly matched patient pairs.

    We see that valsartan does every bit as well
as amlodipine, which is no mean feat because most
of us believe that amlodipine is a very effective
cardiovascular protective agent.

    This is what makes nebivolol special. It is
a vasodilating beta blocker, and this is a study
that was done in hypertensive patients. And the
principal measurement was changes in forearm blood
flow, changes in vasodilation produced by
acetylcholine. This is the standard way of
measuring endothelial function, and nebivolol was
compared with altenolol and with placebo.

You can see that as the doses of
acetylcholine were increased, nebivolol was clearly
associated with a marked superiority in causing
vasodilation, and that does seem to define a
primary mechanism of action of this drug, which
seems to separate it from other agents.

Fixed-dose combinations are an important
tool in hypertension management. Let me go through
this very, very fast because it's stating the
obvious. Most people need more than one drug to
get their blood pressure under control, about
60 percent perhaps. And two-pill regimens are
associated with greater noncompliance to treatment
if they're given a single pill as opposed to giving
the two medicines in one tablet.

Here's one example of how this is being
studied. This is again a small meta-analysis in
which we're looking at persistence, and persistence
in this study was defined as the probability that a
patient would renew their prescription 12 months
after starting treatment. And you can see clearly
on the right of the line of unity, people taking
two medicines as a single pill as compared with
taking the same two medicines as two separate
tablets, clearly are more likely to be showing up
and having their prescriptions renewed. It does
make a big difference.

Tolerability, which will be discussed later,
of course, hypertension doesn't have symptoms, and
so the threshold for side effects, of course, is
very slow in hypertension. And it's critical that
drugs used, either individually or in combination,
be highly tolerable. And I think we can say that
is well established for both of the drugs that
we're talking about today. People who have side
effects stop their treatment.

Right now, beta blocker/angiotensin receptor
blocker fixed combinations are not available even
though they are population. In fact, ARBs and beta
blockers represent two of the four most widely used antihypertensive classes. And I find it particularly interesting that over 40 percent of patients getting ARBs are also receiving a beta blocker.

So if I can summarize what I've been saying, nebivolol and valsartan brings together two very well tolerated, two very efficacious drugs with very safe profiles, both already approved and both currently being administered in pre-pill form as two separate tablets.

We know that these drugs may have benefits beyond just what they do to blood pressure. And let me just finally say, as Dr. Stockbridge pointed out, the agency has approved a lot of two-drug combinations in the last several years, and even valsartan in already available in combination with thiazide and with amlodipine.

Nebivolol/valsartan is a combination that would be of particular interest and importance when, for whatever good reason, physicians would wish to prescribe an ARB and a beta blocker to
their patients. And I think that's the way we have to think of this as a very useful tool for those patients who need this kind of treatment.

So let me move on and introduce now Dr. David Bharucha who is from the Forest Research Institute, and he's going to talk about the clinical efficacy of this two-drug combination.

David.

Sponsor Presentation – David Bharucha

DR. BHARUCHA: Thank you, Dr. Weber, and good afternoon, everybody. We'll now present the efficacy data for the nebivolol/valsartan combination drug. The phase 3 clinical program for this combination studied close to 5,000 patients, and it consisted of two main trials. Our pivotal efficacy data are from a placebo-controlled NAC-MD-01 study, which tested five doses of this FDC.

Safety was tested in both phase 3 trials, including the NAC-MD-02 study, our open label long-term safety trial, and will be the topic of the next talk.

The efficacy study, NAC-MD-01, was designed
to meet several goals. First, it was designed to meet the regulatory combination rule, namely that each component must contribute to the effect of the corresponding FDC and with statistical significance.

The key comparison in this program was the highest dose FDC, 20/320 versus valsartan 320 and versus nebivolol 40, a twofold higher dose of nebivolol as compared with that contained within this FDC.

Second, the NAC-MD-01 study was designed to examine multiple comparisons between each of the five FDC doses and their components as administered as initial therapy. A factorial design was employed, which is standard in allowing for these multiple comparisons among antihypertensive combination products.

The FDCs examined in this program, which are shown in the right-hand column of your slide, are all comprised of the most highly utilized doses of nebivolol and valsartan. The highly utilized doses of each monotherapy are listed in the left and
center columns of the slide with the starting doses highlighted. Utilization data from 2014 and from United States hypertension patients are shown in the lower boxes.

For nebivolol, the majority of patients are on 5 or 10 milligrams, and a moderate percentage are on 20 milligrams. And indeed, these are the doses of nebivolol used in the FDCs we examined. The 40-milligram dose is used less than 1 percent of the time. Valsartan utilization data show that the three doses listed, which are those contained within these FDCs, are also highly utilized in the United States.

For NAC-MD-01, the study procedure started out, as we move from left to right on this schematic, with a placebo washout such that patients were in an antihypertensive drug-free state at randomization, indicated by the red dot on the slide.

At this point, study drug was administered as initial therapy. Patients were administered an FDC, nebivolol or valsartan monotherapy or placebo.
for the first 4 weeks as indicated.

After 4 weeks of treatment, all patients' doses were forced up-titrated, and they were treated with a higher dose, indicated in the right-hand column of your slide, for a second 4-week period. After the second 4-week treatment period, main efficacy assessments were made, and this was followed by a double-blind down-titration period.

Two notes, an ambulatory blood pressure monitoring substudy with assessments made in ABPM over 24 hours was performed in 15 percent of the ITT population.

Number two, prior data for nebivolol and for valsartan show that maximal blood pressure lowering effects are seen after 2 to 4 weeks of therapy justifying the 16 unique 4-week treatments shown on this slide.

Efficacy endpoints are summarized here, particularly the primary and key secondary endpoints. Diastolic blood pressure was chosen as the primary by custom, but the key intention was to
look at both the systolic and the diastolic blood pressures as both comprise meeting the regulatory combination rule and because both are important clinically.

The examination of both systolic and diastolic blood pressure was reflected in the statistical analysis plan with hierarchical testing employed. Other secondary assessments are shown here, and these were made at 4 weeks. In addition, blood pressure control was assessed. This is defined as the proportion of patients attaining both systolic and diastolic goals simultaneously.

These are the prespecified comparisons for the primary and key secondary endpoints on the left and the secondary endpoints on the right. Each FDC shown in the green box was compared with monotherapies that were the exact components of that FDC with the exception of the blue highlighted main comparison shown on the slide. Here, the nebivolol was a twofold higher dose reflecting a particularly stringent comparison.

Statistical ground rules included that
NAC-MD-01 was to be assessed as a positive study if there was a p value of less than .5 for both comparisons. Analyses were multiplicity controlled for the comparisons among doses noted. Testing was controlled for type 1 error for both diastolic and systolic blood pressure comparisons for the FDCs noted.

Select inclusion and exclusion criteria are noted. In the left-hand column, I call your attention to the middle bullet, which is the hypertension criterion for inclusion. This was assessed with the patients in the antihypertensive drug-free state, and thus study drug was administered in this study as initial therapy.

Procession through the trial led to the randomized and ITT populations shown, each greater than 4100 patients. As can be noted in the bottom row, randomization led to well-balanced arms.

Also, as reflected in the bottom row and to be clear, the total size of this study was driven by the number of FDCs examined, the 8 treatment arms, and the resultant 16 unique 4-week treatment
periods. These and only these considerations, as
well as the control for multiplicity, is what led
to the N of this study.

Baseline characteristics shown here are
typical of a U.S. hypertensive population. As seen
in the upper right, the mean baseline SBP/DBP was
155 over 100. This mean is essentially on the
border right between stage 1 and stage 2
hypertension.

Shown here are the primary and key secondary
efficacy results for the comparisons of 20/320 to
the highest approved doses of monotherapy. All
show positive results. Thus from these data, the
study is positive, and these data fulfill the
regulatory combination rule as both components
contribute to the effect of this FDC.

It should be emphasized that this regulatory
hurdle was cleared despite the comparison to the
twofold higher dose of nebivolol. Also, as you've
undoubtedly seen in the FDA briefing documents, one
might conclude that the 40-milligram nebivolol
comparison is not fully reasonable. And what is
suggested there is to consider instead a comparison with 20 milligrams, as shown now on this slide in blue.

These data show larger treatment effects in the systolic and diastolic blood pressure reductions and statistical significance is clearly met. Also, these data for the 20-milligram comparison shown in blue are particularly clinically relevant due to our use here of a truly utilized dose of the drug.

Moreover, to further address the question that we're here to discuss today, clinically meaningful blood pressure effects, one must look at all the FDCs examined, and one must look also more broadly at the data.

What I show here are the comparisons between the five FDCs and the respective monotherapies in the central column with SBP and DBP reductions noted. All the negative signs indicate that treatment with each and every FDC reduce blood pressure more than did its corresponding monotherapies.
Looking at the right-hand column of p values, there are 22 comparisons. Twenty-one of these 22 are statistically significant. Moreover, looking at all the observed blood pressure differences, they're all of a clinically meaningful magnitude.

Now, when assessing treatment effects, it's also important to examine blood pressure reductions from baseline after treatment. This table shows the robust reductions from baseline for each of the FDCs in blue. These are the blood pressure reductions that a physician would observe in treatment his or her patient with this FDC.

The blood pressure reduction observed clinically would obviously be the placebo-unadjusted values shown in the column on the left. However, also shown for completeness are the placebo-adjusted values. The p values are shown on the right.

To summarize, the data on this slide and on the prior slide show that treatment with FDC always leads to a greater reduction than does either of
its components. As well, the treatment effects I presented thus far as reinforced by the 24-hour ambulatory blood pressure monitoring data.

As I've already mentioned, ABPM was performed in a substudy in approximately 15 percent of the patients in this study. To be clear, this substudy was designed to provide data supportive of the main results, and indeed it does.

The table shown here demonstrates robust reductions from baseline in ABPM for each of the FDCs shown in blue. And this is shown for both placebo unadjusted values and quite notably, for placebo adjusted values as well.

Now, blood pressure control, as I've mentioned, is the simultaneous achievement of both systolic and diastolic blood pressure targets. The importance of this type of measure is widely cited in guidelines for the treatment of hypertension. All five nebivolol/valsartan FDCs demonstrated greater blood pressure control, as shown on this slide, than did the corresponding monotherapies and with statistical significance.
As can be seen in the central and right-hand columns, attainment of blood pressure control, here we used a target of 140/90, under treatment with any one of the five FDCs was greater than that of the corresponding monotherapies, all with significant deltas.

Here, we summarize the effect sizes demonstrated in NAC-MD-01 in addition to the reductions from baseline I've already presented. These are the 22 greater systolic and diastolic blood pressure reductions demonstrated by FDC treatment compared with the corresponding monotherapy treatment. To remind you, these reductions are of a magnitude associated with clinically meaningful benefits.

I also call your attention to the 20-milligram comparison, a clinically relevant dose and a more apt comparison. This shows a treatment effect that is 3.7 systolic and 2.2 diastolic.

Next, these responder increments demonstrate greater achievements of blood pressure control with each and every FDC treatment as compared to
monotherapy. Moreover, a responder analysis was also performed assessing how many patients had a blood pressure reduction at or exceeding 20/10 millimeters of mercury.

Rather than looking only at population means, to best understand clinical relevance, it is highly valuable to examine the percentage of individual patients achieving a clinically meaningful response such as the one I'm showing you here, a reduction in both systolic and diastolic of 20/10, respectively.

Now, as described in Dr. Weber's talk and as will also be cited in Dr. White's upcoming talk, a blood pressure difference of 20/10 is associated with markedly better cardiovascular outcomes. And shown in the current blue rectangle, there are greater percentages of patients treated with each FDC who meet this benchmark of having both a systolic and a diastolic reduction of 20/10, respectively. Also, all of the deltas I show you here on this slide meet nominal statistical significance.
There are several conclusions. Number one, the data from this study fulfill the regulatory combination rule. Each component contributes to the FDC effect, and this was demonstrated by significant systolic and diastolic reductions in FDC 20/320 versus the highest approved doses of monotherapy, including the higher hurdle of a twofold higher dose of nebivolol.

Number two, these data demonstrate greater efficacy for all five FDCs versus monotherapies. We've shown you robust systolic and diastolic reductions from baseline, including the same from ABPM data. There is greater attainment of blood pressure control with each and every FDC than with any monotherapy, and there are responder rates of blood pressure reductions at or exceeding 20/10 with FDC.

Thus the totality of these data do demonstrate the efficacy of the nebivolol/valsartan FDC. As well, these data demonstrate treatment effects of a clinically meaningful magnitude.

I thank you, and for the next talk, Dr. Phil
Sponsor Presentation - Philip Hornick

DR. HORNICK: Thank you.

Good afternoon, Mr. Chairman, ladies and gentlemen of the committee. It's my pleasure to present to you the clinical safety data from the NAC-MD-01 and the NAC-MD-02 trials.

Now, the safety and tolerability of this combination was examined in two separate clinical studies. The first NAC-MD-01, that you've just heard about from Dr. Bharucha, was the efficacy and safety study 8 weeks. The FDC was utilized. It was a double-blinded and placebo-controlled trial.

The NAC-MD-02 was our long-term safety study. This was a 52-week open label study whereby the free tablet combination of nebivolol and valsartan was used, and the reason we used that combination was at that time, we hadn't yet made the FDC.

Now, as you'll all be aware, each monotherapy has an extensive long-term worldwide safety experience. The worldwide exposure of...
nebivolol and valsartan is approximately 220 million patient-years. Both nebivolol and valsartan have been widely studied in both hypertension and CV outcomes trials, and no unexpected safety concerns have been detected throughout the extensive postmarketing experience with either of these medicines.

Just to give you an overall summary of the safety populations, for NAC-MD-01, there was an exposure of some 273 patient-years with a mean duration of 53 days, and for NAC-MD-02, the exposure was 631 patient-years with a mean duration of 286 days.

The exposure for the nebivolol and valsartan clinical program, whether received as an FDC or as two drugs in free tablet combination, not only met but also exceeded the regulatory requirement.

Now, topics to be covered in the safety section include an overview of safety, all-cause mortality, SAEs, discontinuations for any reason, AEs that led to discontinuations, treatment-emergent adverse events, and any
important lab, vital or ECG findings.

We'll begin by discussing the safety data from the NAC-MD-01 trial. Our first discussion of safety will be an overview of the key safety items.

This table presents the overview of the safety and tolerability for all the FDCs studied in the NAC-MD-01 trial. As can be seen, there are no dose dependent safety or tolerability concerns with respect to TEAEs, discontinuations due to any reasons, or discontinuations driven by AEs or indeed, SAEs.

As a consequence and because it was part of the key efficacy analysis, we will now focus on the highest FDC dose of 20/320, which was the FDC from the main efficacy comparison.

This slide is an overview of safety and tolerability. In this table, the red highlight indicates the highest values for each category, and green represents the lowest. The fixed-dose combination of 20/320 compares favorably with placebo and even lower doses of monotherapy. So it compares very favorably in the context of TEAE,
discontinuations and SAE with nebivolol 40, 
valsartan 320, and even lower doses, nebivolol 10, 
valsartan 160, and placebo.

We'll now discuss the safety items in more 
detail beginning with all-cause mortality. In the 
NAC-MD-01 trial, there were two deaths, neither 
during the double-blinded treatment phase, and 
neither received active drug.

We will now discuss the number of patients 
who experienced a serious adverse event during the 
placebo-controlled NAC-MD-01 study. Listed are the 
percentage of patients with SAEs. Only FDC of 
20/320 is shown as all FDCs demonstrated similar 
instances of SAEs, as I showed you in the overview 
a few slides ago.

The FDC 20/320 shows similar if not lower 
rates of SAEs compared to both monotherapies and to 
placebo. Rates of individual SAEs were low, and 
there was no obvious clustering of events. Most 
importantly, we saw no new SAEs compared with the 
package inserts from the individual monotherapies.

We'll now discuss the number of patients who
prematurely discontinued the NAC-MD-01 study, and we'll first discuss those discontinuations due to any reason. Discontinuations due to any reasons are fundamental in any assessment of tolerability and are representative of treatment adherence.

About 90 percent of patients completed the double-blinded treatment phase. The most common reasons for premature discontinuation are listed here. They are withdrawal, adverse events, loss to follow-up, and protocol deviation.

The following figure shows a Kaplan-Meier curve, which plots the time to first discontinuation due to any reason during the NAC-MD-01 study. This Kaplan-Meier diagram shows the progression of patients who were initiated on FDC 10/160, nebivolol 20, valsartan 160, and placebo for 4 weeks of treatment and were then up-titrated, as shown by the dotted line in the middle of the slide, to FDC 20/320, nebivolol 40, and valsartan 320.

Even after four doses of treatment, we see fewer patients in the FDC group experiencing a
discontinuation compared with the nebivolol group. This comes in, although not shown on the side, with a nominal significance and a hazard ratio of .53, the p value being .01.

At the completion of week 8, patients in the FDC group continued to experience less discontinuations compared with the nebivolol group, again, with a nominal significance, achieving a hazard ratio of .63 with a p value of .01.

To just continue for one slide longer with the Kaplan-Meier comparison, we will compare FDC 20/320 with even lower doses of monotherapy. And here, you can see the number of patients who discontinue due to any reason was similar if not lower in the FDC 20/320 group as compared with nebivolol 10 and valsartan 160.

I'm going to draw down a little bit now, and we'll now look at the number of patients who experienced an adverse event leading to a premature discontinuation.

This table shows the incidence of discontinuation due to AEs. These findings are
representative of treatment tolerability.

As shown by the data, the fixed-dose 20/320 compares favorably to monotherapy and placebo in terms of tolerability. There are clear differences between the fixed-dose combination of 20/320 and nebivolol 40 milligrams in terms of discontinuations due to AEs, which was driven by the AE of bradycardia; bradycardia defined as less than 50 beats per minute, a very important safety highlight for patients especially those with hypertension and those receiving beta blocker aid.

We'll now discuss the number of patients who experienced a treatment-emergent adverse event during the NAC-MD-01 study. Listed here are all the treatment-emergent adverse events, which occurred in greater than 2 percent of patients. The fixed-dose combination of 20/320 shows similar if not lower rates of individual treatment-emergent adverse events in comparison with mono and placebo. Nebivolol 40, this high dose, demonstrated the highest rates of bradycardia and fatigue.

Coming back to a Kaplan-Meier diagram, this
figure plots the time to a TEAE of bradycardia, fatigue, or dizziness. All three of these are associated with beta blocker use, while dizziness is also a common AE of ARBs. This diagram shows the progression of patients who were initiated as before on FDC 10/160, nebivolol 20, valsartan 160 and, placebo, and had their dose doubled, as indicated again by the dotted line in the middle of the side, by a forced up-titration to FDC 20/320, nebivolol 40, valsartan 320, and placebo.

Patients who experienced any of the TEAEs were only counted once based on the earliest onset of the AE. Over the course of the study, fewer patients on FDC 20/320 experienced these TEAEs as compared with nebivolol 40, again with a nominally significant p value.

Finally, for NAC-MD-01, we look at the lab, vital, and ECG findings. There were no clinically significant changes in lab findings, nor were there any clinically significant findings, nor ECG findings.

We'll now move on briefly to discuss the
safety data from the long-term open label study NAC-MD-02. So the primary objective of the 02 study was to examine the long-term safety over a 52-week period of the nebivolol and valsartan combination. This was given in a free tablet form of nebivolol and valsartan with bioequivalence having been demonstrated previously in the NAC-PK-05 study.

The NAC-MD-02 study was a 52-week open label titrate-to-goal study where hydrochlorothiazide as an additional therapy was needed. Patients discontinued from the study if they were not at goal after the addition of the hydrochlorothiazide.

So this is a 52-week open label study. The goal was 140 over 90 for nondiabetics and 130 over 80 for diabetics, and patients were discontinued if they weren't in goal.

Walking you very briefly through the slide, patients were initially washed out for a 4-week period and were given nebivolol 5 and valsartan 160 for 2 weeks. Patients were then up-titrated to
nebivolol 10 and valsartan 320 for a 4-week period. And if they hit target, they continued on that therapy.

Progressively, they increased in therapy to reach target of going through 20/320, and if that didn't work after 10 weeks, an additional 12.5 hydrochlorothiazide, and 12.5 of hydrochlorothiazide was then added again for further final 10 weeks. If patient didn't reach goal, they were discontinued from the study.

So over 2,000 patients were screened in the 02 study in 130 sites across the United States of America. 810 patients were enrolled in this long-term safety study with 800 patients receiving study drug. The baseline characteristics are broadly similar to NAC-MD-01 study. There's a slight increase in the number of patients with stage 2 hypertension and a slight increase in African American patients.

The long-term safety study NAC-MD-02 demonstrated that the combination of nebivolol and valsartan was both safe and well tolerated over
52 weeks of treatment. Importantly, we see no new SAEs. We see no new AEs as compared with the package inserts of the individual monotherapies.

During the long-term safety study, three patients died. The first patient from a gunshot wound, the second patient from this long-term study had a cardiac arrest but didn't have an autopsy, and the third patient died from a myocardial infarction.

To examine the incidence of SAEs over the 52-week period in this long-term study, there were low rates of patients of SAEs. The only SAEs, which occurred in more than one patient, were non-cardiac chest pain and myocardial infarction, none of which were considered to be related to the investigational compound. No other SAE, including cardiovascular SAEs, occurred in more than one patient. Individual rates of SAEs are similar to those observed in the NAC-MD-01 study.

In the long-term safety study, approximately 40 percent of patients discontinued prematurely. The top four reasons were insufficient therapeutic
response. This was 8.4 percent, not unexpected when trying to treat a population comprising 70 percent of patients with stage 2 hypertension; protocol violation, withdrawal of consent, and adverse events.

To examine discontinuations due to AEs over the 52-week period, individual rates of discontinuation due to AEs were again similar to those observed in NAC-MD-01, with fatigue and bradycardia being the highest individual AEs leading to discontinuation over 52 weeks of treatment. However, both occurred at a rate of less than 2 percent.

In the long-term safety study, there were low rates of TEAEs, which occurred at greater than 2 percent over the 52-week period of treatment. And importantly, we see again no new AEs.

So in conclusion, ladies and gentlemen, members of the committee, all FDCs show favorable safety tolerability versus high and also low-dose monotherapies. We see no new SAEs. We see no new AEs relative to the established monotherapy
profiles. We further see a low number of AEs in all FDC doses. There is no difference in safety findings amongst the FDC doses.

For the comparison of FDC of 20/320 versus nebivolol 40 milligrams, we see fewer premature discontinuations, fewer discontinuations due to AEs, including those attributable to bradycardia.

The safety and tolerability of the fixed-dose combination is supported by a highly extensive safety experience for both of the monotherapies comprising 220 million patient-years. This FDC of nebivolol and valsartan is safe and well tolerated. Thank you very much.

It's now my pleasure to introduce Dr. White, who will bring up the end of our presentations today by discussing the benefit/risks of our fixed-dose combination.

Sponsor Presentation - William White

DR. WHITE: Thank you very much, Dr. Hornick, and good afternoon as well. I'm William White. I'm a professor of medicine in Connecticut. I work in preventive cardiology and
hypertension and have been chief of the unit for
about three decades.

I'm here as a clinical consultant to Forest.
I was not involved with the development program of
this fixed-dose combination, but during the last
few months, I've had the opportunity to review the
data. I've asked for a number of other analyses to
be performed where the focus was more on the
individual patient than the population in the trial
at large to assess more than just the mean
differences.

So I thought it would be of interest to
review some of these kinds of issues during the
course of this brief talk.

I will show some of the clinical efficacy
data, including some of the ambulatory blood
pressure findings; the blood pressure control
rates; and those clinically important blood
pressure reductions that were mentioned by
Dr. Weber; some evaluations of the fixed-dose
combination over monotherapies based on a type of
number-needed-to-treat analysis; and then clinical
use of this fixed-dose combination and dosing recommendations that I would find practical by physicians in practice.

So we've already heard from Dr. Stockbridge and Dr. Weber that fixed-dose combinations are nothing new in hypertension practice. They're utilized and compare to free pill combinations because they're convenient to patients. And surprisingly, a lot of patients feel taking one pill is better and safer than taking two pills, and they ask for this actually all the time in clinical practice.

It's also a predictability of response based on the clinical trial evidence when an FDC has been approved, and there's additive blood pressure reduction versus the monotherapies.

Now, of note, beta blockers and angiotensin receptor blockers are, in fact, used quite frequently in clinical practice for both hypertension and the comorbidities that you see in patients with hypertension, but there is no fixed-dose combination of these two classes of
drugs in the United States.

So first, if we look at the clinical blood pressure reductions from baseline in the highest treatment groups -- and by the way, I am focusing primarily on the higher dosage groups in this talk -- the fixed-dose combination 20/320 lowered systolic blood pressure from baseline by 17 millimeters of mercury, and each of the highest doses of valsartan and nebivolol, about 14; so approximately a 3 millimeter difference between the treatment groups. And both were statistically significant.

For the diastolic blood pressure, the reduction was 15.7 millimeters of mercury for this fixed-dose combination versus 11.4 and 14.5 for the valsartan 320 and nebivolol 40, respectively; again, about a 4 millimeters greater versus valsartan, and 1.2, as you've heard, for nebivolol 40.

Now, I'm showing this for two reasons, for descriptive purposes. These are the curves of ambulatory blood pressure that are the hourly
changes in means at hourly intervals, and keeping
in mind that you're looking at post-dose hours
which corresponds to the time of day of
approximately 7:00 to 9:00 a.m. The investigators
were given this window of time.

The placebo arm in gray shows virtually no
real difference from baseline at 8 weeks, and in
fact, it was about zero millimeters mean change
from baseline comparatively speaking. The green
line represents valsartan, the blue nebivolol, and
the yellow the fixed-dose combination of 20/320.

I have shaded in a period where most people
would typically be sleeping between 11:00 p.m. and
5:00 a.m. because we're not actually sure when
people were, in fact, sleeping or not. But that's
typically true of most patients who have daytime
visits to the study centers.

It is noteworthy that the fixed-dose
combination was separated for most of the daytime
hours for both valsartan and for nebivolol 40.
During the nighttime hours when patients were
asleep, there was a convergence of the curves for
all three treatment groups that were active,
consistent with findings that I've seen in other
studies in which it's associated with lower blood
pressure during the night and a lower activity of
the sympathetic nervous system.

It's noteworthy that starting around
hours 18, 19 post-dosing, corresponding to the
early morning period, a time when sometimes there's
an attenuation of drugs, that is clearly not seen
with a fixed-dose combination, and it does reduce
blood pressure compared to the corresponding
monotherapies.

The proportion of patients who achieve blood
pressure control -- using 140 over 90 as our goal,
which I think most of us in the hypertension
community actually believe is the appropriate
number -- with nebivolol and valsartan fixed-dose
combination compared to the monotherapies was
greater. It was 55 percent on the 20/320 versus
49 percent on nebivolol 40, and 42 percent on the
4-week time period of nebivolol 20 and 40 percent
on valsartan.
So there's this spread here, but in every instance, the combination controlled a higher number of people's blood pressures than did either monotherapy and the lower dose of nebivolol.

We heard that a 20 over 10 millimeter value has been epidemiologically corresponding with a very significant increase in cardiovascular mortality whether that mortality is due to sudden death, ischemic heart disease or stroke. And we therefore looked at this.

I actually asked for a distribution of the changes from baseline in each treatment group, and I can tell you that it's not normally distributed. Despite having a 3 over 1.2 millimeter difference in means, there is actually about a group of 10 percent of people who had a very large reduction from baseline on nebivolol/valsartan 20/320 corresponding to 44 percent of the population versus about 34 percent in the two highest monotherapy treatment groups. So literally 9.5 percent of patients had this larger reduction from baseline.
This is graphed out in this particular figure looking at the two stages of the study in which the first 4 weeks corresponds to the lower doses of 10/160, 20 of nebivolol and 160 of valsartan, and then after the forced titration at week 4, going up to 20/320, 40, and 320, respectively.

You'll note that at weeks 2 and 4, that the fixed-dose combination at the lower dose was already lowering a large -- this is a responder analysis, so lowering a greater number of people at those weeks in time. And then after the dose adjustment up-titration, the fixed-dose combination actually had a significant effect versus both treatment groups.

Also note that in the very first 2 weeks of therapy, more than 40 percent of patients actually achieved a nice reduction in blood pressure of over 20 over 10. So it was a fairly quick effect of the agent, and it continued to increase as the dose increased at week 6 and then at week 8.

So this particular figure evaluates the
additional blood pressure efficacy on nebivolol/valsartan in individuals versus the monotherapies. If the bar is going to the right, it means the fixed-dose combination was better than the monotherapies.

The upper panel shows blood pressure control that is less than 140 and 90, not either, but both, so 162 additional patients out of 1,000 treated with a fixed-dose combination would have control versus valsartan 320, and about 94 more people would have a greater than 20/10 reduction.

In contrast with nebivolol, there would be 66 patients who had better blood pressure control versus nebivolol 40, and 92 such patients would have a 20 over 10 blood pressure reduction, more patients.

In contrasting the safety metrics using mostly the very obvious things like severe treatment-emergent adverse events, serious adverse events, and those events leading to discontinuation or any discontinuation from therapy during the 8-week trial, if we look at the upper panel, there
is evidence that the 20/320 was comparable to the ARB valsartan 320. A few more patients actually discontinued from the valsartan than did the 20/320.

Then if we look down at the nebivolol comparison, 50 more patients in 1,000 would discontinue therapy, which was significant, as was the adverse events leading to discontinuation, 24 out of 1,000 patients more on nebivolol 40 than on the combination of medications.

So we can see that in the individual patient, there is evidence that the fixed-dose combination clearly delineates itself from the monotherapies at their highest dosages.

In considering that, what are the clinical uses of the drug? How will we use it in practice -- how would I use it in practice if I had this available?

First, I'd like to discuss the use of it as initial therapy. The study was designed as an initial therapy study because everybody came in naive to therapy at the time of randomization.
Now, in my experience, which is large -- I still practice and see patients six half days a week, and I take care of a lot of old people. I actually am an advocate for starting the older people on lower dosages, so I would feel very comfortable starting 5/80 as an initial dose in a high stage 1 or a low stage 2 patient.

Now, if the patient was higher, let's say they were 170 over 110 or 165 over 105, it might be reasonable to start with 10/160, but having the option of 5/80 to me makes sense. I can talk more about that during the discussion if you're interested because we have seen a lot of super sensitivity to medications in certain older people. And then we also have the option of titrating up to 20/320.

So this is not necessarily a recipe for everybody, but I think it's a very easy standard for clinical physicians to adhere to in a guidance. Now, if patients are already on nebivolol or already on valsartan, this is very simple if the patients are taking one of these doses or another
and they have all of these options for combining
5/80 up to 20/320 for convenience purposes, as
we've done with many other fixed-dose combinations
in clinical practice.

Now, this is more complicated, but I think
that this is what we'd end up doing quite
regularly. And that is taking a patient who's on a
monotherapy of a beta blocker or an ARB at either a
low or intermediate dose, or a high dose, and
switching them to this fixed-dose combination where
we would have the options of using doses in the
lower range of 5/80 up to 10/160 and then the
higher range of 10/320 up to 20/320, depending on
several things, including the level of their blood
pressure, what their heart rate is at the time, and
what perhaps you know about their individual
clinical features such as the presence or absence
of tachycardia, a history of intolerance of certain
drugs, and so forth.

So reviewing all of the data from the
program, my conclusions are as follows: I think
the fixed-dose combination did have superior
efficacy compared to the highest doses of its monotherapy components. The ambulatory blood pressure data were interesting as they showed substantial reductions from baseline. In fact, the 20/320 reduction control for placebo subtraction was 17 over 15. And that blood pressure lowering did appear to last for 24 hours with that particular narrowing at the time of sleep but the reemergence of its effect when patients were awake.

The adverse event profile of the fixed-dose combination was similar to the ARB and to the placebo and better than the high dose of the beta blocker.

In conclusion, the fixed-dose combination would offer patients with hypertension a well-tolerated therapeutic entity that could improve their blood pressure control and enhance adherence to the therapy.

Thanks very much for listening. This ends the presentation from the sponsor.

Clarifying Questions to the Presenters

DR. LINCOFF: All right. So now we'll have
clarifying questions for the sponsor. Please remember to state your name for the record before you speak. Dr. Sager?

DR. SAGER: Thank you for those really nice presentations. If it's possible to put up slide 34, when this was presented, it was stated that this is what a physician would see.

Is it possible to see slide 34? Great.

So when I looked at this, I looked at the placebo-adjusted numbers. And first when I looked at the top at the 8-week three combinations, fixed-dose combinations, I noted I didn't really see much of a difference between them. And then we've also discussed in the presentation the nebivolol 20 milligrams, which I'm -- if you could just let me know. Is that a post hoc analysis?

DR. HORNICK: Yes, it was a post hoc analysis, yes.

DR. SAGER: And then I looked at -- because it was at 4 weeks, so it has somewhat -- it has the same placebo group but at a different point of time. And then when one looks at the
placebo-adjusted, for the 20 milligrams, it looks very similar to the 40 milligrams.

DR. HORNICK: So if I might, I'll take the first question first about the differentiation between the top three doses. I then would like to bring up our statistical expert, Dr. Koch, to explain the validity of the 20/320 comparison, if that's all right with you.

So you're right, in terms of the distinguishability amongst the top three doses, we would consider the 20/320 dose to be the most efficacious and the best dose of all of them. And the reason for that is that it brings -- you have the biggest reductions in the systolic compartments of the response, the biggest reductions across all of them in the diastolic. You bring more patients to target. You bring more responders to reduction of 20 over 10, so we would consider that to be our best.

As Dr. White sort of said in his talk, we would then propose a three-step routine, 5/80, 10/160, 20/320, for a treatment algorithm. So
therefore -- because you can't start a patient on those two lower dose. We consider that would be risky due to the hyper-responsiveness at the lower doses. So that would be one reason why you need the other.

Then to extend that argument, this FDC when it's used for replacement therapy, we consider you'd need the other dose to make that easier. That's the reason.

Now -- sorry. I was going to ask --

DR. SAGER: Maybe instead of the statistical discussion, we can come back to that. But if we'd now just go to the slide before, slide 33. And here, I don't -- you may not have it now, but maybe during the break, for the 20-milligram cohort, if you could redo the top three for the 20/320 comparisons now using placebo-adjusted because they have a different placebo group, that would be helpful. You may have that now, or if not, then during the break.

DR. HORNICK: We'll certainly attend to that during the break. And if I could ask then Dr. Koch
to approach the microphone just to explain the 20/320 analysis.

DR. KOCH: Gary Koch, University of North Carolina. My only financial relationship with the sponsor is through a cooperative agreement with the University of North Carolina that provides some salary support and travel reimbursement.

Bring up E-208. So the analysis for this comparison to verify how it worked was done with a multivariate repeated measures model. Week 4 had three treatments in common with week 8. They were placebo, the 160, and the 10/160 combination. And so because there were three arms in common between week 4 and week 8 when you fitted a statistical model that accounted for treatment and visit, those three common treatments provided a bridge that would then let you proceed to compare the combination at week 8 to the monotherapy of 20 at week 4.

DR. SAGER: Thank you. Then my last question is I understand the bradycardia AEs were based, in part, on the heart rate either getting to

A Matter of Record
(301) 890-4188
either 50 or less than 50. How about symptomatic bradycardia that actually resulted in symptoms requiring discontinuation, do you have that data?
So not where it was just a number but patients actually had some significant symptom.

DR. HORNICK: Right. To answer the question about bradycardia, the cutoff limit was 50. The patient was seen by their physician. Often they had to return within one or two days. They were rechecked if they still had bradycardia. So that's how we looked at bradycardia.

To answer the specific question about symptomatology, I'm going to ask my colleague Dr. Ferguson.

DR. FERGUSON: William Ferguson, Forest. The protocol was written in two different ways, for a patient to be categorized as either BPM less than 50 for pulse rate or have an AE of bradycardia. This was done both for withdrawals due to AEs and also TEAEs.

So the study physician had the option if he felt it was asymptomatic to just list the patient
as having a lower pulse rate or a pulse rate less than 50. If the study physician felt that there was a symptomatic bradycardia, he could list it as an adverse event. So that's where the difference lies.

DR. SAGER: But did they have to list what the adverse event was? I mean, patient doesn't come in and say I'm bradycardic today. You know, they say I've got something.

DR. FERGUSON: In some cases, there were additional adverse events of fatigue, lethargy, or dizziness that were concurrent or within one or two days of the bradycardia.

DR. SAGER: And would you be able to show us that?

DR. FERGUSON: We can get it to you at break. It was something that was being calculated currently. Thank you.

DR. LINCOFF: I want to ask you to clarify that. So there were no strict guidelines to differentiate an asymptomatic bradycardia reaching that limit from one that was associated with
spontaneously reported symptom, or is that not true?

DR. FERGUSON: The guideline in the protocol was that if a patient had a pulse rate less than 50 beats per minute, he would be classified as either being discontinued for that reason or having an AE of pulse rate decrease. If it was the physician's judgment that this was not just a vital measurement but rather accompanied by an adverse event of what he called bradycardia, which in their minds could have included other adverse events, the patient could be listed as an adverse event of bradycardia.

Now, they could -- so in many cases, we left it up -- in every case, we left it up to the physician's judgment as he knew the medical history of the patient and whether or not that finding was bradycardic or not.

DR. LINCOFF: I'm still not understanding this. So you, Phil?

DR. SAGER: I think that a physician -- if the heart rate was, let's say, 48, my
understanding, correct me if I'm wrong, is the 
physician could say, oh, I'm going to call this an 
AE of bradycardia, and it got listed as an AE of 
bradycardia. But it didn't mean the patient 
necessarily had any symptoms. It might be the 
physician had a reaction to it.

Is that correct?

DR. FERGUSON: It was the physician's 
decision whether to list that patient as an AE of 
bradycardia or simply a pulse rate less than 50.

DR. LINCOFF: Was the physician permitted to 
continue the patient in the study if their pulse 
rate was consistently less than 50?

DR. FERGUSON: If the patient came back 
within one to two days of that finding and had a 
pulse rate less than 50, the protocol asks for the 
physician to discontinue that patient from the 
study and list them as discontinued due to a pulse 
rate less than 50.

DR. LINCOFF: I would encourage the sponsor 
to provide as much information after the break as 
you can regarding how many of these were truly
associated with symptoms and what those symptoms were.

DR. FERGUSON: Certainly.

DR. LEWIS: Can I ask because I'm actually trying to understand what you just said to them, too. So if the physician listed it as a TEAE of bradycardia, that means he thought the patient had a symptom with it.

DR. FERGUSON: Yes.

DR. LEWIS: Otherwise, he would have just listed it as a heart rate less than 50. So there were two different ways they could list it.

DR. FERGUSON: Exactly.

DR. LEWIS: For the ones that are listed -- that's what he just said.

DR. SAGER: I don't think that's -- the physician could say, oh, heart rate's less than 40. The heart rate's 49. I call this an AE of bradycardia because I like to see the heart rate be more than 50, and even if the patient is fully asymptomatic.

DR. LEWIS: So were the physicians allowed
if the patient was asymptomatic, to list it as a bradycardia TEAE if they were asymptomatic, just by the number?

DR. FERGUSON: It was their medical opinion as they knew the patient. They also knew the patient's history of what would be their normal pulse rate.

So if they were normally at 75 and they all of a sudden became 45, a physician might call that an AE, whereas if they were normally at 60 and went to 49, the physician could therefore think is this a pulse rate decrease.

DR. LEWIS: So you're going to break it down for us, those who just list -- that just said, oh, the heart rate's less than 50, no AE and the ones that said AE, right?

DR. FERGUSON: Right.

DR. LEWIS: Okay. I have other questions when it gets to be --

DR. LINCOFF: Dr. D'Agostino.

DR. D'AGOSTINO: On slide 54, I believe it is, you have a substantial dropout for at least
8 weeks stretch of 4/4. And I was wondering what you did with the missing data. Some withdrew consent, so you do nothing with them.

But what did you do with the missing data, and how robust are the results of some kind of imputation method if you did the analysis without the imputation, did it with the imputation? Were most of the dropouts coming from the combination? How were they spread around?

DR. HORNICK: So to discuss how we handled the missing data, I'm going to ask Dr. Koch.

DR. KOCH: Gary Koch, University of North Carolina.

E-197. As you saw in the core presentation, there were actually more dropouts on neb 40 than on the combination of 320/20. So the impact of dropouts would have been somewhat greater on that.

Put the slide up. The sponsor originally did a last observation carried-forward imputation. That was their prespecified method in their protocol, as I understand. They subsequently did a multivariate repeated measures model, which manages
missing is missing using a model like what I
previously described.

They also did an observed case analysis,
which is simply analyzing the data as they are on a
visit-by-visit basis. And then they did a baseline
observation carried forward, which would have been
imputed a change of zero to anyone who
discontinued. So these analyses didn't really
change the findings.

An analysis, which would be excessively
punitive to a particular arm, is sort of
problematic when you're comparing two active
regimens with one another because the patient is
discontinuing an active monotherapy, which would
suggest the monotherapy should have a punitive
effect, and alternatively, you get into complicated
issues.

I think the multivariate repeated measures
model provides the best understanding of how to
deal with the missing data in this setting.

DR. D'AGOSTINO: Thank you.

DR. LINCOFF: Dr. Scott.
DR. Scott: So I have two questions. The first one is in MD-01 within your requirements to be titrated, for instance, could patients not be titrated if they achieved a certain blood pressure reduction?

DR. BHARUCHA: David Bharucha, Forest.

Dr. Scott, could I ask you to repeat the question, please?

DR. SCOTT: So in the Study MD-01, it's at week 4, patients were titrated up to a higher dose of the combination. What were the circumstances under which patients were not titrated? For instance, if they achieved a certain reduction in blood pressure or they achieved control, were they not titrated?

DR. BHARUCHA: Slide up. As shown here, all patients underwent a forced up-titration. So for instance, patients in the upper row who initially received therapy with 10/160, at week 4, all those patients, assuming they weren't having an adverse event or some problem that would lead to discontinuation, had their dose up-titrated to
20/320.

DR. SCOTT: Okay. Thanks. That answered the second question as well. Thank you.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: I have three questions. You didn't share with us any compliance data, which I guess is another measure of tolerability, arguably. So I wonder if you have some to share with us.

   Also, I wonder if you could comment further on the choice of the primary outcome being diastolic blood pressure given the year of the study began by custom didn't seem like it would necessarily be still the custom.

   Then lastly, in Dr. White's group, he isolated a group of subjects who appeared to have a numerically more impressive response to the FDC. Did those subjects have other characteristics that would identify them as being people who would be more responsive for some reason? Would they be more inform -- is there something more you can inform us about those people?

DR. HORNICK: Right. So I think the first
question was about compliance, and we didn't say at
the time -- we didn't measure elements of
compliance within the 01 trial because we feel that
there's enough data out there to more than suggest
that two pills are better than one. And the
reduction of any regimen even by one tablet does
appear to make a compliance difference.

You make a very good point about diastolic
being the primary. The trial was set up by
convention. As you know, no one ever goes to their
doctor to have their diastolic blood pressure
measured. The point was is that we selected
diastolic by convention at that time, proceeding
rapidly to obviously having passed that regulatory
gatekeeper to do the systolic measurements.

When looking at the clinical utility, and
we'll likely discuss this or you'll discuss this
later, you have to see these blood pressure changes
obviously in the totality of the systolic and
diastolic. We had to pick one. It was by
convention. It is also the case that the more
contemporary trials are now using systolic blood
pressure as a measurement.

Then, Dr. Bharucha, the third part.

DR. BHARUCHA: David Bharucha. I believe, Dr. Lewis, your question was about the makeup or the composition of the patients who did have a particularly robust response.

Slide up. When examining demographic features of patients who exhibited a response of at least 20 over 10 as compared to those who did not, as you can see demonstrated here, basic baseline demographic features were quite similar.

DR. LINCOFF: Dr. Fried.

DR. FRIED: Could you pull up slide 72? I have a follow-up question to Dr. D'Agostino's.

This is a safety study, so I'm a little -- the number that withdrew for protocol violations seems high. And I would like a little bit more data on why you withdraw somebody from a study if you're trying to assess long-term safety.

DR. HORNICK: Could I have slide S-47 up, please? So Dr. D'Agostino, the protocol violations, you want a little bit more detail.
There were 61, which comprised 7.5 percent in total. We've already showed that. Twenty-one of those participated in another study, 14 for violations due to their medical history, and 12 for noncompliance.

DR. FRIED: So you would pull people out if they were not following -- if they're not taking their pills? Is that what it was?

DR. HORNICK: So to give further detail on this aspect, I'm going to ask Dr. Ferguson.

DR. FERGUSON: Yes. If patients were found to be noncompliant and were not taking their pills -- in other words, we did a pill count at each next visit. If the blister packs were incorrect or they did not return blister packs correctly with a good explanation, they were found to be noncompliant to the study and were considered protocol violators.

DR. FRIED: Did you explore whether or not they were not compliant because potentially they were having adverse events?

DR. FERGUSON: We definitely made every
effort to ensure that any patient who was discontinued from this trial and from the NAC-MD-01 trial were not discontinued due to an adverse event. If so, they would be put into the adverse event category.

    DR. SAGER: I'm just curious. What kind of medical history in this extension would have caused them to get pulled from the study?

    DR. FERGUSON: Any medical history that would conflict with the inclusion/exclusion criteria of the study, either they were randomized by error and an inclusion/exclusion criteria may have been missed and then detected at a follow-up visit, or if the patient's medical condition had changed. But all the ones that are listed there were due to incorrect randomizations in that study physicians randomized a patient who was missing an inclusion criteria or had an exclusion criteria and was detected by a later evaluation.

    DR. LINCOFF: So to clarify, even if that inclusion or exclusion criteria did not render them at increased risk for participating in the study,
post hoc, you would exclude them?

DR. FERGUSON: No. That would be at the
discretion of the medical supervisor of the study
to ensure the safety of the patient. If that
inclusion/exclusion criteria seemed to conflict
with the patient's future safety, then they would
be discontinued. If it was felt to be not an issue
in terms of the patient's long-term safety, then
they were allowed to stay.

DR. LINCOFF: Are there any other questions
before we proceed with the FDA?

Dr. Temple?

DR. TEMPLE: Yes. This may have been
discussed, and I may have missed it. But the usual
factorial study compares the -- say, it might have
other groups, but it has the highest doses of each
component in a combination with the highest doses
alone. And despite the large size, you didn't
actually do that.

Can you explain a little bit why, for
example, there was no 40-milligram nebivolol group?

No, there was a 40-milligram nebivolol group; why
there wasn't a 40/360?

Some of the things we're talking about wouldn't be here if you had the usual factorial study. Why did you not do that?

DR. HORNICK: Thank you. I'm going to call Dr. Bharucha.

DR. BHARUCHA: A very deliberate decision was made not to test a combination of, let's say, 40/320, although both of those are the highest approved doses of either agent. Factors that went into this decision included the fact that 40 milligrams of nebivolol is very rarely, if ever, used as a drug for hypertension. So we felt that examining 40/320 would produce interesting data but not clinically useful data or clinically relevant data.

We also felt that 20/320 should be our upper dose based on -- slide up -- as presented earlier, 20/320 is composed of two doses of nebivolol and valsartan, each of which have at least moderate usage in the United States. So we felt that, A, based on these utilization data, and B, the comment
I made earlier that 20/320 would be the more clinically relevant comparison.

DR. TEMPLE: Okay. But you didn't have a 20-milligram dose except for the first 4 weeks, which would have gone with our approach. That would have been total sense, but you didn't do that.

DR. BHARUCHA: That possibility was discussed during one of the meetings with FDA, and it was decided that since 40 milligrams was the highest approved dose despite it not being a clinically utilized dose, that would really be the dose that should be used in meeting the regulatory hurdle.

DR. TEMPLE: So the idea is that the combination of 20/320 would have to be better than 40?

DR. BHARUCHA: That was the original intention of the trial, yes. It was an intention that was met.

DR. HORNICK: Dr. Koch would also like to make a comment, Dr. Temple.
DR. KOCH: Gary Koch again. Could we bring up E-871? This partly speaks to your question, although partly indirectly.

Slide up, please. So in order to have some way of evaluating something like 20 at 8 weeks, because we had 320/20 at 8 weeks and we had 10 and 40 at 8 weeks, to get a more direct comparison to 20 at 8 weeks, we looked at weighted averages of 10 and 40. And again, I would emphasize the MMRM analysis because it's an analysis that accounts for the missing data as missing.

So where you see .5, .5 in the first row, that's equally weighting 10 and 40. .4 and .6 is giving a weight of 60 percent to 40 and 40 percent to 10. And then one-third, two-thirds is giving a weight of two-thirds to 40 and one-third to 10.

So again, you can see for the systolic in the upper side and in the diastolic in below, the differences achieve low p values, and they achieve the effect sizes that are noted, so that if one things of 20 as either part of the way between 10 and 40, the 50/50 is halfway on the log scale. If
you're using the 40/60 percent weight or the one-third, two-thirds weight, you're thinking of it a little bit less than that. And this was another way that we approached 20 in a way that accounted for the fact that we could get a comparison at 8 weeks that way.

    DR. TEMPLE: So you calculated that 20 would be in the neighborhood of 2 to 3 depending on which --

    DR. KOCH: The 20 is halfway between 10 and 40 on the log scale, and the other weights give more weight to the 40.

    DR. SAGER: But when you look at the placebo-subtracted value as in slide, I think it's 34, 20 and 40 look identical. So does that really -- given that there appears to be an extremely flat dose response, does that really work? I mean, I think it's a very interesting approach. I like the methodologies behind the approach, but it doesn't look like 20 does anything different than 40.

    DR. KOCH: Gary Koch again. The
placebo-subtracted dose is an informal way that only sort of partly accounts for the structure design. As I said previously, there were three arms that were common to week 4 and to week 8. They were the placebo, the 160, and the 10/160. And so when you're doing the repeated measures analysis, you're accounting for all three of them being in common. The placebo subtracted is only accounting for the placebo.

DR. LINCOFF: Dr. D'Agostino?

DR. D'AGOSTINO: I was just going to say that they used the term "factorial" a few times, but it's far from a factorial design. It's laying out the different combinations and then selecting ones for evaluation. And I think the analysis flows correctly from what they did select.

DR. LINCOFF: Other questions? Dr. Li?

DR. LI: I read in the background material that you used an Omron oscillometric blood pressure device, and I assume that was done across all sites. But oscillometric blood pressure devices are known to overestimate true systolic blood
pressure and underestimate diastolic blood pressure.

So for this particular device, since we're talking about very small differences in the diastolic blood pressure, do you know what the standard error is for the -- as opposed to mercury sphygmomanometer?

DR. HORNICK: Just excuse me for one second.

DR. FERGUSON: We do not have that data here right now. We can get it at break. However, we will say that four measurements were taken with the device, and we used the average of the last three to try to ensure to limit the deviation between measurements.

DR. HORNICK: Also Dr. White will make a comment.

DR. WHITE: I think what you're asking is an interesting question, but one which is sort of an unknown, too, because we make the decision at the beginning of the trial to either use a digital device or a standard device such as a -- we don't use mercury columns anymore. They've been taken
out of every hospital and clinic in the United States. So you're either using an aneroid manometer or some kind of digital device.

Now, interestingly enough, aside from this study, most of the time when you use a digital device, you actually get much smaller placebo effects because the way it's actually done is the patients getting their blood pressure measurement -- there's a printout of the actual values, and they have to be appended to the case report form to avoid observer bias, fraud, which I think used to be rampant in clinical trials in hypertension and has actually declined a lot because of both ABPM and because of digital devices being utilized.

But I really would be highly doubtful that the digital measurements had much of an effect on the deltas. I think it might have been on the absolute values in a patient at baseline and then during the treatment, but not for the actual drug effect.

DR. LINCOFF: All right. We have to move on
now for the presentation by the FDA, please.

**FDA Presentation – George Kordzakhia**

DR. KORDZAKHIA:  Good afternoon. My name is George Kordzakhia. I was the statistical reviewer for this application, so I will summarize efficacy part. I will summarize main efficacy analysis, and then Dr. Madabushi will continue. He will summarize collective evidence from both efficacy and safety together.

So here we focus on the efficacy results for the primary and key secondary endpoints. The primary endpoint was change from baseline in sitting diastolic blood pressure. Change in the sitting systolic blood pressure was listed as a key secondary endpoint.

The diastolic blood pressure was analyzed by an ANCOVA model. The table presents primary efficacy comparisons of the higher dose or the combination therapy, FDC 20/320, with the highest approved doses of the two monotherapies, nebivolol 40 milligram and valsartan 320 milligram.

When compared with valsartan, the
combination therapy showed a better improvement with a mean difference of minus 4.4 millimeters of mercury. The treatment difference from nebivolol was however of smaller magnitude and was equal to minus 1.2 millimeters of mercury. So based on the 95 percent confidence interval, the magnitude of the treatment difference was at most 2.3 and potentially could be as small as .1 millimeter.

To further explore the observed magnitude, whether it is clinically relevant, we estimated the within subjects variability as displayed on the following slide. So the within subjects standard deviation was calculated for every patient individually and every patient who had at least one post-baseline visit.

The figure displays the distribution, or to be exact, box plots of the distributions of the within subjects standard deviations for each treatment arm.

The distributions appear to be consistent across all treatment arms. The means of subjects standard deviations were generally larger than 5
millimeters. So on the plot, they are depicted by these diamonds. These are the means.

The overall global mean, which was obtained by pooling all arms together, was approximately 5.6, which is four to five times as large as the observed treatment difference with nebivolol, which was 1.2 millimeters.

The treatment therapies were also compared by investigating the probabilities of achieving the diastolic blood pressure below 90 millimeters and below 80 millimeters, respectively, by the end of the double-blind phase.

The graph displays the probability curves of achieving BP below 90 for the four arms, the FDC arm, the FDC 20/320, and the two highest dose monotherapy arms, and the fourth arm is the placebo.

So the probability was estimated as a function of baseline blood pressure using the logistic regression model. As we can see, both the FDC therapy and nebivolol monotherapy have higher probabilities than the valsartan monotherapy and
the placebo. However, there appears to be no
discernible hierarchical difference between the
probability curves corresponding to the combination
therapy and the nebivolol arms. A very similar
pattern was observed for the probabilities of
achieving diastolic blood pressure below 80
millimeters, the second goal.

The graph presented on the previous slide
was based on the logistic regression model that
allowed for different slopes across the treatment
arms. This is a typical FDA analysis.

The sponsor used an alternative model, which
assumes a common slope for the four treatment arms.
However, based on both models, both models suggest
that there is little difference between the
combination arm and the nebivolol arm.

In the next slide, we move to the discussion
of the key secondary findings, the findings on the
key secondary endpoint. Similar to the primary
endpoint, change in the systolic blood pressure was
also analyzed by ANCOVA model, and essentially the
same ANCOVA model as was used for the primary
The combination therapy showed higher reduction in the blood pressure for both monotherapies, nebivolol and valsartan. The estimated mean treatment differences were very similar, approximately minus 3 millimeters, as we can see. And the p values were also highly significant.

Similarly, analogously to the primary endpoint, two blood pressure goals were considered for the systolic blood pressure. The first goal was achieving blood pressure below 140 millimeters, and the second one achieving blood pressure below 130.

So the graph pertains to the first goal. As we can see, the estimated probability with the FDC treatment appears to be higher than with both monotherapies, nebivolol and valsartan. And the difference in probabilities between the FDC and nebivolol arm varies between approximately 3 percent and 8 percent. On average, it is about 5 percent, which means that 5 percent more patients
in the FDC arm achieve the blood pressure goal of below 140 millimeters.

For the second goal, essentially the same pattern was observed. So we don't provide the second graph, but we have it as a backup in case people are going to be interested in looking at the second goal.

So this would conclude the short brief summary of the efficacy, and then I'm happy to introduce Dr. Madabushi, who will continue the presentation.

**FDA Presentation – Rajanikanth Madabushi**

DR. MADABUSHI: Thank you, Dr. Kordzakhia.

Good afternoon, everyone. My name is Raj Madabushi, and I am the cross discipline team leader for this submission and will be presenting on behalf of the clinical as well as the clinical pharmacology review team.

To start with, we do not have any significant disagreements with respect to the trial design, conduct, endpoints, efficacy results the way they are presented, the primary efficacy
results, and the key safety findings, to begin
with. So we will not be discussing it in this
presentation.

The presentation will focus on two key
points. First is the clinical significance of the
efficacy findings, and second, is there a potential
for tolerability advantage? Those are the two
topics which we'll be discussing here.

Coming to the efficacy, this information has
been presented by applicant as well as by
Dr. Kordzakhia. I'm not going to belabor this.
The only two points of interest here I want to
bring is the effect size for the comparison of the
fixed-dose combination to the highest approved dose
of nebivolol 40, which is at the heart of the issue
here, and the second point, which Dr. Kordzakhia
raised, within subject standard deviation of around
5.6 millimeter mercury.

So this is the reason why we are here, and
from our perspective, we wanted to look at the
submission, other information that is available in
this development program to help us understand the
clinical significance of this, starting with the
ambulatory blood pressure data.

In this trial, there was a substudy wherein
24-hour ambulatory blood pressure data was
collected. We had anywhere around 77 to
87 patients who provided this information, which is
consistent with our prior experience with previous
trials, large enough subgroup for us to understand.

What I am presenting here is the least
square means for change from baseline and
95 percent confidence intervals for the 24-hour
average ABPM here. The first two represent for the
comparison of the fixed-dose combination versus the
nebivolol 40, and the second two are for the
valsartan comparison, diastolic and systolic.

Looking at the comparison to the nebivolol
40 milligrams, there doesn't seem to be an apparent
difference on both diastolic as well as systolic
for the fixed-dose combination compared to the
nebivolol 40. The findings with the valsartan seem
to be consistent with the primary efficacy
analysis, which we will not be discussing so much
because we do not have so much of an issue there.

So this is another finding which is consistent with our initial concern that does the fixed-dose combination lower blood pressure compared with nebivolol 40. Another way of looking at trying to understand the clinical significance of the blood pressure reduction findings is comparing what we have accepted in recent past.

This is a very busy table here. I'll try to walk through it. What I'm showing here is comparison of nebivolol/valsartan effect sizes compared with the last four fixed-dose combination, which is your first column.

The second column shows the comparisons, the pairwise comparisons, for the fixed-dose combination to the highest approved doses for those particular combinations. And the third column is the sample size in the trial, and the last two columns are the treatment differences at the end of the double-blind treatment periods.

Two key messages from this particular slide, it can be seen that this current trial is the
largest of the trials listed here, and also, the
effect size of 1.2 millimeter mercury on the mean
sitting diastolic blood pressure is the smallest
number we have seen in the last four approvals.

Now, this is a cross-study comparison, and
there are challenges with that, but even comparing
with this has not alleviated our concern for the
clinical significance associated with it.

Another way we looked at it is to see any
differentiating or marked effects of the
fixed-dose combination in important subgroups.
Now, Dr. Kordzakhia showed you the probability
plots based as a function of the baseline, and one
of the conclusions was that there did not seem to
be an apparent difference between the fixed-dose
combination and the nebivolol 40 milligrams.

Here, we are looking at three subgroups of
interest on the X axis, which is diabetes, blacks
and elderly patients defined as age greater or
equal than to 65 years. The Y axis is treatment
difference in mean change in blood pressure during
the double-blind treatment phase. The positive
numbers mean nebivolol is better. The negative numbers would indicate fixed-dose combination is better.

The important message from here is that there were no subgroups with marked effects for us to identify here. On the contrary, if we were to look at the numbers, the trends seem to go in a wrong direction for our convenience. But then again, these are subgroups, so we should interpret them with caution. So these were the three items which we tried to get a handle on the clinical significance with respect to the efficacy.

The second aspect was to see is there a potential advantage for tolerability. So let's see how it looks. To start with, we concurred or we agree with what the applicant has proposed, that we do not see any new or novel safety findings here. They were not identified so that will not be the focus.

The focus will be primarily on tolerability, tolerability issues that may be associated with the nebivolol component. That will be the primary
So if one were to look at treatment-emergent adverse events, the adverse events of interest would be here fatigue and bradycardia. What I'm presenting here on the Y axis is the incidence of these treatment-emergent AEs during the double-blind treatment phase.

For placebo, nebivolol 40 milligrams and fixed-dose combination of 20/320, the numbers in the parentheses are the number of subjects in each of these treatment arms.

A quick look at this would indicate that the rates of bradycardia and fatigue are higher with the highest dose of the nebivolol, that is, 40 milligrams as compared to placebo or fixed-dose combination of 20/320. In fact, one could probably say that there is a threefold increase in the rates of bradycardia.

So to get a better appreciation of what might have driven that, what is associated with the bradycardia, we wanted to take a look at the vital signs which were recorded in this particular study.
I'm showing a table of these vital signs here for placebo, nebivolol 40 and the FDC 20/320. And what we are seeing here is consistent with the finding previously, that treatment arms which contain nebivolol have on an average around 10 beats per minute reduction compared to that of placebo. But if you were to compare between nebivolol 40 and the FDC, there hardly seems to be a one beat per minute difference between the two on an average. An important note is the standard deviation, which is on the range of 10 beats per minute for these pulse rates.

So that was the data with respect to the treatment-emergent adverse events.

Moving on, we wanted to take a look from a tolerability perspective to premature discontinuations. So what I'm presenting here is the incidence of premature discontinuations and how they compare across the placebo, the highest dose of nebivolol approved and the FDC 20/320 in this trial. And it can be seen that the premature discontinuation incidences are higher with placebo
and nebivolol 40 as compared to that of fixed-dose combination of 20/320 milligrams.

So one of the ways of looking at it would be the AEs of interest, which might have driven this particular premature discontinuation, which is what I'm showing in this slide, any AEs as well as the bradycardia here. So the dark bars are any AEs, and the light bars are bradycardia.

If you were to look at it, most of the placebo-related, AE-related discontinuations are due to lack of efficacy or lack of -- to a particular response. As expected, they do not have any bradycardia associated discontinuations, premature discontinuations.

However, if we were to compare between the highest dose of nebivolol and the fixed-dose combination of 20/320, there seems to be an increase in the incidence of premature discontinuations due to bradycardia. So that made us think what might be the reasons for this, what kind of a clinical association is there with this.

So we took a look at the protocol, and the
protocol stipulates subjects can be prematurely
discontinued for 10 reasons, 10 plausible reasons,
among which they could be protocol violations,
withdrawn consents, lack of therapeutic efficacy,
too much of blood pressure reduction.

But of note here is -- which I have copied
and pasted verbatim -- sitting pulse less than
50 beats per minute, except for patients who were
treated with beta blockers and are currently in the
single-blind washout phase, not in the double-blind
phase, there is an option that the patient may be
scheduled for a repeat sitting pulse measurement
within one to two days if deemed medically
justified by the PI. And if that concurs, then the
subject would be prematurely discontinued.

So when we looked at the 11 bradycardia
events which were associated with the
discontinuation for the difference between the
highest dose of nebivolol and the fixed-dose
combination, 3 in the fixed-dose combination, 8 in
the nebivolol, none of these 11 bradycardia events
associated with premature discontinuations had
clinical symptoms reported on the CRFs.

So we think that these discontinuations are prematurely physician behavior driven by the protocol expectation.

So in summary, we think the reduction in the diastolic blood pressure between the fixed-dose combination of 20/320 and nebivolol 40 is small, and the effect size seen in this trial is smaller than the effects of the last four of the submissions that have been approved.

We do not see any remarkable effect in importance of groups of interest, which was shown by Dr. Kordzakhia and some of the three subgroups which I showed. There is definitely a trend for lower pulse rates with nebivolol 40 milligrams. However, there is no evidence that the lower pulse rates were associated with symptoms.

Now, we heard from the sponsors that there could be a comparison of fixed-dose combination 20/320 to nebivolol 20, which is also there in the background document.

Three points on this particular topic. The
division has consistently asserted that comparison of the fixed-dose combinations to the highest approved doses of the monotherapies are most relevant because that ensures us that the fixed dose combination will provide a reduction greater than what can be achieved with either of the components by themselves.

Now, an exception could be made in situations where there is a potential tolerability or a safety issue associated with the highest dose of any of the minor components, but I have shown you information that there were no significant tolerability issues associated with the highest approved dose of nebivolol that were identified in this particular trial.

Now, even if we were to take a look at the post hoc comparison of the nebivolol of the fixed-dose comparison compared with the nebivolol 20 milligrams, this results in a small incremental reduction of diastolic blood pressure.

So in conclusion, the treatment with the FDC does not provide a clinically meaningful reduction
in the diastolic blood pressure compared with the highest approved dosages of one of its components, that is, nebivolol in this case. Further, the treatment with the fixed-dose combination does not provide an opportunity to improve the tolerability of nebivolol while retaining the similar effectiveness.

Thank you very much.

**Clarifying Questions to the Presenters**

DR. LINCOFF: Thank you. Are there clarifying questions for the FDA?

Dr. D'Agostino.

DR. D'AGOSTINO: Thank you for the presentation. Just a few questions. Given what you just said, are you saying that the sponsor's primary analysis is incorrect? Let me add that, is the primary analysis incorrect?

Number two, with the subgroups you showed, were there any significant interactions with the subgroups and the different treatments? You gave the graphs, but not with the interaction test that one would normally look at to decide if the
interactions may have meaning to them.

Then also, what would you say to the criticism, or potential criticism, that all you're doing is post hoc analysis and who knows what we should do with them? I understand what you're saying about the 40 milligrams and so forth, but there is a post hoc aspect to it. So I'd appreciate if you'd respond to those three.

DR. MADABUSHI: To clarify, I don't think I have made an attempt to say that the sponsor's primary analysis is incorrect. If that came across, that's not the intention. We agree with the primary efficacy findings, and Dr. Kordzakhia could add on that part, that aspect.

Now, your second question was with respect to the subgroups and interactions. We wanted to take a look to see if there were any remarkable effects there before we embarked upon any kind of a more quantitative testing. However, we did not see the need to go there because there were no differences that would trigger us to see that, okay, we can identify subgroup where this
combination could be of more value. So we did not need the reason to go there to the next step.

DR. LINCOFF: Dr. Fried?

DR. FRIED: I just wanted to clarify one thing. You had shown in the slides that there appeared to be a higher fatigue. I believe it was slide 10, a little bit of a higher. Is there a correlation? I know you said the 11 individuals who discontinued due to bradycardia did not have other adverse events on the CRFs.

But is there a correlation between the bradycardia and fatigue? Because fatigue is a hard symptom sometimes to characterize, and it could also with beta blocker sometimes be related to CNS effects rather than bradycardia effects.

DR. MADABUSHI: Sure. I will request Dr. Shen Xiao, the clinical reviewer on this, to respond to that.

DR. LINCOFF: Could we get that microphone working?

DR. XIAO: I checked the report form for the present discontinuation, and the time of the come
out of fatigue and the bradycardia is not in
different time. So I conclude the fatigue is not
related to the bradycardia because if there was
this difference, or if there was much difference.

DR. LINCOFF: Could you just identify
yourself for the record, please?

DR. XIAO: My name is Shen Xiao. I'm the
primary medical officer for this application.

DR. LINCOFF: Thank you.

DR. TEMPLE: I'm sorry. Dr. Fried, is that
the question you asked --

DR. FRIED: Well, actually --

DR. TEMPLE: -- whether the bradycardia and
fatigue were related or whether the fatigue seemed
to have caused them to leave the study?

DR. FRIED: Whether or not bradycardia is
related because people can feel fatigued and might
continue on it. It's not just discontinuations,
but whether or not, from a tolerability point of
view, if the fatigue was related to bradycardia,
the correlated.

DR. TEMPLE: For what it's worth, beta
blockers cause fatigue apart from bradycardia and lots of other things.

DR. FRIED: No, but a lot of times it's CNS, particularly because I believe -- and I tried to look it up -- nebivolol crosses the blood-brain barrier; that some people find that those have more fatigue from another point of view.

DR. TEMPLE: Is this one that crosses or not?

DR. LINCOFF: Perhaps the sponsor can address that. Does this cross the blood-brain barrier?

DR. WRIGHT: My name is Harold Wright. I'm a pharmacologist with Forest. There are no clinical data that have looked at its ability to cross the blood-brain barrier. There have been some rodent studies actually in animal models of Alzheimer's. It was a study that was done at Mount Sinai that did show that the product does get across the blood-brain barrier.

DR. LINCOFF: Do you know if there's a dose response in the nebivolol studies of fatigue --
DR. WRIGHT: I believe in those --

DR. LINCOFF: Just for nebivolol in general, is there a dose response with fatigue to suggest that it is a real effect?

DR. WRIGHT: I will let my colleague answer that question.

DR. PATEL: Mehul Patel, medical affairs, Forest. We're going to show the -- and in terms of the monotherapy registrational trials of nebivolol, there does seem to be a dose response in fatigue.

Slide up. So here you can see actually the data from our pooled monotherapy studies. So at the highest doses, you do see some more fatigue.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: Maybe Dr. Weber or somebody, would you comment on what's known about the relative role of beta blockers compared to ARBs in diastolic blood pressure and nebivolol in particular, as that pertains to why diastolic blood pressure might have been selected as the primary endpoint?

Just for my edification, would we have
expected that beta blockers have a greater effect going into this study on diastolic blood pressure than other classes?

DR. WEBER: Michael Weber. No. I think we would have anticipated that a beta blocker added to an ARB would have more of an effect on -- I should say nebivolol would have had more of an effect on systolic pressure because what it brings to the combination that's unique is the vasodilation caused by the action in the endothelium, and one would assume that dilation is going to have a very direct effect on systolic pressure, particularly in large vessels. And we've seen that with other studies with nebivolol.

In fact, this study in some ways -- from a clinical point of view, getting back to the question that Dr. Sager had asked right at the beginning -- isn't that helpful in some ways in understanding what this combination does in clinical practice because if you think about it, this is a trial where patients were randomized to single therapy or combination therapy often in
patients whose blood pressures were not necessarily that high. So we in a sense were reducing the probability that two drugs would be superior to one. Nevertheless, that is the way these trials have to be designed for regulatory purposes.

We do have evidence when nebivolol is added to ARBs in patients who are getting an ARB and whose blood pressure is not well controlled, which, of course, is what the clinician would be thinking about and looking for -- and actually, if we can put this slide up on the screen, please.

These are patients, and we're looking at changes in the systolic and diastolic pressure when different doses, 5, 10 and 20 of nebivolol, are added to angiotensin receptor blockers in patients whose blood pressures are not controlled. And we are seeing a rather more robust effect on blood pressure than we saw in the trial that we've been talking about earlier today.

I think, Dr. Sager, this is probably more in keeping with what we would anticipate in the clinical domain from the use of this combination.
DR. LINCOFF: Dr. D'Agostino.

DR. D'AGOSTINO: Do you have graphs of what would be the comparison if you did whites with the two treatments and if you did under 65? You showed us subgroups where there were no differences even with the over 65 possibly going in the direction that wouldn't be anticipated. Given the significant results, there must have been something in other subgroups.

Do you have other subgroups? And what were the numbers of subjects in the subgroups that you actually looked at? I'm trying to get a sense of how important those results are.

DR. MADABUSHI: Sure. I don't think we looked all subgroups apart from a typical representation, which comes with the package.

Now, you asked a question about what is the size of these subgroups. These subgroups are small in number. For example, the diabetes group represents 15 percent of the overall population. We realize that these are small numbers, but we are looking for some kind of a remarkable
differentiation the combination product may bring
to the table. So that would be my answer to that
question.

    DR. LINCOFF: I suspect the sponsor has --

    DR. HORNICK: Yes. With respect, Chair,
we'd like to -- we can probably help with that and
show some data around some of these subgroup
analyses.

    DR. BHARUCHA: Focusing on what I believe
the question is, in terms of the subgroup analysis
of blacks and non-black patients, the effects
are -- can I see the first slide again and slide up
then?

    This slide depicts reductions in blood
pressure from baseline in black and non-black
patients, as shown respectively in blue and orange
for each of the FDCs and for each of the
monotherapies that were used as comparators.

    Now, the black subgroup of patients in this
study was smaller, so there will be some
variability, understandably. However, there were
blood pressure reductions from baseline observed in
both black and non-black patients.

This is systolic blood pressure. Slide up.

This is diastolic blood pressure, Dr. D'Agostino, and similar findings are observed.

DR. D'AGOSTINO: And that 411 for the blacks, that's spread across all of the different treatments, obviously, so you've got small sample sizes in each of these. You got a small sample size in each of these groups.

DR. BHARUCHA: Yes.

DR. LINCOFF: Are there any other questions for the FDA or for the -- Dr. Temple?

DR. TEMPLE: Those last results -- I mean, you've got to know who the population is -- are at least somewhat surprising because you don't expect drugs that work the renin-angiotensin system to do very well in blacks. So maybe, I wonder if you think so, this has something to do with vasodilatory property, which would not be expected to be as racially distinct.

DR. HORNICK: I'm going to ask Dr. Weber just to make another comment about that. Thanks.
DR. WEBER: You're quite right, Dr. Temple. Nebivolol works well in black patients. In fact, it's probably no difference between black and white patients, which is, as you would point out, unusual for a beta blocker. And I think it's entirely due to the fact that it has this effect in liberating nitric oxide, which by the way is well established as being in a somewhat deficient state in African American patients. So in fact, it's a very logical treatment for African Americans.

DR. TEMPLE: Actually, one of my first questions when I heard about this is why would anybody put two drugs that work through the renin-angiotensin system together. You don't combine ACE inhibitors and ARBs because you don't expect any benefit. And at least going in, I wouldn't expect any additive effect from beta blocker, which works mostly through that system also even if it does some other things.

But I think you're perhaps making some case for why you might combine these things even though they work predominantly through the
rennin-angiotensin system because they have another
effect. And maybe that's why you show some effect.
Anyway, just a thought.

DR. LINCOFF: Dr. Lewis.

DR. LEWIS: I tried to tease out as I read
this. Like to me, a comparator group that was
logical would be the 20 to the 20/320, especially
since we can't prescribe 40, right? They don't
make it or something. As I understand, they don't
manufacture it. And there is some data about
efficacy in 20 versus 320 that we've heard about,
nebivolol 20 versus 20/320.

Did you look at -- I assume from your
comments that the safety data would be no
difference between the nebivolol 20 and the
combination 20/320?

DR. MADABUSHI: There are a couple of things
here. First of all, the highest approved dose is
40, and it's still labeled. I don't think the
40-milligram strength is being marketed. That's
what I understand, but someone could prescribe two
tablets of 20 milligrams to get that 40 dose of
same. That's one part of it.

Second is we said that as per the combination rule, it is possible for one to go against a dose of a monotherapy, which is not the absolute highest in case there is someone -- there is an ability to show some tolerability advantage. We did not see that clearly, at least demonstrated in this particular trial, to make a case that one should compare with 20.

The trial aspect is, yes, even if we went ahead and did this post hoc comparison of comparing the fixed-dose combination with the 20, we still thought that the effect on an average, which is projected out, is not that great. And that's expected probably because of the shallow dose response, which is there at these particular doses. So those would be my answers.

DR. HORNICK: I just wanted to clarify just one thing. We don't actually make the 40-milligram tablet. If you wanted to prescribe, and very few people do, you'd get it as two 20s. And in terms of the 20/320-milligram safety comparison that you
alluded to, difficult to do because it has to be post hoc. But we did do it, and we don't find -- and there's no decrease in tolerability with 20/320. In fact, it's probably numerically better.

DR. LINCOFF: Dr. Sager, and then we'll break.

DR. SAGER: Is it okay if I ask a question to the sponsor?

The point was raised earlier that there could be clinical need for a combination of a beta blocker such a nebivolol and an ARB, and I thought it would be helpful for myself and also the panel to kind of hear what that is since that doesn't exist at the current time.

DR. HORNICK: Thank you. And I think this gets right to the core of the issue. There is indeed a need, and I'm going to ask Dr. White to step up to explain how he, for example, would use this in his practice.

DR. WHITE: So if you remember, back to all these JNCs that came out over the last 30 or
40 years, these classes of drugs were always paramount in the treatment of hypertension. And in addition to that, there was these compelling reasons to use certain drugs in certain kinds of patients.

For example, if you were hypertensive and had ischemic heart disease, obviously, a beta blocker would be appropriate. If you had a history of rapid atrial fibrillation, even if it had been converted, being on a beta blocker as the background so that you would avert a rapid ventricular response if you went back into the AF would be a very reasonable drug to be on.

Then subsequently, there was a whole host of studies that looked at hypertensive patients and even non-hypertensive patients and the use of an ARB to protect them against the deterioration of renal function if they had diabetic nephropathy.

So I think that when clinicians look at these two classes of drugs, they would think to themselves, well, I've got a person with a remote history of angina stent. They happen to be
diabetic. They've got a little proteinuria. So these two drugs would clearly come up in the minds of that physician to be utilized for the treatment of their hypertension, and they'd get the bonus of treating those other conditions simultaneously.

It's actually very common. I would say that 80 percent of the patients that I see in my own practice have those comorbidities. It's just really fairly rampant.

Now, the primary care physician's office, they probably see a lot more uncomplicated patients, but still they would be utilizing either an ARB or a beta blocker alone or in combination with a diuretic or dihydropyridine calcium channel blocker, depending on the need for blood pressure control.

DR. LINCOFF: Okay. There will be opportunity later.

So we will now take a short 15-minute break. Committee members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the
audience. We'll resume at 2:40.

(Whereupon, a brief recess was taken.)

Open Public Hearing

DR. LINCOFF: Okay. We'll get started.

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 believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee
if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully, treated with dignity, courtesy, and respect. Therefore, speak only when recognized by the chair. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. MAZZUCCO: Hi. My name is Dr. Anna
Mazzucco, and I'm representing the National Center for Health Research. I'm actually speaking on behalf of my colleague, Dr. Lauren Doamekpor, who couldn't be here today at the last minute, so I apologize that I'm speaking off my electronic device with her comments.

"Good afternoon. I'm speaking on behalf of the National Center for Health Research. Our nonprofit research center assesses scientific and medical data and provides health information to patients, providers, and policymakers. Our organization does not accept funding from pharmaceutical companies, so therefore, I have no conflicts of interest today.

"We know that hypertension is a condition that affects millions of Americans. One in three adults has high blood pressure and is at risk for other serious health conditions such as heart disease and death. Our medical and scientific experts have carefully reviewed the data provided to you by the FDA, and we want to share our concerns.
"Data from the pivotal trial showed that the trial's primary and key secondary endpoints were met. Patients on the highest dose of the FDC 20/320-milligram combination had very small but statistically greater mean reductions in DBP and SBP as compared with the highest approved dose of the monotherapy drugs.

"However, patients in this trial were only treated for 8 weeks. Most hypertension patients require medication for years, if not longer. As all of you know, this trial could have been longer, and we would have liked to have seen longer-term data.

"We share the FDA's concerns about the clinical relevance of the small reduction in blood pressure, and we are concerned about approving this combination drug and whether it will really make a difference in patients' health.

"Is a small improvement worth the risk of adding a second drug? With only 8 weeks of data, it is hard to say with any conviction about the potential risks of this product. And this means
it's also difficult to say whether benefits potentially outweigh risks, which may be unknown.

"And since there is so little benefit, we are also concerned about the lack of diversity in the efficacy and safety pivotal trial endpoints. Most patients were white and younger than 65 years.

"African Americans are more likely to have high blood pressure compared to any other racial or ethnic group, and adults over the age of 60 are much more likely to develop hypertension as well. But only about 10 percent of the patients in the efficacy trial were black, and only 9 percent of both pivotal trial samples were over 65.

"Older adults also metabolize drugs in cases differently than younger adults. In some cases such as beta blockers, we know that blacks tend to metabolize blood pressure medications differently than whites.

"Fortunately, the sponsor conducted subgroup analysis in both trials. The results showed racial differences. There was no difference in blood pressure reduction for black patients on the
combined drug compared to patients in the monotherapy 40-milligram arm. Those results indicate that the FDC 20/320 combination does not work well for black patients, and we are concerned about whether this drug should be approved for them.

"In addition, with the small number of blacks in the different dosage groups, it is also very difficult to conclude with certainty that this FDC at any dosage is more effective for blacks than the monotherapy drugs alone. If the company wants to approve this combination for non-black patients, they need to study a larger number of patients to really demonstrate efficacy.

"Subgroup analysis in the safety pivotal trial also suggests other important differences. Although there was generally a low incidence of adverse events across the short-term study, patients over the age of 65 in either the experimental group or the monotherapy group were more likely to have bradycardia than younger patients. That's important information for the
label for the monotherapy drug, which is already on
the market as well as the combination drug if it is
approved.

"In summary, we're concerned that the
sponsor has not yet definitively proven that their
drug is safe for patients using it for more than
8 weeks. And secondly, we are concerned that the
sponsor has not yet definitively proven that this
drug is effective for a non-white population
compared to monotherapy.

"Hypertension is a major cause of death. If
FDC is approved on the basis of this data, it could
potentially harm patients, and so we express
concern also about simply requiring post-market
studies to answer these questions that we really
need to know before the drug is approved. And so
we ask the committee respectfully to consider
requesting longer-term data with larger numbers of
minority patients before approving this
combination. Thank you."

DR. LINCOFF: The open public hearing
portion of this meeting is now concluded. We will
no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Before we begin the panel discussion portion, I want to give a last opportunity for people to address questions either to the FDA or to the sponsor.

(No response.)

Questions to the Committee and Discussion

DR. LINCOFF: No questions? All right.

We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

There's quite an introduction to this set of questions, which I have to read into the record, so bear with me, please.

"Antihypertensive drugs, single agents, are approved in the United States on the basis of
demonstrated effects in lowering blood pressure, a well-established surrogate for primary and secondary prevention of major cardiovascular adverse events. At least among patients whose blood pressure is considered elevated and possibly among all individuals, the relationship between blood pressure and risk of CV events is continuous, monotonic and exponential.

"Combination antihypertensive products are approved in the United States on the basis of a demonstration of increased effect of the combination compared to the highest approved dose of the other component or components. Combinations comprised of just two-drug products are also expected to characterize the dose response relationship for each component, but that becomes impractical with more than two component drugs."

"In either context, one can expect some clinical benefit of a drug or a combination regardless of how minute the treatment effect, but there are several considerations."

"First, the smaller the reduction in blood
pressure, the larger the corresponding safety
database would need to be and the more benign the
safety profile must be to make the risk-benefit
tradeoff clearly attractive.

"In this case, the exponential relationship
between the effect on blood pressure and the
expected effect on cardiovascular outcomes
magnifies the corresponding increase in the safety
database size and benignity required.

"Second, most hypertensive patients are far
enough from treatment goals that they require more
than one drug to achieve goal. And even the most
effective antihypertensive drugs have an effect
smaller than excursions in blood pressure
attributable to diurnal variations, meals and
stresses of daily living. So detecting a small
blood pressure effect is difficult.

"Third, the time required to titrate
treatment to achieve a goal blood pressure leaves a
patient at risk for cardiovascular events and
reduces the likelihood that the treatment goal will
ever be achieved. The time period required is, of
course, increased if minimally effective therapy is used during that titration.

"For these reasons, we've adopted a policy not formalized in guidance of expecting some minimal effect size for antihypertensive effects, and this policy has been implemented in several settings.

"First, although a sponsor will generally do extensive and well-powered dose ranging studies of a new antihypertensive sufficient to resolve small differences among doses, we have in recent years only approved doses that represent clinically important steps. So aliskiren, for example, was approved on only two doses with mean difference of 3 to 5 over 1 to 3-millimeter mercury in various studies. And azilsartan was approved at only one dose.

"The second place we've considered minimally clinically important treatment effect size has been with the pediatric clinical development programs conducted under the Best Pharmaceuticals for Children Act. BPCA incentivizes sponsors to
conduct studies in children by granting an
additional six months of marketing exclusivity
applicable to all products containing the active
ingredient under study regardless of whether the
studies are successful in finding a treatment
effect.

"To ensure that the studies provide useful
information about the effectiveness of the drug,
our contracts with the sponsor under BPCA call for
them to power the studies to resolve an effect of
3-millimeter mercury, i.e., to be able to rule out
with 95 percent confidence limits an effect of
3-millimeter mercury if the true effect was zero.
We believe this is the only place where a line has
been drawn to provide an explicit minimally
clinically significant effect.

"We are challenged then by a combination
product with a quite small treatment effect over
the highest marketed dose of one of its components.
The small effect was successfully anticipated by
the applicant, accounting for the largest sample
size we have ever seen for a factorial
"The advisory committee is therefore asked whether the effect size seen here is compatible with approval, or, as is the division's position, is the effect so small that considering this product as a step in someone's care simply delays the time to adequate blood pressure reduction?

"An alternative basis for approval of a combination with little or no increased effectiveness compared with its individual components might be that it offers similar blood pressure reduction with better tolerability.

"There is no precedent for such a basis for approval of a fixed-dose combination of antihypertensive drugs, but the case of Ziac, bisoprolol plus hydrochlorothiazide, is pertinent. More clearly than with nebivolol plus valsartan, both components contribute to the antihypertensive effect of Ziac, and you get less hypokalemia than you would with hydrochlorothiazide alone and less bradycardia than you would on bisoprolol alone at doses of the combination that achieve greater blood
"It is therefore pertinent to consider whether the combination of nebivolol plus valsartan is better tolerated than are both monotherapies, or whether the net effect in terms of blood pressure and tolerability commend the combination. "While the primary comparison should be between some dose of the combination, various doses of which in this case are very similar, and the highest approved doses of the individual drugs, it's worth noting that the dose response relationships for both nebivolol and valsartan are quite shallow.

"If you could not tolerate, say, 40 milligrams of nebivolol, is the possible next logical step a lower dose of nebivolol plus some dose of valsartan, or would you always try a lower dose of nebivolol, a high dose of valsartan or some other combination?"

Okay. Question 1. Absent other advantages, is it reasonable to require some minimum blood pressure effect of a dose or combination? If so,
what should it be, or alternatively, how should it be set?

Who wants to start? Dr. Lewis.

DR. LEWIS: The way the question is asked, it just makes -- obviously, there's no other advantages to the combination. It would make no sense to approve it if it was like a .1 -- yes, there would be a minimum blood pressure effect is the answer. I mean, what that number would be could be a point of discussion. But, yes, there is a minimum, I would say.

DR. LINCOFF: Dr. Fried?

DR. FRIED: I agree, though I think the first part of that sentence is a little bit unclear because I think -- I really sort of am more interested in the sort of second part of the proposed issue, which is the second, which is can you get similar blood pressure reductions with better tolerability? And that's actually I think clinically the more relevant question.

If there was absolutely no difference and no different tolerability, then I also don't see the
DR. LINCOFF: Question 3 comes to that

tolerability. Dr. Sager?

DR. SAGER: I guess I'd add to that, that
thinking about what the effect is on a population
level and what would happen in a population with
reducing blood pressure 1 or 2 millimeters of
mercury versus seeing a doctor -- seeing a patient
in the office. And if it's a very marginal 1 or
2 millimeters of mercury, is that something that's
even going to be something that I as a physician
can really tell that there was a change?

So I think it has to be a level of blood
pressure reduction that is discernible on an
individual patient basis that would have some
clinical meaningfulness because if one uses drug X,
and I'm trying to titrate that up, but it's really
having minimal blood pressure effects, then I could
have potentially used something else.

I could delay care, or obviously, patients
who have hypertension are often undertreated.

That's a big issue in the blood pressure arena,
that it's important to use the therapies that are
going to have significant impact, particularly if
we're going to be on monotherapy because the
patient hasn't had an adequate response.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: So I answered the question
concretely that, yes, there would be a minimum
absent other advantages. Then the question is how
it should be set. And I guess I would consider,
and as I read the material, should the within
patients standard deviation be one criteria that
you use to set it. And that's within patient
variation in the setting of a study.

I think your comments about what happens in
our clinics and in the real world and discerning
these changes is even more relevant.

DR. LINCOFF: Actually, I'd like to address
in that context. I think that from my standpoint,
it is reasonable. And I also think that although
you've got to take some sort of summary measurement
such as mean to make sure that there aren't people
who actually respond in the other direction, once
you establish at least a significant effect on that, I think responder analysis more directly addresses the issue of is this a meaningful step in titration. Because if you have a very small difference in the number of patients who respond to some threshold and therefore would fail that step, then I think that may be a more useful way of identifying how you might on individual patients alter therapy on that basis.

Dr. Scott?

DR. Scott: I think it should be clinically meaningful, but one should remember that small differences in blood pressure in clinical trials have shown things that are very clinically meaningful.

I perhaps would draw people's attention to the ASCOT study, in which I was involved, where the blood pressure reductions are 1.9 and 2.7 over 5 years, and that contributed to a significant 11 percent reduction in all-cause mortality and 24 percent reduction in CV mortality. So small differences in blood pressure can make quite a big
DR. LINCOFF: Dr. DeLemos.

DR. DELEMOS: Yes. I think there absolutely has to be a minimum difference, and the question is whether you define it based on epidemiology, first principles, or whether you define it based on variation. I think the variation is going to be hard because it makes it very difficult for a sponsor to plan in advance for something like that. I think if you set it arbitrarily somewhere around -- I think the place it's set is reasonable based on the epidemiology, not far off. The 3 millimeters is not far off from the variation. It's a very reasonable, practical approach that can be powered for.

This study is crazy complicated for what they needed to do, right? All they really needed to do is have a three-arm trial. It didn't have to be even this big because they didn't need to power it for such -- power it for a 3 millimeter blood pressure difference and have three arms is all you really need, the two individual arms and the
combination, and then that meets regulatory approval. It didn't have to be eight arms of various doses based on the guidance that they have.

So I think you could make it simple, and I think 3 millimeters is reasonable. Certainly that would be a clinically meaningful effect based on -- as Ralph points out with the epidemiology.

DR. LINCOFF: Dr. D'Agostino?

DR. D'AGOSTINO: I agree pretty much with what was being said. One thing I would like to say, I'd like that to somehow or other be systolic blood pressure, that it's clear that we're talking about -- I think the epidemiology is there that you could come up with a reasonable dose response in terms of what it means to reduce it by 3 millimeters and so forth.

The other thing is I would think that we would want to have built in some reasonable time, the length of the study. The 4 weeks, 8 weeks seems like a very short period of time that we're facing. I know we're supposed to be answering this in general, but I think the study, the reduction
should be sustained over a reasonable amount of
time.

DR. LINCOFF: Dr. Temple?

DR. TEMPLE: To what extent, if at all, do
you think this consideration should include other
possible things that one could do other than move
to this combination? So if the effect is very
small, are you supposed to think about what the
effect of adding a diuretic or adding some other
drug would be? Does that come into this at all?

DR. LINCOFF: Dr. Fried?

DR. FRIED: I see a very skewed population.
Obviously, I see those with kidney disease. And I
must say that my next step after an ACE or an ARB,
using one or the other, is a diuretic. I find that
it's synergistic more than just additive, and I
tend to think of beta blockers as, truthfully, my
fourth-line agent. I use in order pretty much an
ACE or an ARB, a diuretic, a dihydropyridine
calcium channel blocker, and a beta blocker.

That said, there are patient populations
that I might feel differently. If they have
ischemic heart disease or if they have a low
injection fraction, I may be titrating those other
drugs because they have other indications first.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: I think that there are clearly
guidelines that suggest that you need to start two
drugs on certain categories of patients. And if
you're not working in a practice where they have
the advantage of bringing the patient back after
the X number, when they have its maximum effect,
and in fact, you're going to bring them back who
knows when, that's unfortunately a big part of our
healthcare system, choosing this combo as you're
starting two drugs might not be the most
efficacious way to start two drugs. So I think
that that is a concern.

DR. LINCOFF: I'd like to respond to
Dr. Temple's question. We're not being asked to
decide the proper strategy or the relative
effectiveness of different combinations of drugs
because people have spent years and different
generations of guidelines trying to sort that out;
otherwise, most of our discussions here would be, well, this therapy is better than placebo or better than an alternative, but is it better to the other alternative.

So I think probably in fairness, we have to confine ourselves to is it better than the components, does it provide an incremental benefit.

I'd like to ask -- because two people have now brought up the issue of duration of therapy. It's my impression, but I may be wrong, that these drugs work relatively quickly, and that it's been pretty well established that you asymptotically sort of reach your peak effect, that this is a 4-week -- that this 4-week period is adequate.

Does either the FDA or the sponsor have any data with these individual components or with your own drugs to suggest, this combination, regarding whether or not 4 weeks provides a sufficient picture of the effect?

DR. HORNICK: We do have some data to show you. I'm going to ask Dr. Bharucha to show you the difference in blood pressure using the fixed-dose
combination both with and without hydrochlorothiazide.

DR. LINCOFF: That's not what I asked. I asked about persistence after 4 weeks. In other words, does 8 weeks give you anything more than 4 weeks? We've had calls for longer-term therapy and whether or not 4 weeks was an adequate period of time to fully evaluate the effects.

Dr. Temple or Dr. Stockbridge?

DR. STOCKBRIDGE: The typical new molecular entity is worked up with a 4- to 8-week trial to show effectiveness and then some kind of withdrawal study after long-term use that confirms that you've still got effectiveness.

We have that here, so there's not been any call to establish long-term use here. The trials have to be long enough so you get a blood pressure effect, and 4 weeks is probably enough, or 8 weeks is plenty. But nobody's ever thought you had to reconfirm that there's long-term effectiveness with these.

DR. TEMPLE: We've accepted the known
long-term effects of the single entities as
probably applicable to the combination, and if not,
asked for additional long-term data or even another
randomized withdrawal study. Maybe that's wrong,
but that's not what -- we have not done that.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: So I just want to follow up on
your comment. I do think that it is -- I'm not
trying to argue what combos you would use, but the
question is, if you looked at the diastolic, would
you count a 1.2-millimeter difference of mercury as
two drugs? Is it reasonable to say you've started
two drugs if that's the guideline we're using to
start two drugs because they have whatever, really
high blood pressure, whatever the risk thing says
that says you should start two drugs.

Now, having said that, I actually think -- I
look at the systolic blood pressure effects of this
combo and weigh them much more strongly than I do
the diastolic for reasons that have been stated.

DR. HORNICK: We actually do have some
monotherapy data we would like to show you for the
nebivolol, if that's okay.

DR. LINCOFF: Yes, briefly because I think it's been answered.

DR. PATEL: Right. I just want to go back to the question about the effect over time. So we do have nebivolol monotherapy data to show and very similar effects with valsartan, although I don't have a slide.

Slide up. Now, you can see here that efficacy is reached as quickly as 2 weeks, and it's pretty flat after that. So I think we can see right here that we probably don't need a very long study, and we can actually MD-02 data to support that as well, if you'd like.

DR. LINCOFF: No. I think between the FDA's position on that and your data, that's helpful. Hopefully that settles the issue.

Dr. Sager, did you have a comment?

(Dr. Sager gesture no.)

DR. LINCOFF: Okay. Dr. Rich?

DR. RICH: The question that's on the table is whether a minimum effect size should be
considered. And just to respond to that, my answer is, yes, it should be epidemiology based because we're dealing with populations here, and it should be systolic because that's the current state of the art.

So I would argue that if the agency is looking for a direction to establish a minimum effect size for an antihypertensive, they should choose a systolic blood pressure delta that the epidemiology studies support reduces morbidity.

DR. LINCOFF: Dr. D'Agostino?

DR. D'AGOSTINO: In terms of the length, I was not talking -- when I was saying sustained, I was not talking three years. I was talking something like we're seeing here, that it drops, that it maintains itself.

A number of us around this table, myself included, have seen trials where we follow individuals over time, and you see the blood pressure drop immediately. Then you suddenly see it rising up later on. Is it because of dropping out? Is it because of not taking it as you should
and what have you? But this idea of having some sustained period I think is important, and I think the type of data that was shown would address that.

   DR. LINCOFF: Dr. Sager?

   DR. SAGER: I feel that the blood pressure reduction that one needs to see has to be a little bit more than what is just seen epidemiologically or that one has to be able to -- you know, the mean value should translate into a reduction that at least one can measure in a patient.

   I understand that there will be outliers with greater effects. In fact, 10 percent of the patients in this trial had a really nice reduction of blood pressure. But if we're using these medications and titrating them up, we want to have as clinicians, I think, medications that will really result, on an individual level, in general a somewhat substantial reduction of blood pressure.

   We have a number of combinations that do do that, and I know we can't focus comparing this to other combination drugs; I think the chair made a good point. But on the other hand, it's going to
delay therapy or patients may never get to blood pressure goals and be titrated because medical practice isn't perfect. And as Dr. Lewis said, every patient comes back and they're all being titrated, that just doesn't happen in clinical practice.

So I think we do need drugs that have optimal therapeutic effects, and while 1 millimeter change in blood pressure in a high risk population over a long period of time is going to really result in beneficial effects, I think we have to set the bar somewhat higher in terms of which drugs we actually move into clinical use.

DR. LINCOFF: Well, you have said that you want it to be discernible in individual patients, so what is that? What can you discern in an individual patient? What would you expect a mean to --

DR. SAGER: I think in the order of 3, 4 millimeters of mercury for systolic.

DR. LINCOFF: Any other comments, or should I try to summarize?
(No response.)

DR. LINCOFF: So the only thing I can summarize is, yes, absent other advantages, it is reasonable to be a minimum. It seems like most believe that that should actually be based more on the systolic rather than diastolic because that's current state of the art. And although variation is one approach, it seems most feel that an epidemiologic basis would be more fair from the standpoint from being able to plan and also have the scientific basis of predicting outcome in terms of mortality and morbidity.

The level, of course, there's no consensus. It seems that 3 to 4 millimeters is about the range that most mentioned, if any was mentioned. And issues such as where does the responder analysis fit in in terms of whether something is worthwhile was also brought up.

Question 2. If you thought there was a minimally clinically relevant treatment effect in this study, does the combination with valsartan and nebivolol provide it compared with single agents in
this study? So as most seem to believe there is a minimal effect, do we believe this trial showed that?

    DR. LI: I believe that this trial did show -- I mean, it was well powered, and it did demonstrate a difference. But I think that's really not the issue at hand here. It's more whether it's clinically significant. But I think it's really hard to distinguish between what a difference is between a 1 millimeter systolic versus 3 millimeters systolic or diastolic, what that really means in terms of cardiovascular morbidity and mortality. It's hard to translate.

    DR. LINCOFF: Dr. Rich?

    DR. RICH: I think when compared to monotherapy valsartan, the answer was clear. The combination was better. I think the conundrum we face is single dose nebivolol at 40, and the problem is that there is no 40. At least if you want to prescribe 40 in this country, you have to prescribe 20 twice. So your monotherapy becomes two pills, and, apparently, it's not done in this
country with any frequency at all. 

So now we're asked to make a judgment on a combination therapy versus a monotherapy that's not available, and that's really difficult to do because my sense is the drug works. The drug works better than valsartan alone. It probably works better than nebivolol alone at lower doses, but we don't have the 20-milligram dose as the comparator in the study.

So you're going to be left for the rest of this discussion with a hypothetical. I think that's what really the problem is, because if we had clear-cut data against 20 all the way through, we could make probably an easier decision here. So I don't know how else to say it, but against valsartan for sure and against nebivolol, maybe.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: I think if we say that the minimal treatment effect is 3 and that you have to beat each individual component, the answer is no. It didn't meet that criteria. It's not necessarily -- I agree with Dr. Temple. It's not...
an obviously logical combination from a mechanistic standpoint, and that's borne out by a remarkably weak effect. It is the effect of adding the drugs together.

    Either way, I agree with Stuart that adding it to valsartan, you get more of an effect, but it's still a relatively weak effect. And the combination is not one that is a robust blood pressure lowering. Doesn't seem to meet -- there was not a direct comparison with 20. It doesn't seem to meet the standard for comparison with 40. And they did go out for diastolic blood pressure, and didn't even come close. So it wasn't like the systolic blood pressure was a secondary endpoint.

    So I think it's a weak effect, a combination that's not -- there would be a role for it, but it's not an intrinsically biologically obvious combination, and the effect falls below the clinically meaningful standpoint.

    DR. LINCOFF: But in the first question, did anybody suggest a threshold for diastolic?

    (No response.)
DR. LINCOFF: Would you like to suggest a threshold for diastolic?

DR. DELEMOS: I think 3 makes sense based on where they started, the original guidance. I think it's simple and biological. It fits. I don't know that -- it's not maybe quite as steep of a dose response curve, but I think it's -- again, though, you have to power it --

I think it would be easier to just in the future say a reduction in systolic blood pressure because here you'd get a discordant result, right? You could argue against valsartan, you hit for systolic, maybe not diastolic. You could come up with situations where you meet systolic criteria and not diastolic criteria. And I think it would be easier if it was in the future just systolic blood pressure. And obviously, you don't want a negative with diastolic.

DR. LINCOFF: Other -- Dr. Sager.

DR. SAGER: I agree, and I think it's an important point that Dr. Rich raised, that compared to valsartan, those were -- that seems like a
clinically significant reduction, but not compared
to nebivolol alone.

DR. LINCOFF: Dr. Unger?

DR. UNGER: Can I just get some
clarification from Dr. Sager?

So the blood pressure we were interested in
is systolic, and the delta we're interested in is 3
to 4. That's what I took from the last question.
And for this combination, the 20/320 versus
nebivolol 40, it's 2.9. Right? Which is close
to --

DR. SAGER: I personally was looking at both
the systolic and the diastolic. I wasn't just
looking at systolic.

DR. UNGER: Well, that's kind of what I
wanted. So 3 to 4 millimeters would be -- I
mean --

DR. SAGER: Well, I guess systolic --

DR. UNGER: -- the higher bar is diastolic,
obviously.

DR. SAGER: -- 2 to 3 for diastolic, for me,
but that's not -- Dr. DeLemos had a different
number. I think that's an area -- I think how much reduction is an area that really needs a lot more discussion.

DR. LINCOFF: Well, in the first question, before we were talking about this individual thing, no one proposed a diastolic threshold. Everybody proposed a systolic threshold, which they almost meet. And if you compare the imputed, or however you want to discuss this, against the 20-milligram nebivolol dose, as valid or invalid as it may be, that was 3.7.

Dr. D'Agostino?

DR. D'AGOSTINO: If I'm understanding what the FDA has given in this preamble to these questions, when they say a 3, they're talking about ruling out a 3, not a point estimate of 3. Isn't that correct?

DR. STOCKBRIDGE: Well, we've certainly never asked anybody to do that, but I think that's an appropriate question at this point, is whether people are satisfied with a point estimate on the order of 3 for systolic or diastolic, or whether
you actually think the trials ought to be powered
and designed to test whether the incremental effect
of the combo exceeds the monotherapy by some
minimally clinically relevant effect size. Very
different.

DR. TEMPLE: But, Norm, tempting as that may
be, we have not generally done that.

DR. STOCKBRIDGE: We have never done that.

DR. TEMPLE: We've looked at the result, for
better or worse.

DR. STOCKBRIDGE: I agree, but it's still a
good question.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: So there's actually -- I think
it's a Cochran analysis that shows if you combine
an ACE and an ARB, it'll lower your blood pressure
by about 3 millimeters of mercury on average.
Those are rough numbers, but that's about right.

I know that when I have a patient with
poorly controlled blood pressure, and my fellow
says to me, "Well, let's add a second drug," it's
time to add a second drug, and they're already on
an ARB, but he wants to add an ACE, or she -- there are a lot of reasons you might not want to do that anymore. But in any case, I point out to them, they're not going to get them 10 millimeters of mercury down.

I think we come back to the question, will a clinician realize when they order two drugs now in different categories -- like they look sort of different to them, arguably, more different than an ACE and an ARB -- are they going to think I'm ordering two drugs? And should they think that if the difference in blood pressure for the two drugs is going to be of this magnitude, this lack of magnitude, if you will?

The other combos that you showed us in your presentation, it's a lot bigger difference than the monotherapy, so that when a doctor orders one of those combos, they are kind of getting two drugs for one pill.

So I think that's like conceptually what we have to think about to me because that's really what the doctors -- the doctors aren't all going to
remember the label that says it's 2 millimeters or 3 millimeters. I guarantee you, my trainees, none of them know that. I don't know. I think that's the key issue.

DR. LINCOFF: Dr. Sager?

DR. SAGER: I think I also took into consideration the lower confidence interval for the diastolic was 0.1 millimeters of mercury, but I also wanted to -- we've mentioned 20 milligrams a few times, and we had asked the sponsors to put together the placebo-subtracted data for the 20 milligrams.

If they have that, would that be okay for them to show? It was redoing slide 33; well, the first part of slide 33, the first three lines, I think.

DR. LINCOFF: Okay. Do you want to show that?

DR. WHITE: We can show that. Do you mind also if I participate a little bit in this conversation? I know it's a little out of the ordinary, but I think there's a couple things that
do need to be clarified.

The difference between the 20/320 and the 20-milligram systolic was 3.7 over 2.2. Okay? So that's a reasonably appropriate comparison even with the 4-week. You saw how fast the dose comes down.

The other thing is about the responder analysis that I presented. Just so there's no confusion, 45 percent of patients on the 20/320 had a 20-millimeter systolic blood pressure reduction versus about 35 percent on the highest doses of the monotherapies.

So it's actually a pretty substantial proportion of people who came down. And it turned out that there was not a typical normal distribution of the changes, of the population of changes, but that there was a certain group of people, for whatever reason, that had a very nice response to this combination at the range of 20 over 10 or higher that started out at 155 over about 100. So they came down to about 130 over 90 from 155 over 100.
DR. LINCOFF: I'm going to ask you to actually show this, because you showed two different types of responder analysis, those who met control, which I believe was --

DR. WHITE: Yes, yes.

DR. LINCOFF: -- and those who had the 20 over 10.

DR. WHITE: Slide up for this one. This is the actual proportions who had a reduction of at least 20 over 10, 44 percent of the 20/320 and about 35 percent of the two other groups at the highest doses. It was actually a 9.5 percent difference between the combo and the nebivolol 40.

Then if we go to the next slide, it interposes the 20-milligram dose, which is now control. This is control. It's about 12 percent more people or 13 percent more actually achieved a blood pressure of less than 140 over 90 on the top fixed-dose combination versus the 20 of nebivolol and about a 15 percent greater proportion versus valsartan.

I agree. We cannot see 2-millimeter
differences in a patient in clinical practice, but we're mixing terminology here between population means and individual patient responses. So I just wanted to mention that.

DR. LINCOFF: Okay. Now if you could provide the data Dr. Sager had --

DR. SAGER: Also note those numbers were not placebo subtracted.

DR. LINCOFF: All right. First, Dr. Lewis.

DR. LEWIS: I don't mean this to sound flip, but I'm not that mathematical, I guess. But how could 44 percent almost have a greater than 20-millimeter mercury benefit and your average be 3, or less than 3?

DR. WHITE: It was --

DR. LEWIS: Was there a whole bunch of people that were zero?

[Crosstalk and inaudible discussion.]

DR. LEWIS: Okay. Got it.

DR. WHITE: And that's the effect of the combination.

DR. LINCOFF: Wait, wait. Please show the
data that Dr. Sager asked for.

DR. KOCH: Gary Koch. I was just going to respond to your question. Small differences in means can translate into 10 percent or so differences in responder variables. That's why responder variables are important to look at when there are small differences between means.

DR. HORNICK: Let's come back to the data that you requested. Can we have slide 33 up, please?

DR. BHARUCHA: Dr. Sager, I believe you were asking about the comparison between 20/320 and nebivolol 20. And if I recall, there were two aspects to your question. One, you questioned whether or not the exposure of nebivolol 20 during week zero through 4 would be applicable since we're comparing it against FDC 20/320, which was exposed during weeks 4 through 8.

Oh, that's no longer a question.

DR. SAGER: No. I just wanted to -- slide 34 had the placebo-subtracted values. The concern with this slide was that if we want to
look at placebo subtracted, we can't directly
compare the 20 milligrams to the combination
because one was from zero to 4 weeks and the
other's 4 to 8 weeks. So the placebo responses may
well be different. I think they are different
during those two time periods.

So it'd be nice to see this slide redone,
just the first three lines of it with the
placebo-subtracted values.

DR. BHARUCHA: And that's exactly what I was
going to respond to.

Part of the analyses that Dr. Koch described
earlier was a correction for that period effect.
In other words, what the analyses that Dr. Koch
described earlier did was corrected for the fact
that one drug was treated -- both drugs were
administered during 4-week treatment periods.
However, since they were administered during
separate 4-week treatment periods, the analysis
that was described corrected for that, making the
analysis valid.

DR. SAGER: So do you have the requested
update to the slide, or it wasn't possible to do it?

DR. KOCH: Gary Koch, University of North Carolina. What was shown for placebo-adjusted, which is slide 34, is an informal calculation, which simply subtracts placebo from the corresponding arm in the corresponding period. But the statistical comparison against 20, which best informed is the one through the multivariate repeated measures model, which accounts for the fact that not only was placebo in week 4 and week 8, but so was valsartan 160 and the 160/10 combination.

So when you're trying to somehow adjust for an effect of the first 4 weeks against the last 4 weeks, you were going to do some kind of thing. Lack of subtraction, you'd be subtracting the average of placebo val 160 and the 10/160 combination to remove the effect of 4 weeks versus 8 weeks. But that's actually better done through the multivariate repeated measures model, which I showed the results for earlier.
An informal placebo subtraction only would
tell part of the story, and that may be why this
slide is a bit confusing.

DR. SAGER: Yes, because I was just struck
here how the 20-milligram and the 40-milligram
placebo subtracted were virtually the same. I
understand -- I appreciate --

DR. KOCH: Yes --

DR. SAGER: -- your multivariate approach.
I was just interested in seeing slide 33 redone,
but it sounds like you want to stick to the
multivariate. I hear you.

DR. KOCH: Yes. So the multivariate
repeated measures gives the most informed
assessment against 20. This is an informal
calculation that's based on a direct calculation of
placebo from each of the arms in the corresponding
period.

DR. LINCOFF: Dr. D'Agostino, can I ask you
for your statistical expertise? Do you see any
problems with that approach? Educating perhaps the
committee.
DR. D'AGOSTINO: No. I think the repeated-measure analysis is actually a way of addressing these questions because then you have the data that's available over the time, and you're doing adjustments with those time periods, taking it into account. Now, I obviously didn't see the procedure statements that were used by the sponsor, but the description is an appropriate way of doing that analysis.

DR. LINCOFF: Thank you. I think that probably sets that to rest.

DR. KOCH: Also for further clarity, that's why I also added the comparison against the average of 10 and 40 in week 8, and you get a similar assessment. So if you're willing to think of the average of 10 and 40 at week 8 as approximating 20, that again gives a similar comparison to 20. And that was done through the model as well.

DR. LINCOFF: Dr. Fried?

DR. FRIED: One of the problems with responder analysis against an active treatment is if you drop 19, you're not a responder. Then if
you drop 20, you are. And when you talk about differences, do you have a slide with the histogram of change or a box plot, something that gives us -- if we're saying that the problem is with population means and that doesn't bring out individual responses, can you show us it?

DR. LINCOFF: Or a cumulative distribution curve or something?

DR. HORNICK: If we could just confer for one second.

DR. LINCOFF: While they're preparing that, then Dr. Scott.

DR. SCOTT: So I just wanted to come back to the clinically meaningful differences. If we decide that a systolic blood pressure reduction of 3 or 4 millimeters is appropriate, then by definition, the diastolic blood pressure reduction is going to be less than that. Since you start from a lower number, it typically just is a lower number, so maybe 2 is the right number then.

DR. LINCOFF: Dr. Lewis, you had had your hand up a while ago, but I don't know if -- it's
been answered. Okay.

Any other comments while we're waiting for the sponsor to provide more information on the responder analysis?

(No response.)

DR. LINCOFF: If the sponsor thinks it's going to be more than another 30 seconds or so, we'll move on to the next question.

DR. WHITE: I don't think there's a picture of that exact question. You're talking about a distribution of histograms like zero to 5, 5 to 10, 10 to 20?

DR. LINCOFF: Or a cumulative frequency distribution curve of the change, something that would not be dichotomous.

DR. FRIED: Yes, just give us a distribution of change. You're showing us means, and you've shown us a categorical variable. What we haven't seen is distribution of change, which might give us a better sense of response compared to, as I said, a categorical variable.

DR. WHITE: I'm sorry. I don't think that
exact thing exists.

    DR. KOCH: E-877, so slide up. So this basically shows cumulative distributions for systolic and diastolic for the extent of change. The reductions could be between zero and 30. The 10 to 20 is in the middle. The 20 to 30 is further to the right.

    The bigger changes are for the systolic. The yellow curve is more clearly on top of the other curves there. But there is also changes for diastolic, but diastolic reductions are a certain fraction of the systolic reductions. But this is showing the proportions of individuals that showed a reduction of at least a given amount.

    DR. FRIED: I understand. What I want is just a simple histogram of what the change in blood pressure is.

    DR. LINCOFF: They don't appear to have that. I'll invite them if they find it to bring it in later, but we're going to move on.

    To summarize on the second question, it's very clear that there's relevant treatment effect
versus valsartan. Versus nebivolol, I have to say it's sort of split. There's no consensus. Some believe that it achieved at the systolic threshold, but others are not convinced.

Question 3. In general, is improved tolerability a reasonable basis for using a combination product that does not offer greater blood pressure reduction than do its components? So in general, so this is not specifically.

Dr. DeLemos?

DR. DELEMOS: Absolutely, no question. But it has to be meaningful improvement in tolerability. But I would think it's no question for me.

DR. LINCOFF: So question 3, just in a general sense, is improved tolerability a basis for using?

Dr. Fried?

DR. FRIED: I agree because you're really trying to take a medication -- that your patient can take on a long-term years' basis. And in order to get a blood pressure goal, you need a tolerable
medication.

DR. WHITE: Excuse me, Dr. Lincoff. I found the slide, if you want to see it, the distribution of changes.

DR. LINCOFF: Okay.

DR. WHITE: Slide up. So this is the actual changes in millimeters of mercury in bins of five for systolic blood pressure, and it looks very similar for diastolic. And the green is the fixed-dose combination. In this case, the orange is nebivolol 40, and the purple is valsartan 320.

You can see that the biggest difference is in the largest changes to the left-hand side of the figure where a higher proportion of patients had more than a 20-millimeter reduction, whereas that particular finding was absent from the other bins.

So that's why I mentioned it wasn't really a typical, normal distribution around a mean or central tendencies. It's odd, but that's the finding, about 9 percent.

DR. LINCOFF: That's interesting.

Anybody else want to comment on whether
tolerability is enough of a reason to approve, if
everything else is the same?

(No response.)

DR. LINCOFF: All right. To summarize the
answer to that question, yes.

Question 4. Has the combination of
valsartan and nebivolol demonstrated better
tolerability than 40 milligrams of nebivolol? If
so, is the evidence in this regard sufficient for
supporting a regulatory decision?

Who's going to go first? Dr. Sager?

DR. SAGER: I'll go. It seemed like the
major difference was in bradycardia defined as a
heart rate less than 50, but we're told that those
were not clinically symptomatic episodes. So I
guess I was underwhelmed.

DR. LINCOFF: Well, and as Dr. Sager
reminded me, we did ask you for more information on
that, and I neglected to give you a chance. So
this would probably be a good chance to produce --

DR. HORNICK: We need to get back to you on
the bradycardia data, sir.
DR. FERGUSON: Yes. To clarify, to have a discontinuation due to either bradycardia or a study physician could have selected a discontinuation due to a heart rate less than 50 -- slide up.

So on the CRF, they had to check one of two boxes. If the patient came in and they felt that the patient was symptomatic and let's say had a low pulse rate for that patient, then the study physician could choose a discontinuation due to bradycardia, sinus bradycardia, or heart rate decrease, all classified as an adverse event. That would total 3 for the FDC 20/320 and 8 for the neb 40.

Separate from that, on the same CRF, the study physician could have chosen heart rate less than 50 if he felt it was just a vital sign finding not accompanied with symptoms that he would consider to be bradycardic. We wrote this protocol specifically for this reason as it is a beta blocker, and we did expect to see lower pulse rates.
DR. LINCOFF: So the result was -- I mean, the FDA has said these 11 cases showed no difference in symptoms.

DR. FERGUSON: Can I go to slide 58 from the core deck, please?

As shown in the second row, these are patients who were discontinued due to bradycardia, not because they had a pulse rate less than 50, because that was a totally separate category on the CRF for discontinuations. These were patients in which the study physician felt that the patient was bradycardic and had an actual adverse event, based on their medical history and the study physician's interpretation of the symptoms.

This finding was statistically significant in the 20/320 versus neb 40 with a p value less than .05.

DR. LINCOFF: But earlier you said that interpretation of the patient's condition could be they normally had a heart rate of 70 and now they were 49. And so would that have qualified as an adverse event?
DR. FERGUSON: If the study physician felt it was an adverse event, based on the patient's condition, then he would check off the box "adverse event bradycardia." If he felt it was a simple vital sign finding not accompanied with other symptomatic findings, he could just check off the box less than 50 pulse.

DR. LINCOFF: Do you have any other data or is this --

DR. FERGUSON: Slide 61, core. We also looked at TEAEs. These are pure adverse events grouping together bradycardia, fatigue, and dizziness to look at symptomatic findings. And again, we saw that FDC 20/320 showed lower incidence of these symptomatic events compared to neb 40.

DR. LINCOFF: Dr. Sager?

DR. SAGER: I think maybe the data that we're really looking for is on slide 58, if you could put that back up, where some of the symptoms we associated with bradycardia include fatigue, dizziness. Sometimes if someone had heart failure,
I guess it could even be dyspnea.

But if we look at the 20/320 group and the 40-milligram monotherapy, those don't seem to really be any difference, at least for those that led to discontinuations.

DR. FERGUSON: For discontinuations due to fatigue, I agree that the incidents are similar.

DR. SAGER: Thanks.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: I wonder if the FDA could help clarify their slide 14 and the information we just heard about bradycardia discontinuations because it doesn't exactly seem the same to me. Are we talking apples and oranges, or conceptually, how is it different?

DR. MADABUSHI: Raj Madabushi. What we were looking is when Dr. Xiao went and looked at each of the CRFs to see for symptoms, if there were recorded any symptoms, we did not find that. There was no evidence.

Now, what we saw was there is consistently a blood pressure going below a threshold. And, for
example, I can tell you in our backup -- if we can go to slide 19, for example.

This would be the time course of the pulse rates, for example, in this particular individual who is on nebivolol 40 who dropped out, and he dropped out around day 29. That would be the nature of this.

In some cases, there is a repeat measurement, which looks below 50 consistently. In some cases, it fluctuates, just to give you an idea. But we did not find specific symptoms written out that would correlate as a bradycardia.

So that is the reason why we said we did not find evidence. What we found consistently was an evidence that there is a one time breach or more often a two times breach of that particular threshold of 50 beats per minute.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: It certainly wouldn't surprise me if a lower dose combination was better tolerated than high dose beta blocker, but it was not shown. I think that the bradycardia is protocol driven,
not clinical. And there's nothing else in any of the data to suggest that, in fact, the combination was better tolerated.

DR. LINCOFF: I would say from my standpoint, I agree. I think they have provided not at all a compelling case that these were important bradycardias. We know beta blockers cause the heart rate to go down. It doesn't matter if it started at 70 and went to 50, if the patient didn't have symptoms. I think they could have anticipated the need to prove this and was an artificial measurement.

Does anybody have a dissenting opinion or other opinion on this question?

(No response.)

DR. LINCOFF: So I'll summarize this question as we do not believe that they demonstrate better tolerability of this combination.

Question 5. Patients who cannot tolerate 40 milligrams of nebivolol may tolerate 20 milligrams. Is the combination better tolerated than 20 milligrams of nebivolol? What is the blood
pressure reduction of the combination over
20 milligrams of nebivolol? Is this clinically
relevant?

Who wants to start? Dr. Fried?

DR. FRIED: If we really didn't find a
difference between 40, I don't think that it makes
sense to think there would be a difference with 20.
But there was at least at the 4 weeks; so if you
can use a somewhat better blood pressure reduction
between 20.

DR. LINCOFF: Well, then I'll contribute. I
agree. I think that we wouldn't expect
necessarily, given that it's the same dose and the
same drug, to be a difference in tolerability
unless you expect valsartan to protect you against
the adverse effect of nebivolol. But I actually do
believe -- I think it's a reasonable analysis to
compare against the 20-milligram dose within the
first 4 weeks, and I'm convinced of that efficacy.

Anybody else? Dr. DeLemos?

DR. DELEMOS: You said you were convinced?

DR. LINCOFF: No, I said I do believe the
efficacy, even though it's at different time periods -- the 8 weeks of the combination versus 4 weeks of nebivolol -- I believe that data is sufficient to say that it would have reached its peak.

DR. DELEMOS: I think it gets more difficult here because -- I tend to agree. I wish the study was set up a little differently to evaluate that, but we're getting closer to the benefit. We may cross the benefit for systolic blood pressure that we would have set forth. If we say 3 millimeters, we're getting closer for diastolic.

I think it's a more difficult question. And in fairness, it is the highest used dose on a regular basis. So I think it's a little bit more difficult of a question to say -- it's still weak, but is there a clinically meaningful benefit relative to 20 milligrams in terms of blood pressure lowering? In my opinion, it's closer but still not -- the evidence isn't sufficient for me, but it's much closer. And I think there's a better debate there than against 40.
DR. LINCOFF: I also think in fairness it's relevant to point out in the regulatory history, it was noted that the company had considered comparing against 20. But because the regulatory standard, at least at this point, appears to be at the highest dose for which they're labeled, they did compare to 40.

It would have been fortunate if they had had another arm that actually had gone to the 8-week completion with 20, but there were circumstances that were perhaps a variety of different reasons why they didn't.

Any other comments on this question? Dr. Sager?

DR. SAGER: I personally was underwhelmed on the robustness of the 20 milligram versus the combination. And again, I have to take into consideration, somewhat, it's different time periods, post hoc analysis. Obviously, would have been ideal if that was one of the arms that was carried through, but there was a lot to consider putting together this complex study.
DR. LINCOFF: Dr. Lewis?

DR. LEWIS: I have a question for the FDA. So there are a lot of patients for a variety of reasons who are on a beta blocker and an ARB. You didn't ask us any questions about whether we thought combining those would be of any value because they'd only have to take one pill instead of two, sort of the subject of tomorrow, I guess, to some extent.

You really want us to only think about this in terms of treatment of hypertension.

(FDA members nod in the affirmative.)

DR. LEWIS: Thank you for clarifying.

DR. LINCOFF: Any others?

DR. TEMPLE: Relevant to that is what claims nebivolol has. It doesn't have a heart failure claim. It doesn't have a post infarction survival claim. So that's a little tricky.

DR. LEWIS: Because I think that's the population that you see on beta blockers and ARBs together --

DR. TEMPLE: And I'm sure people use them
highly interchangeably whether they should or not.

    DR. LEWIS: Yes.

    DR. LINCOFF: Any other comments?

    (No response.)

    DR. LINCOFF: So then we're going to go to the voting question. Oh. The summary is no difference in tolerability and some equivocal -- some believe, some don't believe that sufficient evidence of efficacy against 20 milligrams of nebivolol monotherapy.

    Question 6. Should the combination of valsartan and nebivolol be approved to treat hypertension?

    So first we'll have it open for any comments. Please during these comments, don't indicate how you will vote. We'll have the opportunity after the vote to do that. But if there are any last comments that you'd like to make regarding this or any of the other previous questions, this is the time to do that.

    So yes? Dr. Arkus?

    MS. ARKUS: There was some confusion I
thought with adding HCTZ to the treatment at the end of this trial. So I thought that the data was kind of not out there and straightforward enough.

DR. LINCOFF: Could you clarify what you mean?

MS. ARKUS: From what I read, there was some last minute decisions that if you didn't have a response to a treatment, that HCTZ was added towards the end. Is that not true?

DR. LINCOFF: I think that is true, but I think it was the dose escalation study. Could the --

DR. HORNICK: Yes. That was added in the safety study to get the patients ultimately to target. You had one dose of 12.5, and then that was increased to 25. And if the target wasn't reached at that point, the patient was discontinued.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: I'll just make the comment before we vote. I think it's important to recognize where this started in terms of delays in
therapy. I think the challenge will be that if this drug is approved, people may reach for this combination when there are multiple other combinations that are more efficacious. And given how long it takes people to get to goal anyway, I think the idea of approving combination products that are only minimally effective is a problem.

If people want to use these drugs, they can anyway. It's just a question of the combination product, but I think if you do this, they ought to work. We're only looking at blood pressure here.

DR. LINCOFF: Dr. Lewis?

DR. LEWIS: I know I asked this question, but I just want to make sure the answer is still the same. When you showed us the histogram, you can't in any way identify those people who were having that robust response?

DR. WHITE: Right. I was surprised as well, but they had the same baseline blood pressure of about 155 over 100. They had the same distribution of black, white, men, women, and the different ages. So there was no predictors of who would be
the perfect patient to get this combination to get
that more robust 20 over 10 response.

DR. LINCOFF: Dr. DeLemos?

DR. DELEMOS: That's misleading because the
average response is 17, so it's not really -- we're
talking about a couple of points above the mean in
terms of the -- that group is the largest -- is
almost 40 percent of the group when we look at
hyper-responders. The mean response in the
combination group is 17, and we're talking about
20. It's a little misleading to call them sort of
hyper-responders, I think.

DR. LINCOFF: Aren't we talking about 20
relative to --

DR. DELEMOS: It's 20 from baseline.

DR. LINCOFF: Oh, 20 baseline.

DR. DELEMOS: It's not placebo subtracted,
so it's just -- the average response, depending on
the arm, was between 14 and 17. And here you have
40 percent that had 20, which is what you'd expect.
I'm not sure that there's any evidence that it's
really not normally distributed.
DR. LINCOFF: Ms. Leighton, you had a --

MS. LEIGHTON: Thank you. My concern is this from a patient perspective. Throughout the study, they kept talking to about 60 percent of patients will require at least two drugs to reach goal. I know that clinicians have guidelines that, say, okay, if they have this and they have this, then chances are they're not going to respond.

But what's the likelihood that you're going to fall into that 40 percent who might or you might be an outlier in that other 60 percent? And do we immediately want to reach for a drug that's going to be a combination of two?

DR. LINCOFF: Any other comments? Dr. Rich?

DR. RICH: Just to stir the pot a little bit with the agency, in this new era we're coming to of personalized medicine, which we're really going to tackle tomorrow, it seems that, in my experience, all of these drugs that we evaluate seem to work really good in a small subset and so-so in most everybody else. And yet once a drug is approved, all you hear about in the ads on TV and whatnot is
how spectacular these drugs are for everyone with this underlying problem.

I would love to see something in the label, which is where your power comes from, that says only a small percent of the people really get a good response to this. And we highly recommend physicians if they use this drug, use it for a limited period of time. And only if those patients exceed that response rate should this drug be continued.

I've not seen language anything remotely close to that in approved therapies. I think I would kind of throw it back at you and say, I would approve if you would help me make sure that it's being used properly, but the agency's position is we don't practice medicine. We approve drugs, and doctors decide what they do. But I think that's old times. I think new times -- it's time to get closer together on this.

DR. UNGER: Well, this is actually one of Dr. Temple's favorite subjects, but he's not going to the microphone.
(Laughter.)

DR. UNGER: Yes, he is.

We have been trying lately to provide more of this information in labeling, and we have particularly in the way of histograms that show responses like the slide we got up here a few minutes ago, finally. And we've done that for a pulmonary hypertension drug. I think you're probably familiar with that, where we show what happened in the clinical trial and what one might reasonably expect in the real world.

So we are trying -- we're not trying. We are moving in that direction.

In terms of a statement, I really like that idea, to say the effect you get in any given patient could be less, whatever, and one should monitor where one can. And clearly, this is an area, blood pressure, where one can monitor.

So now you want to say something? Yes, his mike is already on.

DR. TEMPLE: Well, there are two different things. One is how much do you have to tell people
who are treating blood pressure about how you better watch how you're doing. One could say that
don't the people who are doing this know that?

But leaving that aside, we are very interested in individual response and whether it's a cumulative distribution, which, as Ellis likes to point out, is sort of hard to interpret, or those bar graphs. We like that a lot. And we will actually have guidance coming out -- I'm not allowed to talk about it yet -- that's going to urge more attention to things like that.

I don't know if anybody knows this, but the Alzheimer's drugs all show a cumulative distribution of results. And our purpose was to show that nobody responds very well, which is what the cumulative distribution shows. But sometimes it really does show that there's a subset of people who respond very dramatically. So it is nice to see how people respond.

One of the reservations about this is that could be very population dependent, who got in the study and all that, so you've got to be at least a
little nervous about that. But we like the idea of showing individual responses, and we're moving toward that.

   DR. RICH: Unless there's newer data, isn't the track record of physicians in the United States of America treating hypertension still dismal; that only about 30 percent of the people who are identified as being hypertensive actually have their blood pressure under control?

   DR. TEMPLE: Well, a large fraction of people leave therapy.

   DR. RICH: Right, so --

   DR. TEMPLE: I don't know if it's --

   DR. RICH: -- I think in terms of --

   DR. TEMPLE: I don't know if it's poor treatment or just that they leave --

   DR. RICH: Whatever it is, in terms of being reluctant, I would say don't be reluctant to educate physicians on one of the most common problems we have in this country, which we do such a poor job with.

   DR. TEMPLE: Well, you raise a good
question. My impression is that most people simply
leave therapy just the way they leave their
lipid-lowering therapy. But maybe you're right.
Maybe they're treated but don't get controlled. I
don't know which of those is true.

DR. WHITE: Do you mind if I make a comment
about that? I just finished a term as the
president of the American Society of Hypertension.
And blood pressure goals and guidance for that to
physicians was one of our mantras. And I'm happy
to tell you that in the United States, about
55 percent of treated hypertensive are controlled.
And in some healthcare systems, it is much higher
than that.

For example, in the Kaiser Permanente
system, it's close to 75 percent because they
actually have these beautiful algorithms with
combination therapies for stage 2 patients, and
then also offering guidance and having an
electronic medical record that helps all that
stuff.

So it's not as dismal as you think it is.
It's actually a lot better. And I actually think that doctors like Dr. Lewis, Fried, and myself take care of these patients. They're not on two drugs. They're on five drugs. They're on six drugs. So if they're on five drugs and it's two pills or two and a half pills, it's a lot better than taking five pills.

I can't emphasize enough how much patients hate taking a whole handful of pills and how much better they psychologically feel if they can take two pills and four drugs instead of four single pills. It makes a huge difference to them. I don't know why, but it does.

DR. LINCOFF: Other comments before we vote?
(No response.)

DR. LINCOFF: If there's no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If
you're unsure of your vote or you wish to change
your vote, please press the corresponding button
again.

I'm sorry, but I should have read a previous
lead-in paragraph here.

For the voting question, we'll be using an
electronic voting system for this meeting. Once we
begin the vote, the buttons will start flashing and
will continue to flash even after you've entered
your vote. Please press firmly.

If you're unsure of your vote or you wish to
change your vote, you may press the corresponding
button till the vote is closed. After everyone has
completed their vote, the vote will be locked in.
The vote will then be displayed on the screen.

The DFO will read the vote from the screen
into the record. Next, we will go around the room,
and each individual who voted will state their name
and their vote into the record. You can also state
the reason why you voted as you did. We will
continue in the same manner until all questions
have been answered or discussed.
All right. So let's begin the vote.

(Vote taken.)

DR. TOLIVER: The vote is as follows: 4 yes votes, 6 no votes, zero abstentions, zero no votes.

DR. LINCOFF: So we'll go around the room starting perhaps with Dr. D'Agostino. If you could state your name, your vote, and then feel free to -- any comments regarding your reason.

DR. D'AGOSTINO: Ralph D'Agostino. I voted no. While I think the studies have a lot of merit to them, I felt that the effect size that was observed was not really sufficient to justify the combination.

I have some concerns about the subgroups, the blacks and the over 65, maybe not being represented enough and the effect that's in those groups. So I don't think this material is enough to give a yes vote. I voted no.

DR. LEWIS: I voted no. I thought it was a very difficult --

DR. LINCOFF: Just identify yourself into the record.
DR. LEWIS: Dr. Lewis. I voted no. It was actually a very difficult decision, but I think one of the -- the final thing that sort of swayed me was the other existing combination drugs effect size are, in my mind, clinically significantly and numerically significantly higher. And I am concerned about a physician selecting this drug and thinking they're prescribing the equivalent of two drugs in terms of what they would normally mean.

DR. RICH: Stuart Rich. I voted yes. I was thinking more in terms of the clinic, the patient coming in. I would hope that my physician colleagues would check blood pressures after they prescribe a medication. And if they saw a substantial fall, would say this is a good combination for you. And if they didn't, they would move on to something else.

But I didn't see any harm in this combination of two drugs that have been well accepted and treated for a while. I think the trend is it makes sense to put them together if you could. All the other qualifications, I agree with
as well, but that was what swayed me.

DR. FRIED: Linda Fried. I voted yes for very similar reasons to Dr. Rich. I didn't see a safety concern. I think this isn't the drug for everybody, but there's a population that seems to respond, and it might be a good response for certain individuals. And again, if you don't see a response, it's time to move on.

DR. LINCOFF: Dr. Lincoff. I voted yes for many of the same reasons, and I too found this a very difficult decision. I think it clearly has less of an effect as many of the other combination drugs. On the other hand, I think the effect did reach a threshold, at least by systolic, that is probably clinically relevant.

I would not believe this should be a first choice of a combination. I would hope my physician colleagues would have the sense and attention to determine in individual patients whether or not this was an appropriate drug. I'm not sure they will, but I'm not sure also that we should be in a position, from the regulatory standpoint, of saying
this combination is not as good as some other combination, so it shouldn't be approved. I think that gets to be difficult where you draw that line.

So I would hope that the clinic acumen of practitioners would ultimately assess the individual drug and perhaps inform their decision of which sequence to try different combinations based on other characteristics that the patients have.

DR. SAGER: Philip Sager. This was also a difficult vote for me. I voted no because I thought the size of the effect just wasn't robust enough, and actually from a public health standpoint might delay patients in either getting to goal more efficiently or getting to goal at all, depending on the number of steps physicians wanted to go through.

I do think the responder analyses were powerful, and it's a conundrum. If we could identify patients who would be responders, obviously, that would be really terrific in terms of more personalized approaches. But I felt where
we are at the current time, we can't do that. And thus, it just wasn't a robust enough effect.

DR. LI: I'm Jennifer Li. I voted yes. I too like everybody else found this a difficult decision, but, nevertheless, I felt like the drug was safe. The study met the primary endpoint. And even though the primary endpoint of diastolic blood pressure was probably clinically insignificant, I felt that it approached significance in systolic blood pressure both for the 20 and the 40, although there are issues with the arms and the comparator. But overall, the systolic effects, which I think is more clinically meaningful, led me to vote for a yes.

DR. DELEMOS: James DeLemos. I voted no. Guidance from the FDA was the combination product needs to demonstrate efficacy advantage over both of the individual components, and I think that the primary endpoint -- they went with the primary endpoint of diastolic heart failure and the effect was trivial.

I also share Dr. Sager's concern that
approving a drug with a very small effect like this will lead to choosing this agent over other combinations or individual agents that work better.

So I think we don't need 47 combinations of blood pressure medicines. We need a fewer number of combinations that offer advantages, and I think the ones that get approved should offer clear advantages over the individual components.

MS. ARKUS: I voted no as I thought that the data was not robust enough to support the two-drug combination. And as a consumer, I think it might be confusing for some patients and relating that to their doctor, what's going on with their side effects.

The special concern is bradycardia, and perhaps some of the information may be not there in regards to women and long QT. I know that was not a requirement of the study, but I'd love to see more gender separation of outcomes in reports and we'd have a better understanding of how women and men differ in how drugs affect them and the safety margins.
DR. LINCOFF: Could you just read your name into the record as well? Just state your name for the record.

MS. ARKUS: Bonnie Arkus.

MS. LEIGHTON: Susan Leighton, and I voted no. Reducing pill burden is certainly important to the patient population, but more important to us is that the drugs actually deliver the clinical benefit that we expect them to deliver. And I just didn't see the evidence that this would help anybody get to goal any faster. Thank you.

DR. LINCOFF: Before we adjourn, are there any last comments from the FDA?

I'm sorry. There's one more question. If the combination of valsartan and nebivolol is approved to treat hypertension, should the combination be indicated for use as initial therapy, use in patients not already on a rennin-angiotensin system inhibitor or beta blocker?

So I'm not sure how we're supposed to do this in a conditional way. Let's just assume it's
approved whether you liked it or not. So the
question is would you consider it as initial
therapy. Who'd like to start? Dr. Rich.

DR. RICH: I'd say no, your best gun first.
And the one thing we all agreed upon, whether you
voted yes or no, was that the effect size was not
very impressive.

So I think the cardiologists in the room,
since we use these drugs together all the time,
feel more comfortable. But in general, no. I
would say this should not be a first-line therapy.

DR. LINCOFF: Maybe I can clarify -- go
ahead, Dr. Lewis.

DR. LEWIS: Well, actually the indications
that they asked for were 3, and one was replacement
therapy, which was my question to the FDA, were we
supposed to consider that?

Obviously, replacement therapy would mean if
somebody's already on these drugs, would you give
them one pill instead of two. And so I wouldn't
have any trouble with them getting replacement
therapy.
DR. LINCOFF: Dr. Sager?

DR. SAGER: I didn't see any safety issues that would preclude, if these were approved, using the combination in appropriate patients as first-line therapy. And I think it also has a niche in patients who are on valsartan who don't have the optimal response.

DR. LINCOFF: From my standpoint, I think it's a no-brainer for the replacement because two pills and one. But as initial therapy, I think it's pretty clear that a combination therapy is preferred to initially starting with monotherapy in patients with certain levels of hypertension.

So I think this would fit into that niche, even if it's not as good of an initial therapy, as a combination as are some other combinations. But again, I think that gets back to the idea that we hope that clinicians would discriminate based on the data, whether or not they actually will.

Dr. Temple?

DR. TEMPLE: Just a historical note. A long time ago, all of these approvals were based on
replacement for people who were already on them.

We then added it's okay to -- if they're already on a diuretic, you can add the renin-angiotensin system block this way.

Then we added a few cases where people were unlikely to be controlled, and we looked at curves and said it can be initial therapy for people who have only a 10 percent chance of being controlled on a single drug.

The novelty here, of course, is if you're not already on an renin-angiotensin system, you're now getting two of them at once. So that's interesting, and I don't think we have a breathing example of that before.

DR. LINCOFF: Any other comments?

(No response.)

DR. LINCOFF: So now I'll ask, if there are no other comments before we adjourn, does the FDA have any?

DR. STOCKBRIDGE: I don't. I appreciate the committee's input today, and that's been very helpful. Thanks.
Adjournment

DR. LINCOFF: With that, thank you very much, and we're all adjourned.
(Whereupon, at 4:13 p.m., the meeting was adjourned.)